Update on Epilepsy and Pregnancy

European Network of Teratology Services (ENTIS) Meeting, RCSI, Dublin, Saturday, 2nd of September, 2023

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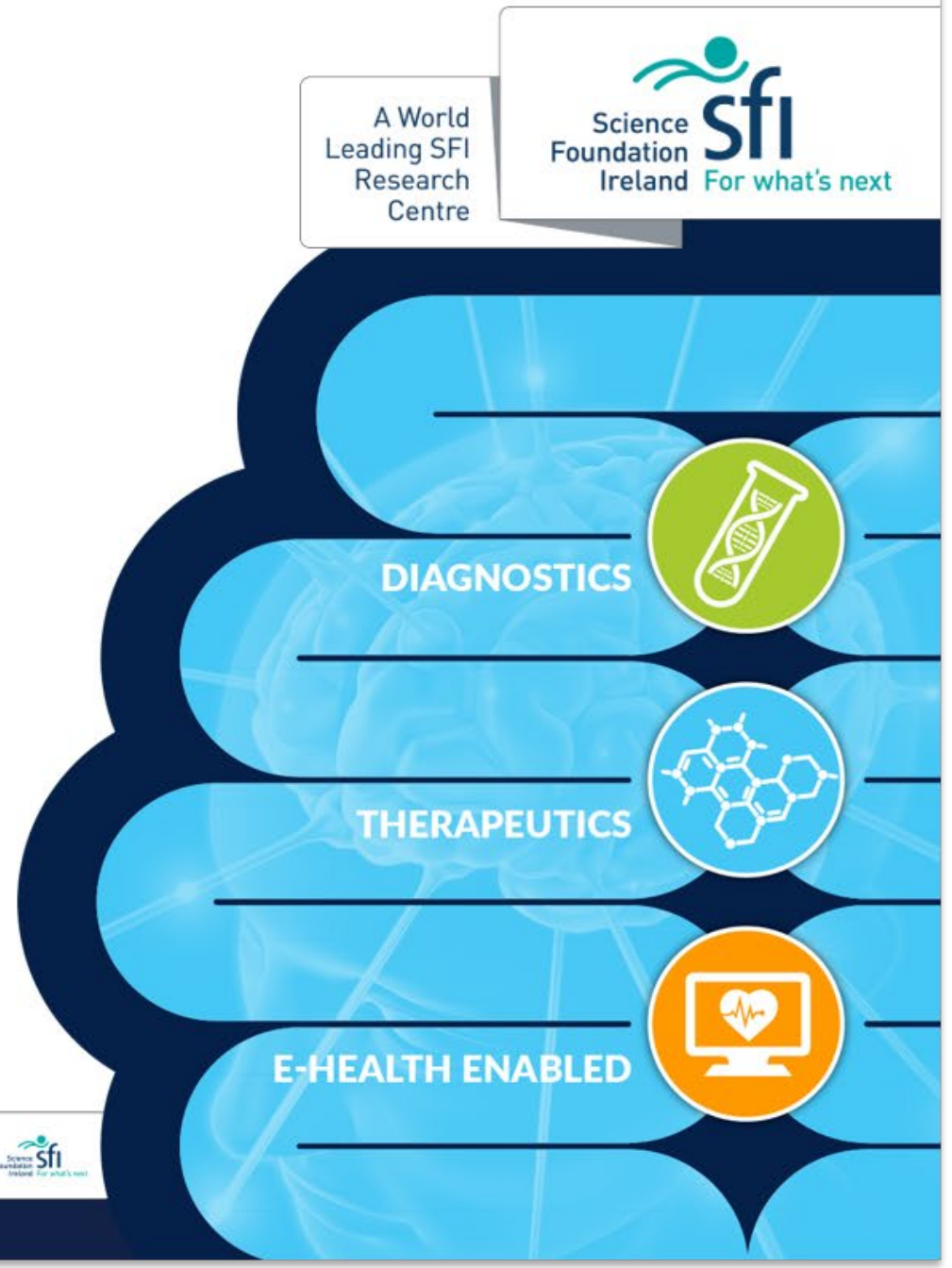

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Conflict of Interest disclosures

Over the last three years, I have served as a paid advisor and / or speaker for:

- Angelini Pharma
- Eisai
- Jazz Pharma
- Radius Pharma
- UNEEG Medical

Take Home Points

- Pregnancy issues are important in women with epilepsy
- Valproate is the most teratogenic anti-seizure medication
- On available data, lamotrigine and levetiracetam are the safest anti-seizure medications
- We have little / poor / no data on some anti-seizure medications
- International pregnancy registers are ongoing and important
- Recent re-focus on folic acid use (and dose)
- It's more than just malformation risk – cognitive and learning outcomes
  - Rebecca Bromley
- Shared joint care is important to reduce adverse outcomes, including adverse maternal outcomes

