Introduction

The 2003 Merritt-Putnam Symposium was held in Auckland, New Zealand, as part of the Epilepsy Society of Australia’s Annual Scientific Meeting. Pfizer Australia again sponsored this important symposium, a fact appreciated and acknowledged by several of the speakers.

Professor Warren Blume commented that Pfizer “have a very high reputation… for their continuing support of educational endeavours whether they have a new drug coming or not, and that indicates to us a sincerity for improving our educational level, not just marketing.”

Drug treatment in refractory epilepsy: when is enough, enough?

Not every patient requires treatment for their seizures; if the seizure precipitants are avoidable, (e.g. stress, insomnia, alcohol), if the seizures are part of a transient illness, or if the physical examination and EEG are normal, treatment may not be required.

Adverse drug reactions

Anecdotal evidence suggests the two principal adverse drug reactions (ADRs)† which most bother patients in practice for each of the antiepileptic drugs (AEDs) are: CBZ: fatigue, rash
CLB: irritable, fatigue
ESM: fatigue, psychosis (dose-related)
LEV: aggression, fatigue
LTG: rash, insomnia
OCZ: hyponatraemia, fatigue
PHT: fatigue, gum swelling
PRM: slow introduction, fatigue
TPM: fatigue, weight loss
VPA: weight gain, fatigue
Zonisamide (not registered in Australia): somnolence, fatigue.

As can be seen, fatigue occurs with many AEDs, yet physicians often forget to question patients about this. Fatigue may also be a manifestation of disturbed nocturnal sleep. Epilepsy patients may suffer decreased REM sleep through nocturnal seizures, or from AEDs (e.g. benzodiazepines, barbiturates, carbamazepine, or PHT). Sleep efficiency may also be decreased because of increased sleep latency. The manifestations of impaired nocturnal sleep include excessive daytime sleep, microsleep episodes resembling seizures, impaired concentration and organisation, and irritability and depression.

LTG and GBP have only a minimal effect on sleep, as does successful temporal lobectomy (resulting in improved sleep structure and decreased daytime sleep).

Table 1, over, lists some of the important ADRs associated with AEDs.¹ There is a
Table 1. Some important adverse drug reactions associated with antiepileptic drugs†

<table>
<thead>
<tr>
<th>Adverse drug reaction</th>
<th>CBZ</th>
<th>ETX</th>
<th>PHB</th>
<th>PHT</th>
<th>VPA</th>
<th>FBM</th>
<th>GBP</th>
<th>LTG</th>
<th>TPM</th>
<th>TGB</th>
<th>OXC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agranulocytosis</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X**</td>
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<tr>
<td>Stevens-Johnson syndrome</td>
<td>X</td>
<td>X</td>
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<td>X</td>
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<td>X+</td>
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<tr>
<td>Aplastic anaemia</td>
<td>X</td>
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<tr>
<td>Hepatic failure</td>
<td>X</td>
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<td></td>
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<tr>
<td>Allergic dermatitis/rash*</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Serum sickness reaction</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Pancreatitis</td>
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<td>X+</td>
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</tbody>
</table>

* Allergic dermatitis and rash may be avoided by very gradual drug introduction
** Leukopenia has been reported from the Approved Product Information
† Post-marketing surveillance from the Approved Product Information.

danger of missing the early signs of what could be a serious reaction. Patients should be encouraged to discuss with their doctors about their medications, to ensure symptoms of serious ADRs are not mistakenly attributed to a ‘superficial diagnosis’ such as a viral illness.

**Intractability**

Hauser defines intractability as seizures which are recurrent, true seizures (as opposed to pseudoseizures, although some patients with epilepsy will also have pseudoseizures), which occur despite appropriate therapy (i.e. correct drug for the syndrome), or seizure control only with AED side effects. Intractability occurs in approximately 30% of patients.

A study of 525 patients, followed for an average of about 5 years, found that, in the long term, the percentage of patients who were seizure free was inversely proportional to the number of AEDs they received: 77% of patients were seizure free on no AEDs, 68% on one, 23% on two, 0% on three AEDs. Overall 69% of patients were seizure free on no or one AED. When the data were analysed for use of sequential AEDs, 222/470 patients (47%) were seizure free on their first drug, 61/248 (25%) on their second drug, and 18/187 (10%) on their third drug. Seizures recur in approximately 20-30% of patients on monotherapy.

