Metro North Hospital and Health Service *Putting people first*

Women with Epilepsy- Managing contraception and pregnancy

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Comprehensive Epilepsy Program

Royal Brisbane and Women's Hospital

GP Network talk, 26 March 2019

Queensland Government

Abbreviations

- OC- oral contraceptives
- AED- anti-epileptic drug
- CBZ- carbamazepine
- CLB-clobazam
- CLZ- clonazepam
- ESM- ethosuximide
- FEL-felbamate
- GB- gabapentin
- LAC-lacosamide
- LTG-lamotrigine
- LEV-levetiracetam
- OXC-oxcarbazepine
- PER-perampanel
- PB-phenobarbitone
- PHT-phenytoin
- RUF-rufinamide
- TPM-topiramate
- VPA-valproic acid
- ZNS-zonisamide

Women with Epilepsy

- Intricate balance of risks and benefits for each individual patient

PRECONCEPTION MANAGEMENT

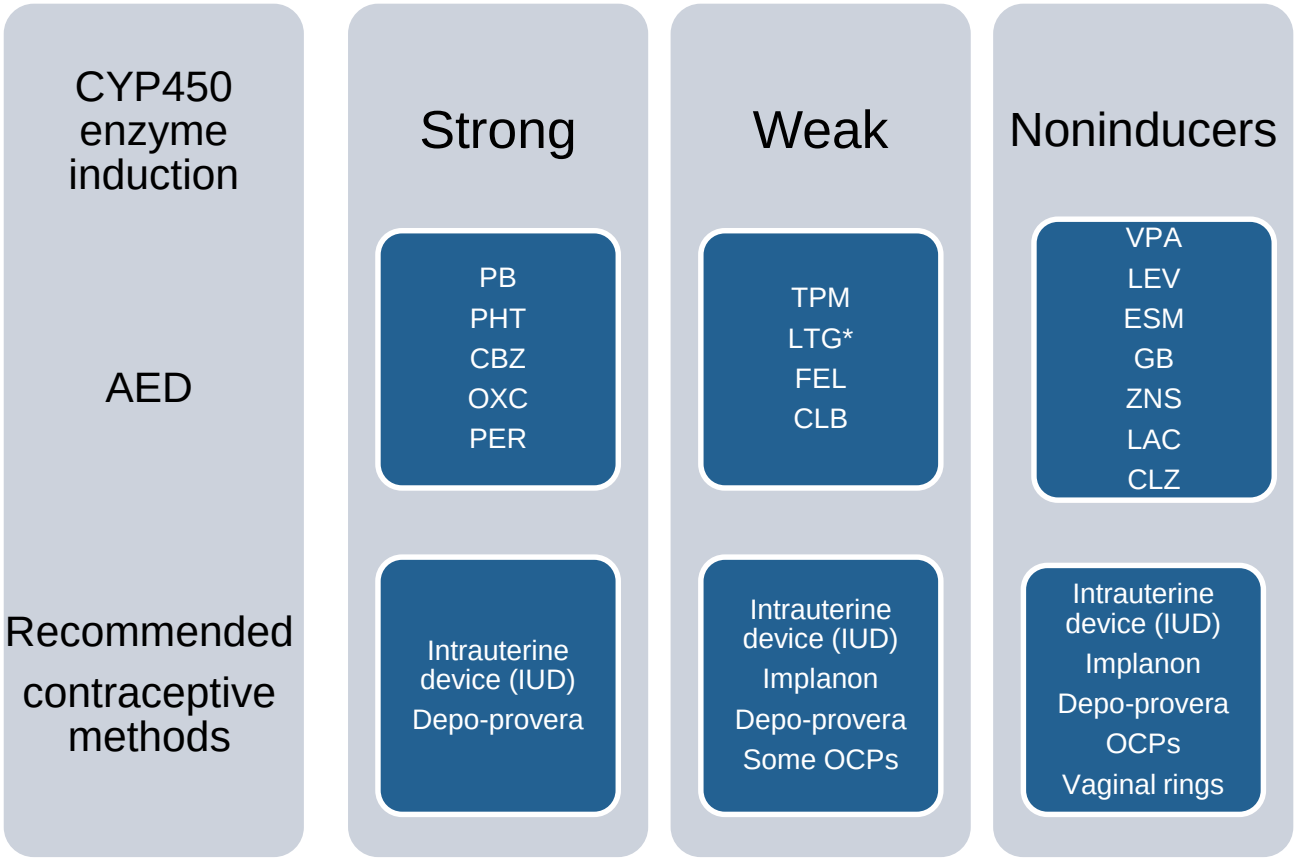
- Adequate contraception- IUD preferred option
- Effect of contraception on the AED level
- AED baseline concentration
- Folic acid (1-4mg daily) and prenatal vitamin supplements
- Optimize AED regimen
  - Monotherapy preferred to polytherapy
  - Reduce to minimal effective dose
  - Consider switching AEDs
  - If polytherapy, some combinations are preferable (LTG, LEV), some to be avoided (VPA, PB, TPM)