In practice predictors of intractability include poor initial response, remote symptomatic aetiology (i.e. lesion), high seizure frequency (especially with dysplasia), status epilepticus, cognition impairment, and MRI focal cortical abnormality.

† Statements on adverse events are solely based on the presentation by Prof. Blume (GBP, VGB, and TGB were not discussed). For commonly reported adverse events of at least twice the frequency that of placebo, please refer to the Approved Product Information for the respective products discussed.

**Abbreviations**

<table>
<thead>
<tr>
<th>Anti-epileptic drug</th>
<th>AED</th>
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<tbody>
<tr>
<td>Benign childhood epilepsy with centro-temporal spikes</td>
<td>BECTS</td>
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<tr>
<td>Benzodiazepines</td>
<td>BZ</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>CBZ</td>
</tr>
<tr>
<td>Clobazam</td>
<td>CLB</td>
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<tr>
<td>Complementary medicines</td>
<td>CMs</td>
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<tr>
<td>Ethosuximide</td>
<td>ESM</td>
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<tr>
<td>Felbamate</td>
<td>FBM</td>
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<tr>
<td>Foetal malformations</td>
<td>FM</td>
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<td>Folic acid</td>
<td>FA</td>
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<tr>
<td>Gabapentin</td>
<td>GBP</td>
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<tr>
<td>Hydrocortisone</td>
<td>HC</td>
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<tr>
<td>Lamotrigine</td>
<td>LTG</td>
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<tr>
<td>Levetiracetam</td>
<td>LEV</td>
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<tr>
<td>Lennox-Gastaut syndrome</td>
<td>LGS</td>
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<tr>
<td>Neural tube defects</td>
<td>NTD</td>
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<tr>
<td>Neurodevelopmental outcomes</td>
<td>NDO</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>OCZ</td>
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<tr>
<td>Phenobarbitone</td>
<td>PHB</td>
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<td>Phenytion</td>
<td>PHT</td>
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<tr>
<td>Primidone</td>
<td>PRM</td>
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<tr>
<td>Temporal lobe epilepsy</td>
<td>TLE</td>
</tr>
<tr>
<td>Tiagibine</td>
<td>TGB</td>
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<tr>
<td>Topiramate</td>
<td>TPM</td>
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<tr>
<td>Valproate</td>
<td>VPA</td>
</tr>
<tr>
<td>Vigabatrin</td>
<td>VGB</td>
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<tr>
<td>Woman with epilepsy</td>
<td>WWE</td>
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</table>
Drug-efflux transporters can impact on AED seizure control. Drug-efflux transporters are multi-drug resistant proteins which exist in the neurones, glia, and capillary endothelium, and which prevent AEDs from passing into the central nervous system (CNS), and into epileptogenic focal regions. Originally it was thought that AEDs were creating their own efflux transporters, but more recent experimental and clinical data have shown that the seizures themselves create these transporters.

**Surgery**

Wiebe *et al.* reported a seizure-free rate of 63% following temporal lobectomy, versus 12% in patients treated medically. Memory loss has been a concern with surgery, but a recent study reported a 60% memory loss following left temporal lobectomy, 51% following right temporal lobectomy, and 50% in patients treated medically. Surgery can be considered at any feasible age. Congruency of semiology, EEGs (interictal, ictal) and MRI should be sought.

**Depression in epilepsy**

Wiebe *et al.* for the Ontario Healthcare survey of 1990 patients with chronic illnesses, reported that depression occurred in 30% of epilepsy patients, compared to 17% of patients with diabetes, and 16% with asthma. Furthermore, the quality of life of epilepsy patients was less than those with moderate arthritis.

Causes of depression in patients with epilepsy include the social stigma of epilepsy, discrimination, vocational difficulties, restricted activities, and AEDs. Such depression results in impaired functioning, insomnia (which may lead to more seizures), non-compliance, and suicide. Patients may avoid disclosing their depression to avoid further stigma, and physicians may fail to enquire or “sense” depression. Physicians need to be aware of poor performance during the consultation, and consider depression in patients who are antagonistic, irritable or lethargic.

Physicians may also be reluctant to treat depression, because of concerns about lowering the seizure threshold; in such cases it is likely that the benefits of appropriate antidepressant treatment will outweigh that risk.

**Treatment plan**

The goals of treatment are no seizures, and a ‘normal’ life, and the therapeutic sequence should be:

1. Ensure all episodes are seizures
2. Optimise lifestyle
3. Review previous AEDs: assess ADRs, allergy, review previous treatment failures (were serum levels and trial periods adequate?)
4. Review other medications for therapeutic necessity, potential drug interactions
5. Explain the long-term plan to patients; patients need to know they are being helped for the long term. Include ‘if’ statements i.e. “If this doesn’t work, here’s what we’ll do…”

In adults substituting one AED for another is preferred over adding drugs to the regimen, to minimise triple or quadruple therapy. If agents must be added, gradual introduction will reduce the likelihood of side effects.

**References**

Choice of treatment in children: does syndrome diagnosis matter?

Professor Olivier Dulac,
Department of Neuropaediatrics,
Hospital Necker-Enfants Malades,
Paris, France.

Characteristics of antiepileptic drugs:

Antiepileptic drugs (AEDs) are poorly adapted for treatment in children; not only are they unpalatable, but also the pharmacokinetics are problematic. Bioavailability may be poor, particularly in neonates, half-life varies according to age, and the blood-brain barrier is highly permeable during the first weeks of life. Studies of drug pharmacokinetics (PK) in children are usually performed on 8-12 year olds, but these data cannot be extrapolated to infants or very young children since the PK is often more variable than in those aged under 5 years.

Some key considerations with AED use in infants and children include:

- **PHT**: IV PHT is effective for frequent seizures or status epilepticus in the newborn but efficacy is usually lost upon switching to oral administration, because of poor oral bioavailability.
- **Age-dependent tolerability**: This is well established with regard to hepatic failure and VPA, which is about 100 times more frequent in infants than in adults. With CBZ the short half-life in infants means doses need to be given three or four times daily, which could impact on compliance.
- **Introduction rate**: AEDs must be introduced slowly; for VPA no less than 10-15 days should be used to reach the full dose in order to prevent hallucinations and somnolence. This is also true for CBZ and LTG with which there is a risk of rash (and toxidermy with LTG).
- **PHT/PHB combination**: should only be used in patients in whom blood levels can be monitored in order to prevent cerebral, particularly cerebellar, toxicity.
- **Retinal toxicity with VGB**: Vanhatalo showed that retinal constriction is only discovered on laboratory investigation and has no clear impact on everyday life, that it correlates with duration of therapy and cumulative dose, and that there is no significant risk of visual field impairment before 15 months of treatment.1

Antiepileptic drugs for epilepsy syndromes

Different seizure types respond to different AEDs but paediatric patients often have several types of seizures. The response of epilepsy syndromes to AEDs is much more relevant, but at onset, distinguishing between epilepsy syndromes can be difficult. Of equal importance, however, is the risk of symptoms worsening when certain AEDs are used in particular epilepsy syndromes (Figure 1).

**Dravet syndrome**

The aim of treatment in Dravet syndrome is prevention of status epilepticus, which correlates with worsening cognitive and motor function. TPM appears to be very active in Dravet syndrome. When trialled at doses of 2-6 mg in 36 children (aged 1.5-20 years), 62% responded (>50% decrease in seizure frequency), and 27% were seizure free for ≥3 months.2 Some relapses occurred after 3 months, but in this syndrome, even three months seizure-free is positive. Most patients improved at doses of 1-2 mg. Episodes of status epilepticus occurred when attempts were made to decrease concomitant medications, so polytherapy was continued.3

The treatment approach for Dravet syndrome usually involves initiation of VPA after the first complex and very early onset febrile seizure, when Dravet syndrome is first suspected. After the first prolonged seizure or repeat seizures, consider adding TPM or clobazam plus

- **Absence epilepsy**: CBZ, GBP, OCZ, PHB, PHT, VGB
- **Myoclonic epilepsy**: CBZ, GBP, OCZ, VGB,
- **Dravet syndrome**: CBZ, GBP, LTG, OCZ, PHB, PHT, VGB,
- **West syndrome**: CBZ, OCZ, PHB, PHT
- **Lennox-Gastaut syndrome**: BZ (tonic seizures), CBZ, OCZ, PHB
- **Epileptic encephalopathy with continuous spike waves in slow sleep**: CBZ, LTG, PHB, PHT, OCZ

**Figure 1.** AEDs which may worsen epilepsy syndromes.
stiripentol. CBZ, LTG, OCZ, PHB, PHT and VGB should be avoided.

Treatment of infantile spasms

VGB and steroids have demonstrated efficacy in infantile spasms (IS) but efficacy also depends on the aetiology of the seizures.