Considerations with AEDs

- **Teratogenic risks**
- **Dose-dependent risks**
- **Neuro-developmental outcomes for the children exposed to AEDs in-utero**

Effect of AEDs on OC- risk of OC failure

(Voinescu and Pennell Semin Neurol 2017:37:611-623)



- Avoid low dose OCs with enzyme inducers, higher failure rates
- LTG slightly reduces progestin concentrations without evidence of ovulation, safe with low dose OCs
- Mid-cycle bleeding may suggest risk of contraceptive failure

Effect of OC on AED levels- risk of seizure deterioration

- Estrogens lead to increased drug glucuronidation
- Can lower LTG level and may require dose adjustments, check LTG level within 1 to 2 weeks
- VPA and OXC levels may also be lowered by OCP
- Wide inter-individual variability, multiple co-variants- other drugs, genetic and environmental factors
- Monitor plasma levels before and after introduction or cessation of OCP, watch pill-free week as risk of toxicity. (Sabers Seizure 2008;17:141-144)

AED baseline concentration

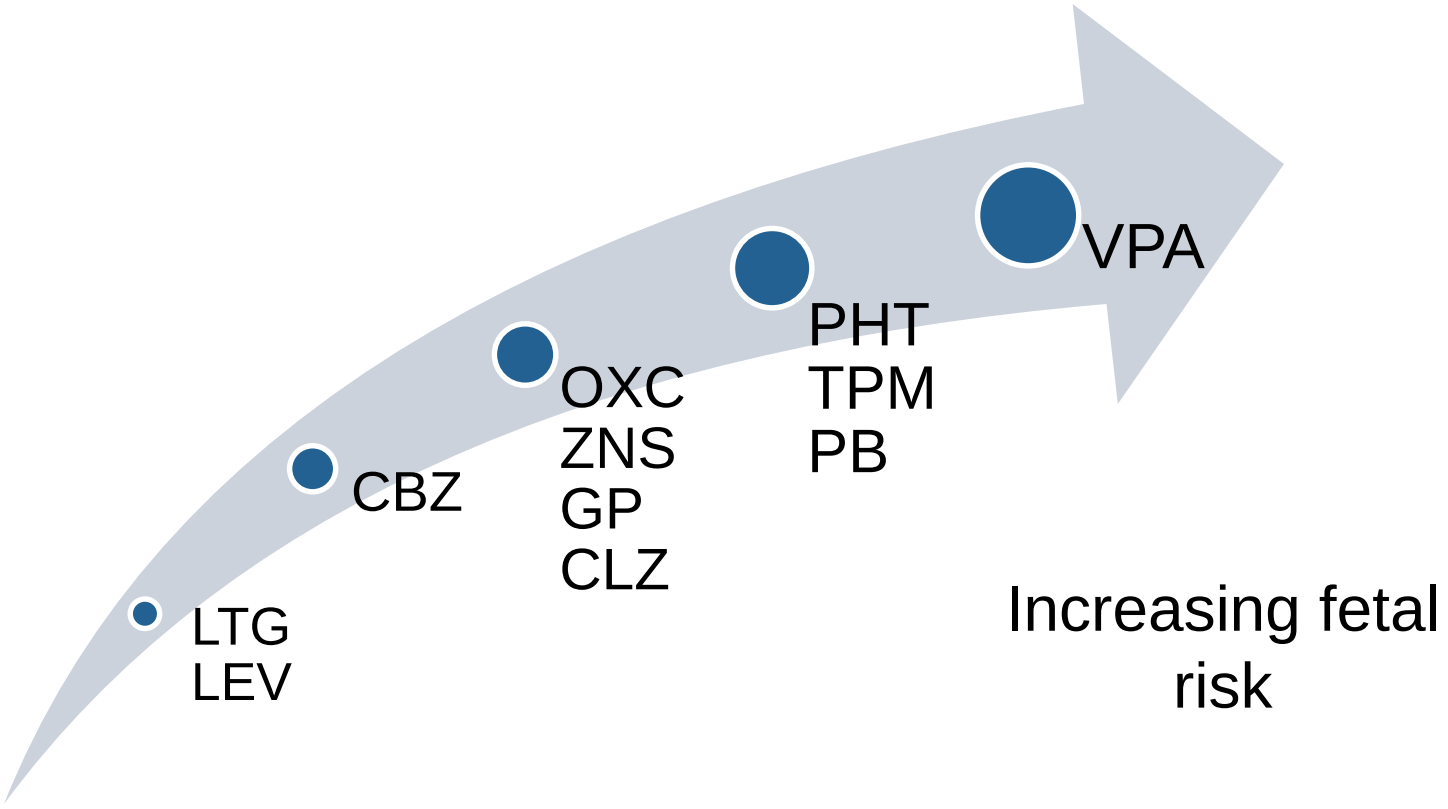
- Obtain baseline drug levels to enable target for pregnancy management
- AED concentration on the minimal **effective** dose
- Can obtain serum LEV and LTG levels (S and N)