In a large study of steroid-naive infants, high-dose VGB (>100 mg/kg/day) showed a clear advantage over lower doses (<40 mg/kg/day) in both response rate (36% vs 11%, p<0.01) and response lag (p=0.04). A better response was seen in infants with tuberous sclerosis (TS) than IS from other causes. Tolerability at 100 mg/kg/day was very good.4

Chiron et al. conducted a prospective study of VGB 150 mg/kg/day vs hydrocortisone 15 mg/kg/day as first line monotherapy in 22 patients with TS.5 Patients were evaluated at one month, and crossed over into the other arm if they failed on the first treatment. VGB was more effective than hydrocortisone in terms of spasms, and was better tolerated. VGB was also better tolerated than the hydrocortisone in this study.

The effect of VGB on cognitive function is also very important. Patients with IS have a much lower developmental quotient (DQ) value than those who have partial epilepsy (PE). Jambaqué et al. found that controlling spasms with VGB significantly increases the DQ to a value very similar to that of PE patients (p=0.03).6

The minimal effective VGB dose in infants seems to be 70 mg/kg/day; efficacy is very much reduced at lower doses.7 In 250 cases of IS, first line treatment with VGB monotherapy was particularly effective in very young patients, with seizures ceasing in 90% of patients aged less than 3 months, compared to a 68% spasm cessation rate overall.8 This is in clear contrast to steroids, which in general have poor results in very young patients.

The aim of IS treatment is cessation of spasms and disappearance of spikes on EEG. One treatment strategy involves a graded approach, starting treatment with VGB 100 mg/kg/day for 1 week, and if response is insufficient, proceeding to (i) increase VGB dose to 150 mg/kg/day for 1 week, (ii) add hydrocortisone 15-100 mg/kg/day to VGB for 2 weeks, (iii) replace the hydrocortisone with adrenocorticotrophic hormone (ACTH).

Treatment of Lennox-Gastaut syndrome

VPA is the most useful AED for the first seizure, before diagnosis. However VPA monotherapy is insufficient in Lennox-Gastaut syndrome; once this is suspected, LTG should be very slowly introduced. PHT is very useful in tonic seizures, and ESM is used for absences. Felbamate is useful in cases of drop attacks, although this is not available in Australia. If drop attacks persist, callosotomy (anterior or total according to age at epilepsy onset) may be required. CBZ, GBP, OCZ, PHB, PHT and VGB should be avoided.

Treatment of myoclonic-astatic epilepsy

Start treatment with VPA, and add in LTG as soon as the diagnosis is suspected. If seizures recur, BZ or ESM should be used; if seizures still persist, TPM appears to be useful. In patients having daily seizures, a ketogenic diet may be useful for a few weeks whilst the correct AED and its dose are established. CBZ, GBP, OCZ, PHB, PHT and VGB should be avoided.

Treatment of epileptic encephalopathy with continuous spike waves in slow sleep

BZ monotherapy is effective in 10-20% of cases, and ethosuximide or sulthiame may help some patients. In cases of repeat seizures or deterioration, steroids are most efficient. High-dose therapy is required initially to stop the process, but the dose should then be rapidly titrated down to avoid side effects but maintained for one or two years to prevent relapse. Avoid using LTG which may worsen the condition. CBZ, GBP, OXC, PHB, PHT and VGB, should also be avoided.

Treatment approach following first non-febrile convulsive seizure

Treatment subsequent to the first non-febrile convulsive seizure depends very much on the EEG. In the absence of generalised spike waves, the relapse rate is less than 40%, and no treatment is required. If Rolandic spikes are present the relapse rate is quite high (85%), but given that seizure frequency is low, treatment is usually not necessary.

Decision following repeat seizures in children

If an epilepsy syndrome is identified:

**Symptomatic partial epilepsy:** VPA followed by CBZ (except in infancy, where IS may be suspected, and VGB should be used instead of CBZ)

**West syndrome:** VGB/ACTH (depending on the country)

**Dravet syndrome:** VPA, followed by the addition of CLB+stiripentol, or TPM

**Myoclonic-astatic epilepsy:** VPA+LTG, ESM

**Lennox-Gastaut Syndrome:** VPA+LTG, FBM

**Continuous Spike Waves in Slow Sleep:** BZ, ESM, HC
If an epilepsy syndrome is not identified
A compound with a large spectrum of action in terms of seizure type and epilepsy syndrome and a low risk of worsening the condition is required. VPA would be the drug of choice in epilepsy with generalised seizures and in PE, especially in infants, except if an inborn error of metabolism is suspected that could be worsened by VPA such as urea cycle deficiency, in which case CLB should be used. CBZ would be the AED of choice in the other cases.

Conclusions
In clinical practice, the treatment strategy should be decided according to epilepsy syndrome. Seizure type is not reliable; often different seizure types coexist, and a given aetiology may produce several types of epilepsy with different response to drugs.

What we need for our children is a range of selective and specific compounds; we look to the future with hope.

References

Treatment issues in pregnancy

While there are definite teratogenic risks associated with the use of antiepileptic drugs (AEDs), the pregnant woman with epilepsy (WWE) usually needs treatment. It is vital to discuss all the issues with the patient and partner and try to ensure they understand the possible outcomes. Factors to consider when discussing whether AED withdrawal during pregnancy is appropriate include:

- The risks of:
  
  **Sudden unexplained death in epilepsy (SUDEP):** Some work suggests that good treatment, not changing treatment, and ensuring appropriate drug levels reduces SUDEP, but the evidence remains imprecise.
  
  **Status epilepticus:** with associated high foetal and maternal mortality, reported to be 48% and 31% respectively.¹
  
  **Seizure recurrence:** Generalized tonic-clonic seizures (GTCSs) can cause maternal and foetal hypoxia and acidosis, foetal intracranial haemorrhage, and depression of foetal heart rate during and following seizures. Recurrent seizures may cause incremental damage.

- **Lifestyle issues:** the need to keep driving, working, caring for other children

| 1. Pre-pregnancy counselling with the patient and her partner |
| 2. Review prior to pregnancy: ensure condition is epilepsy, and confirm the need for treatment |
| 3. Use folic acid supplements |
| 4. Diagnose the epilepsy syndrome and ensure the most appropriate treatment |
| 5. Take into consideration: epilepsy control, past history, family history, lifestyle issues, possibility of monotherapy |
| 6. Discuss risks. The risk of abnormalities in babies of WWE is 2-3 times higher than the normal population, however, this is counterbalanced by the fact that 85-90% of WWE (and their babies) will not be affected. |

Table 1. Minimising the risks for women with epilepsy

Findings of the Australian Pregnancy Register

The Australian Pregnancy Register (APR) is a national resource, thus far holding 40 months of data on 396 pregnancies and 403 outcomes.
Incidence of foetal malformations in the Australian Pregnancy Register

When foetal malformations (FM) were analysed according to AED, VPA was associated with a significantly greater incidence of FM than patients who received no AED (16% vs 3.1%, p<0.01), however causality is complicated because VPA is used in particular epilepsy syndromes, which may in themselves be implicated. No other AEDs showed a significant difference to the no-AED control group (Table 2).

Table 2. Incidence of malformations for each anti-epileptic drug in the Australian Pregnancy Register (40 months of data)

<table>
<thead>
<tr>
<th>AED</th>
<th>Incidence of malformations</th>
<th>p-value (vs no-AED)</th>
</tr>
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<tbody>
<tr>
<td>Carbamazepine</td>
<td>4/157 (2.5%)</td>
<td>ns</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>4/76 (5.2%)*</td>
<td>ns</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>2/26 (7.6%)</td>
<td>ns</td>
</tr>
<tr>
<td>Sodium valproate</td>
<td>19/119 (16%)</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>0/28 (0%)</td>
<td>ns</td>
</tr>
<tr>
<td>No AEDs</td>
<td>1/32 (3.1%)</td>
<td>-</td>
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</table>

* All FMs involved polytherapy

Folic acid

Most of the work done on folic acid (FA) involves familial neural tube defects (NTDs) whereby FA dramatically reduces such NTDs. Trials of preconceptual FA have consistently shown a 60-86% reduction of risk of recurrent NTDs in women with a previous NTD pregnancy. The evidence for FA in WWE is slim. Kaaja recently showed FMs associated with maternal serum folate levels were <4.4 nmol/L. However there are many case reports where even high-dose periconceptual FA failed to prevent NTDs; after analysing the Swedish Medical Birth Register, Kallen was “skeptical” regarding the FA benefit in general.