Folic acid controversies- how much and for how long?

- 0.4 mg-5 mg/day
- Recommendation based on evidence in general population that folic acid reduces major congenital malformations, in particular neural tube defects
- No evidence reduces risks in women with epilepsy taking AEDs
- One study that > 5mg folic acid/day was associated with delayed psychomotor development
- Studies to support peri-conceptual folate
  - Improved cognitive outcomes (Meador et al, Lancet Neurol 2013;12:244-52)
  - Improved language/verbal skills (Husebye et al, Neurology 2018;91:e811-821)
  - Reduced autistic traits (Bjork et al, JAMA Neurol 2018;75:160-68)
- Studies to support folate throughout the pregnancy
  - Improved psychosocial benefits (Henry et al, Acta Paed 2018;107:1370-78)

Teratogenic risks

- (Voinescu and Pennell Semin Neurol 2017:37:611-623)



Neurodevelopmental Outcomes

The NEW ENGLAND JOURNAL of MEDICINE

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Cognitive Function at 3 Years of Age after Fetal Exposure to Antiepileptic Drugs

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IQ at 6 years after in utero exposure to antiepileptic drugs

A controlled cohort study

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ABSTRACT

Objective: To delineate the risk to child IQ associated with frequently prescribed antiepileptic drugs.

Methods: Children born to women with epilepsy (n = 243) and women without epilepsy (n = 287) were recruited during pregnancy and followed prospectively. Of these, 408 were blindly assessed at 6 years of age. Maternal and child demographics were collected and entered into statistical models.

Results: The adjusted mean IQ was 9.7 points lower (95% confidence interval [CI] −4.9 to −14.6; $p < 0.001$) for children exposed to high-dose (>800 mg daily) valproate, with a similar significant effect observed for the verbal, nonverbal, and spatial subscales. Children exposed to high-dose valproate had an 8-fold increased need of educational intervention relative to control children (adjusted relative risk, 95% CI 8.0, 2.5–19.7; $p < 0.001$). Valproate at doses <800 mg daily was not associated with reduced IQ, but was associated with impaired verbal abilities (−5.6, 95% CI −11.1 to −0.1; $p = 0.04$) and a 6-fold increase in educational intervention (95% CI 1.4–18.0; $p = 0.01$). In utero exposure to carbamazepine or lamotrigine did not have a significant effect on IQ, but carbamazepine was associated with reduced verbal abilities (−4.2, 95% CI −0.6 to −7.8; $p = 0.02$) and increased frequency of IQ <85.

Conclusions: Consistent with data from younger cohorts, school-aged children exposed to valproate at maternal doses more than 800 mg daily continue to experience significantly poorer cognitive development than control children or children exposed to lamotrigine and carbamazepine.