What is best practice regarding FA? In Australia, the Prescribing Medicines in Pregnancy handbook recommends WWE have FA 5 mg/day for 4 weeks before conception and throughout the first trimester.

AEDs in pregnancy

The aim with AED use during pregnancy is for low-dose monotherapy, but more severe epilepsy usually requires higher doses and/or polytherapy. Ultimately we have to prioritise the mother first and control the epilepsy.

VPA is the drug of choice for some generalised epilepsy syndromes but it may have the highest risk. LTG is effective in some patients, and it may be more efficacious in combination with VPA. However the risk of LTG in combination therapy is unknown. TPM may also be effective in this group of patients but again the risk is unknown.

Data are very limited for other AEDs:

GBP: one study assessing 51 outcomes in 39 WWE receiving monotherapy and polytherapy, reported a FM rate of 4.5%.

TPM: teratogenic in animals. Breast feeding is not advisable during treatment.

OCZ: no FMs observed with monotherapy in 25 WWE recorded in the APR.

LEV: high secretion into milk.

TGB: no known published data.

Neurodevelopmental outcomes

Neurodevelopmental outcomes (NDO) are difficult to assess, because so many factors are influential. The majority of reports indicate an increased risk for mental deficiency (1.4-6% in WWE vs 1% controls). IQ score correlates negatively with CBZ, PHB, PHT, PRM, VPA and polytherapy.
### Practical considerations for managing pregnancy in WWE

In summary, some pointers to managing pregnancy in WWE include:

- **Best control of seizures is required; treat mother first**
- **Educate before pregnancy**
- **Use FA supplementation**
- **Ensure continuous communication and care**
- **Document discussions and ensuing decisions**
- **Avoid VPA when possible; use doses below 1000 mg/day and be guided by the findings of the APR, as more data become available.**

### Table 3. Antiepileptic drugs in pregnancy – factors to consider

<table>
<thead>
<tr>
<th>AED</th>
<th>Pregnancy-related pharmacokinetic considerations</th>
<th>Clinical considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>VPA</td>
<td>• 50% increased clearance&lt;br&gt;• decreased total drug level&lt;br&gt;• free drug level increased slightly relative to total&lt;br&gt;• decreased protein binding</td>
<td>• increased risk of FM (16% vs 3.1% on no AED)&lt;br&gt;• breast feeding risk small†</td>
</tr>
<tr>
<td>CBZ</td>
<td>• modest, usually insignificant increase in clearance&lt;br&gt;• fraction of CBZ epoxide relative to CBZ increases; may cause myelotoxicity&lt;br&gt;• small decline in free and total drug levels in 3rd trimester&lt;br&gt;• serum drug levels helpful</td>
<td>• increased risk of NTDs (0.5%);&lt;br&gt;• risk of other FMs ~3%, especially when combined with VPA&lt;br&gt;• may increase prostaglandin E&lt;br&gt;• may need to increase dose in 3rd trimester&lt;br&gt;• breast feeding OK†</td>
</tr>
<tr>
<td>LTG</td>
<td>• 55% protein bound&lt;br&gt;• clearance increases dramatically early in pregnancy&lt;br&gt;• drug levels rise quickly after delivery&lt;br&gt;• serum levels helpful</td>
<td>• risk of FMs 1.8% with monotherapy*&lt;br&gt;• increase dose very substantially early in pregnancy&lt;br&gt;• reduce dose within the first 2 weeks after delivery&lt;br&gt;• breast feeding uncertain†</td>
</tr>
<tr>
<td>PHT</td>
<td>• ~20-100% increased clearance&lt;br&gt;• decreased total drug levels&lt;br&gt;• Michaelis-Menton kinetics&lt;br&gt;• serum levels essential</td>
<td>• FMs occur ~2-5%**&lt;br&gt;• increase dose&lt;br&gt;• decrease dose within 2-3 months of delivery&lt;br&gt;• breast feeding OK†</td>
</tr>
<tr>
<td>PHB</td>
<td>• increased clearance&lt;br&gt;• free and total drug levels decreased by 55% (p&lt;.005)</td>
<td>• teratogenic especially in combination</td>
</tr>
</tbody>
</table>

* According to the International LTG Registry
** PHT has been largely superseded, so little data are available
† Statements on breast feeding are solely based on the presentations by A/Prof. Lander. For recommendations on breast feeding, please refer to the Approved Product Information for the respective products discussed.

### References

15. Topiramate Approved Australian Product Information.
A lack of hard data about withdrawal of antiepileptic drugs (AEDs) means the withdrawal process remains an art rather than a science. The key limitation of withdrawal studies is that they assess mixed patient populations, ages, seizure types, duration of therapies etc, precluding conclusions which can then be applied to individual patients.

Reasons for withdrawing antiepileptic drugs

Adverse drug reactions

One third to one half of patients report side effects with AEDs, and 50% of these patients will withdraw from treatment as a result. Even with newer AEDs, meta-analysis of trials indicates a 1.4-4.2 times increased likelihood of discontinuation due to ADRs, compared to placebo. Generally these complaints relate to fatigue and psychomotor slowing, but concerns about hepatotoxicity and other organ system damage are commonly cited as a main reason for withdrawal. Cosmetic issues, particularly weight gain and hirsutism, are major consequences of the use of many AEDs, and the impact of these issues on patients’ lives is perpetually underestimated.

Teratogenesis

Concerns about teratogenesis are a very common reason for attempted withdrawal. The teratogenic risk with AEDs is real, and must be carefully balanced against the risk of seizures in pregnancy.

Other consequences of use

Cost: not a major concern for most Australian populations but is certainly a significant factor in some other countries.

Interactions with other medications: especially the oral contraceptive pill.

Issues relating to self-image: Patients may feel ‘dependent on medications’, or that taking medications classifies them as ‘abnormal’ or ‘sick’. Cosmetic issues can impact significantly on self esteem and confidence.

Strigma: the stigma associated with the diagnosis is reinforced, often several times daily, by the need to take medications.

Inconvenience: with frequent dosing and/multiple therapy regimes.

Risks of withdrawal

The decision to attempt withdrawal is highly individual, and best initiated by the patient, having ensured they are aware that withdrawal is an option. Careful enquiry should be made regarding occupation, driving and hobbies which might place patients at special risk if seizures were to recur. Social and geographic factors should also be taken into account – those living alone or in remote locations may be at particular risk with recurrence. Counselling about the consequences of recurrence is critical. Such consequences may include:

- injuries resulting from seizures
- effects of seizure recurrence on employment and driving
- if pregnant, effects of seizures on mother and foetus
- possibility of status epilepticus
- possibility of sudden unexpected death in epilepsy (SUDEP)
- the impact of seizure recurrence on self-confidence and independence.

Another concern physicians and sometimes patients have is that there will be ‘resistance’ to reinstituted therapy after relapse. There is no good evidence for this common misconception.1 Concerns about medico-legal risks are rarely assessed in studies, and are often significant concerns for the physician.

Factors predictive of successful withdrawal

A number of factors influence the outcome of attempted withdrawal. These include:

Aetiology: Symptomatic and cryptogenic epilepsies are much more likely to relapse; structural pathology is associated with a relapse rate of at least 50%.

Epilepsy syndrome: Some syndromes have extremely good prognosis: benign childhood epilepsy with centrotemporal spikes (BECTS); Rolandic epilepsy; and childhood absence epilepsy; while others have a predictably poor prognosis (e.g. juvenile myoclonic epilepsy, cryptogenic and symptomatic partial epilepsies).
Seizure type: is important, although often this is a surrogate for syndromic diagnosis. Absences in isolation have a better prognosis; any generalised tonic-clonic seizures types and myoclonus-associated syndromes have a worse prognosis.

Age at onset: is again a surrogate for syndrome, with earlier age of onset associated with increased likelihood of remaining seizure free after withdrawal. Seizures with an onset after age 12-14 years are very likely to remain uncontrolled after withdrawal.