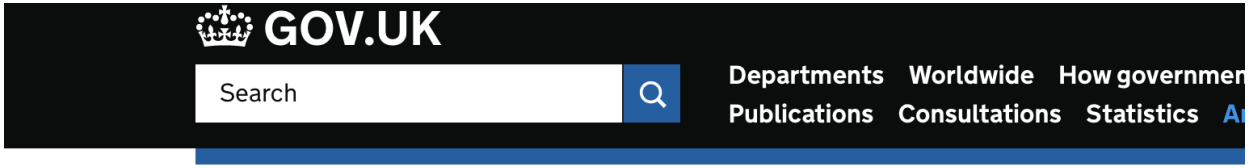
Neurology® 2015;84:382–390

Neurodevelopmental Outcomes

- Two large studies
- NEAD (Neurodevelopmental Effects of Antiepileptic Drugs) study- cognitive function at 3 years
  - LMNDG (Liverpool and Manchester Neurodevelopment Group)- IQ at 6 years
- Developmental outcomes with in utero exposure to LTG, PHT, CBZ, VPA
- LMNDG also addressed LEV and TPM
- **In-utero exposure to VPA associated with a 10-point decrease in full scale IQ**
- **Dose-dependent effect**
- Probably increased risk of autism and autism spectrum disorders with VPA
- Limited information on other AEDs and autism spectrum disorder

Changes in VPA prescribing

UK Medicines and Healthcare Regulatory Agency (MHRA) and European Medicines Agency guidelines in 2018



Press release

Valproate banned without the pregnancy prevention programme

Valproate must no longer be prescribed to women or girls of childbearing potential unless they are on the pregnancy prevention programme (PPP).

Published 24 April 2018
From: Medicines and Healthcare products Regulatory Agency

VPA pregnancy prevention programme

Sisodiya (Epilepsy Advisory Group for British Neurologists) BMJ 2018,1-3

- Assessing patients for the potential of becoming pregnant
- Pregnancy tests before starting and during treatment as needed
- Counselling patients about the risks of valproate treatment
- Explaining the need for effective contraception throughout treatment
- Carrying out reviews of treatment by a specialist at least annually
- Introduction of a new **risk acknowledgement form** that patients and prescribers will go through at each such review to confirm that appropriate advice has been given and understood
- It is important that no woman should stop taking sodium valproate without first consulting her doctor

Changes in VPA prescribing cont.

- More balanced approach (Tomson, Lancet Neurology 2016;15:210-216)
  - "valproic acid should not be used as a first-line drug in women of childbearing potential whenever equally or more effective alternative drugs are available—as in the case of focal epilepsy"
  - "In some generalised epilepsy syndromes, such as juvenile myoclonic epilepsy, valproic acid has better documented efficacy than alternative drugs"
  - "drug selection should be a shared decision between the clinician and the informed patient based on careful risk–benefit assessment"
- Epilepsy Society of Australia 2018 statement in line with this approach
- Real risks of increased seizures which are under-reported such as
  - Sudden unexplained death in epilepsy
  - Status epilepticus
  - Dropping babies, eg myoclonus
  - Smothering baby in a seizure
  - Higher perinatal morbidity

Take-home message on valproate

- Valproate has established teratogenic and developmental risks to babies
- Where possible, valproate should be avoided in women of childbearing age
- Documentation of contraception and pregnancy plans for female adolescents and women of childbearing potential on valproate
- The choice of valproate should be a shared decision weighing risks and benefits for a particular disorder
- If valproate is prescribed, the lowest effective dose is suggested (less than 600mg/day)
- Other current topics of discussion
  - The role of risk acknowledgment forms
  - Pregnancy testing and how often

Teratogenic risk

- If taking VPA or previous pregnancy resulted in a malformed foetus, increased hazard of foetal malformation in current or future pregnancy
- Parental history of major congenital malformation increases the risk more than 4-fold
- History of fetal malformations in a previous pregnancy on the same AED leads to a more than 15 fold increased risk
- Genetic factors must be involved

Will my child develop epilepsy?

1 in 26 people will develop epilepsy sometime in their life

If a first degree relative has generalised epilepsy, 8 times risk of epilepsy in the proband

If a first degree relative has focal epilepsy, 2 times risk of epilepsy in the proband

Higher if the mother has epilepsy

If you have generalised epilepsy the chance your child will develop epilepsy is only 1 in 12 and if you have focal epilepsy the chance your child will develop epilepsy is 1 in 50

(Peljto et al Brain 2014;137:795-805)

PREGNANCY MANAGEMENT

- Plan at least 3 visits during pregnancy, more if increased seizures
- Increased AED clearance causes significant AED blood concentration fluctuations
- Recommendations - monthly AED levels
- In practice (generally 3-4 levels on average)
  - Consider AED levels 12 weeks, 20 weeks, 28 weeks, 36 weeks and more frequently if required
- Dose adjustments as required, evidence that reduction in AED levels to 65% or less of baseline associated with seizure worsening
- Re-dose medications if vomiting occurs within 1 hour of taking the dose
- Discuss the Australian Pregnancy Register