Associated CNS deficit or cognitive impairment: A number of studies have shown this is a significant risk factor. The type of deficit may increase the risk, with hemispheric cortical lesions resulting in hemiparesis carrying the largest risk.

EEG: The predictive value of EEGs is difficult to establish. Studies are confounded because sensitivity of EEGs varies across differences in age and definition (abnormal vs epileptiform). Furthermore, if very effective, medication may completely suppress EEG changes.

Previous seizure control: Seizures not quickly controlled by medication have a less favourable remission rate.

Previous withdrawal attempts: If seizures have recurred on previous withdrawal attempts, they are highly likely to recur again.

When to attempt withdrawal
Generally, this is an easier decision in younger patients. The only systematic reviews relating to withdrawal have been conducted in children, and while there is still no consensus, many physicians believe that in patients with one or few seizures, particularly children, AEDs should be withdrawn early. In adults the cut-off period tends to be 2 years.

Withdrawal rate
Two studies have determined rapid withdrawal rate to be an adverse prognostic factor. Some AEDs (e.g. BDZ, PHB, VGB), are thought to carry a particular risk of recurrence unless withdrawn very slowly, although work on this is limited. Generally AEDs should be withdrawn over a period of 3-6 months, but this depends on the patient and their personal circumstances.

Unexpected consequences of withdrawal
Unexpected consequences of withdrawal may include recurrence of seizures which manifest differently to those experienced previously.

Very frequently patients experience mood disturbances, insomnia, anxiety and headaches. If on polytherapy, withdrawal of one AED may lead to unexpected toxicity from other AEDs, typically as a result of withdrawing an enzyme inducer.

When attempting withdrawal:
- ensure driving restrictions are explained
- ensure workplace is safe
- remind patients that they might experience manifestations of seizure activity not previously experienced.

Withdrawal of therapy after epilepsy surgery
Enormous variation exists regarding the use of AEDs after epilepsy surgery. Examining this, Schiller et al. found the seizure recurrence rate after complete AED withdrawal was 14% at 2 years and 36% at 5 years, compared to 3% and 7% in those who did not alter AED treatment after surgery. After AED discontinuation, seizures tended to recur more often in patients with a normal preoperative MRI. Extent of surgical resection, postoperative EEG, and seizure-free duration after surgery were not predictive of seizure outcome after AED withdrawal.

Conclusions
More studies addressing the optimal timing of withdrawal, and the possibility of withdrawal in more adult patients, are needed. Studies also need to emphasise quality of life issues, especially regarding work and driving, and greater examination of the role of structural imaging.

AED withdrawal is not attempted often enough. All patients should be offered the option of withdrawal; personal preference, driving and work are the key considerations for most patients when deciding whether to attempt withdrawal.

References
At least half of all Australians use complementary and alternative medicines (CAMs). Personal expenditure for herbal remedies and nutritional supplements amount to twice the out-of-pocket costs of prescribed medicines. With regard to patients with epilepsy, a survey at the Royal Perth Hospital found that 57% were taking alternative therapies, and 12% were taking these specifically for epilepsy.1

Complementary and alternative medicines for epilepsy
There is no evidence that CAMs are effective in the management of epilepsy, except for important but non-specific improvements in well-being and sometimes seizures provided by practices such as relaxation, meditation, physical exercise and fitness. Self control techniques like a counter-measure when a seizure is emerging – cognitive (focusing on a thought), smelling an essential oil, hand pressing or breathing – may help some people avert seizures.

Cannabis for epilepsy treatment
Cannabis was first used for epilepsy by Western medicine in 1839, and animal experiments of delta-9 THC have demonstrated its efficacy.2-6 There have been a number of recent animal studies.7,8 There is little more than anecdotal evidence regarding the clinical use of cannabis in epilepsy in humans, and indeed there are reports of it exacerbating epilepsy on occasion. Considerably more work is required to ascertain if there is a role for cannabinoids in epilepsy treatment.

Key points for medical practitioners:
• Medical practitioners need to accept that patients may choose alternative therapies, and must not be judgmental
• Ask patients about any CAMs or over-the-counter pharmaceuticals they are taking (only 31% of patients inform their doctors about these)

All decisions on the role of any treatment should be based on evidence of efficacy and a risk/benefit calculation, and CMs should be no exception to this.

References