PREGNANCY MANAGEMENT CONT

- Detailed foetal ultrasound at 18 weeks
- Discuss peri-partum issues in 3rd trimester
- Peri-partum management
  - Seizures are not an indication for a caesarean section
  - Continue AED and patient to bring to hospital in case ward does not have stock
  - Early epidural and avoid prolonged labour
  - Acute seizure control iv benzodiazepines (clonazepam or midazolam)

Predictors of maternal seizures during the pregnancy

- Baseline seizure frequency in the prior 9-12 months
  - Probability of remaining seizure-free during the pregnancy (if they are seizure-free for at least 9-12 months prior) is estimated to be around 84-94%
- Pregnancy has a greater impact on seizure control in focal seizures
  - 2013 EURAP- seizure freedom was higher in generalized epilepsy (73.6%) versus those with focal epilepsy syndromes (59.5%)
- AEDS at the beginning of the pregnancy- lamotrigine, oxcarbazepine, polytherapy associated with higher risk of seizure worsening
- Use of therapeutic drug monitoring
- Patient adherence to AEDs

Risks of maternal seizures to the pregnancy

- Trauma
- Premature labour and placental abruption
- Seizures may have a detrimental impact on fetal development
  - Brief seizure has been shown to depress fetal heart rate for more than 20 minutes
  - Long or repeated tonic-clonic seizures can trigger maternal and fetal hypoxia, acidosis, possible miscarriages and stillbirth
- Tonic-clonic seizures may lead to reduced cognitive ability in the child
- Higher rates of Caesarean section
- Correlation between uncontrolled seizures, even focal seizures, and poor neonatal outcomes
  - higher rates of preterm deliveries, low birth weight and small for gestational age infants.

AED monitoring

- Significant fluctuations in AED blood concentrations due to increased clearance
- AED-dependent
  - Continuously increased LTG clearance through-out the pregnancy, peak in third trimester
  - Little change in CBZ clearance
  - LEV clearance changes by the first trimester (Voinescu et al 2018:e1228-1236)
  - OXC and TPM by the second trimester (Voinescu et al 2018:e1228-1236)
  - PHT decreases early in pregnancy
- Substantial inter-individual variation

POST-PARTUM MANAGEMENT

- Risk of seizures increased and may persist for several months due to sleep deprivation
- Post-partum AED taper, often not back to baseline
  - Pennell (Neurology 2008;70:2130-2136) recommendations for LTG, decrease dose by steady decrements at Day 3, 7 and 10
  - Aim for a dose that was 50 mg above the pre-pregnancy doses due to sleep deprivation
  - Post-partum AED levels
- Sleep hygiene
  - At least 6 hours of sleep, at least one 4 hours stretch/24 hours cycle
  - Early introduction of the bottle given by family member if breast feeding
  - Ensure childcare support
- Safety precautions with a newborn
  - Not bathing baby alone
  - Changing nappies on the floor
  - Epilepsy QLD and Epilepsy Action have useful handouts

Breastfeeding

- Breastfeeding encouraged as benefits outweigh risks
- Benefits- nutrition, protection against infectious and immunological disease, promotion of attachment
- Potential side effects lethargy and poor feeding in the infant
- Minimize risks by BF when drug concentrations in the milk low, reduce maternal AED dosage to pre-pregnancy levels, mixed nutrition
- Some drug transferred to breast milk more than than others
  - Greater transfer LEV, LTG, TPM, OXC, GP
  - Lesser transfer VPA, PB, PHT, CBZ
- Final dose in the infant determined by amount of breast milk ingested, metabolism of the drug and elimination, relevant in premature infants with an immature capacity to metabolize and excrete drugs
- NEAD study demonstrated breastfed children had better neuro-psychometric scores

Summary Women and Epilepsy

- Complex, individualized management weighing risks versus benefits
- Contraception- Intrauterine device (IUD) preferred
- Optimize drug choice and lowest effective dose
- LEV and LGT are the drugs of first choice for pregnancy
- Avoid VPA if possible and use less than 600mg/day
- Baseline pre-pregnancy AED levels and monitor regularly during pregnancy
- Breast feeding is encouraged
- Ensure care of both mother and baby in the post-partum period