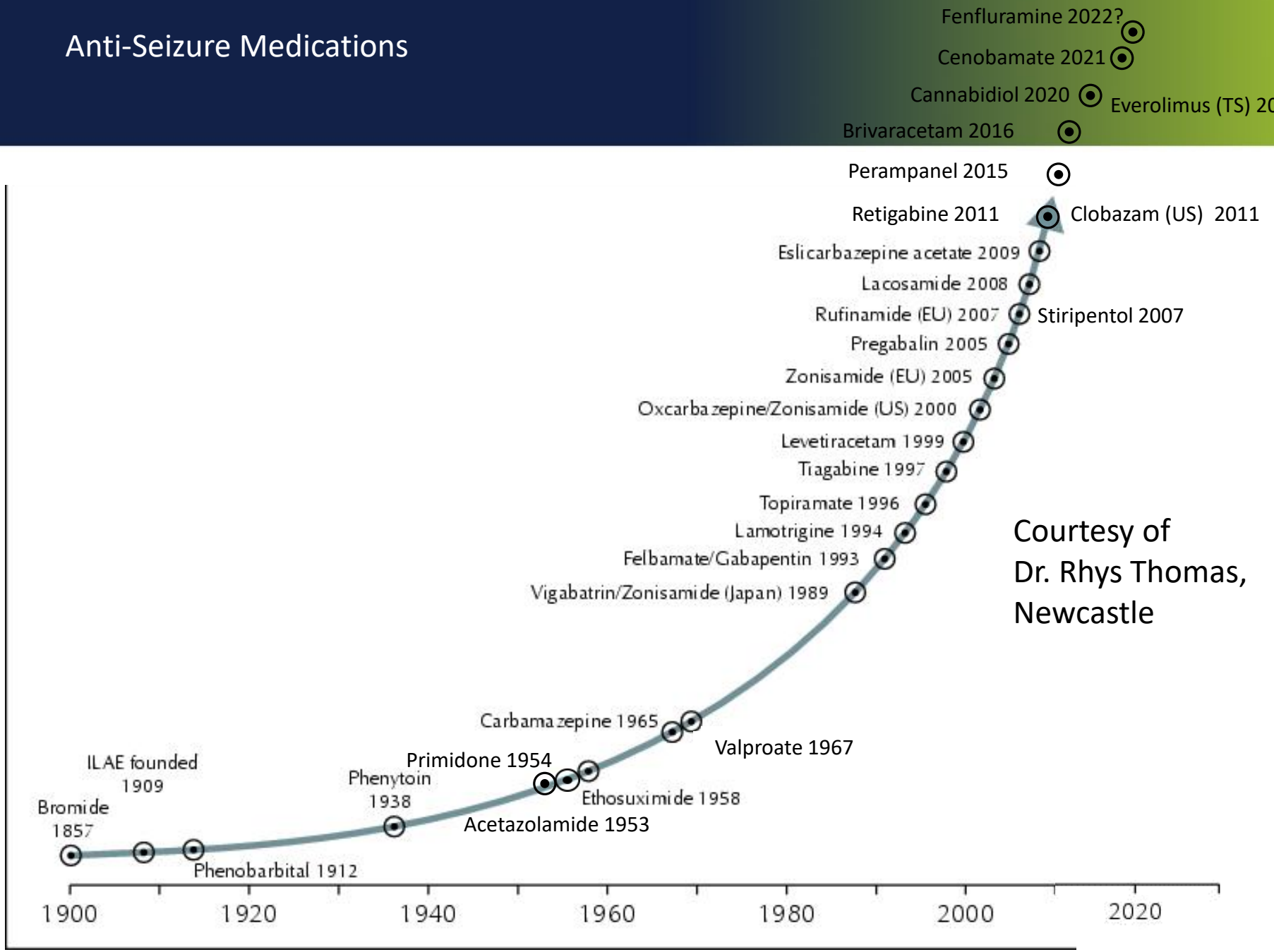
The Epilepsies

- The epilepsies define a common group of brain disorders affecting individuals of all age groups, of varying and often of unknown cause, characterised by recurrent unprovoked seizures, or by one unprovoked seizure but with an “enduring predisposition” to further seizures. The epilepsies may have significant consequences in terms of adverse educational, vocational, and psychosocial functioning, and physical morbidity (and potential mortality), especially in the one third of patients with drug-resistant disease.

Management

- Lifestyle and self care
  - Rest and sleep
  - Diet, e.g., avoiding excess high glycaemic foods, caffeine and alcohol
  - Managing stress
  - Exercise
  - Managing mental health – nature, meditation, yoga, downtime, other
  - Managing travel
- Specific therapies
  - Medications
  - Surgery
  - VNS
  - Dietary

Anti-Seizure Medications



Courtesy of
Dr. Rhys Thomas,
Newcastle

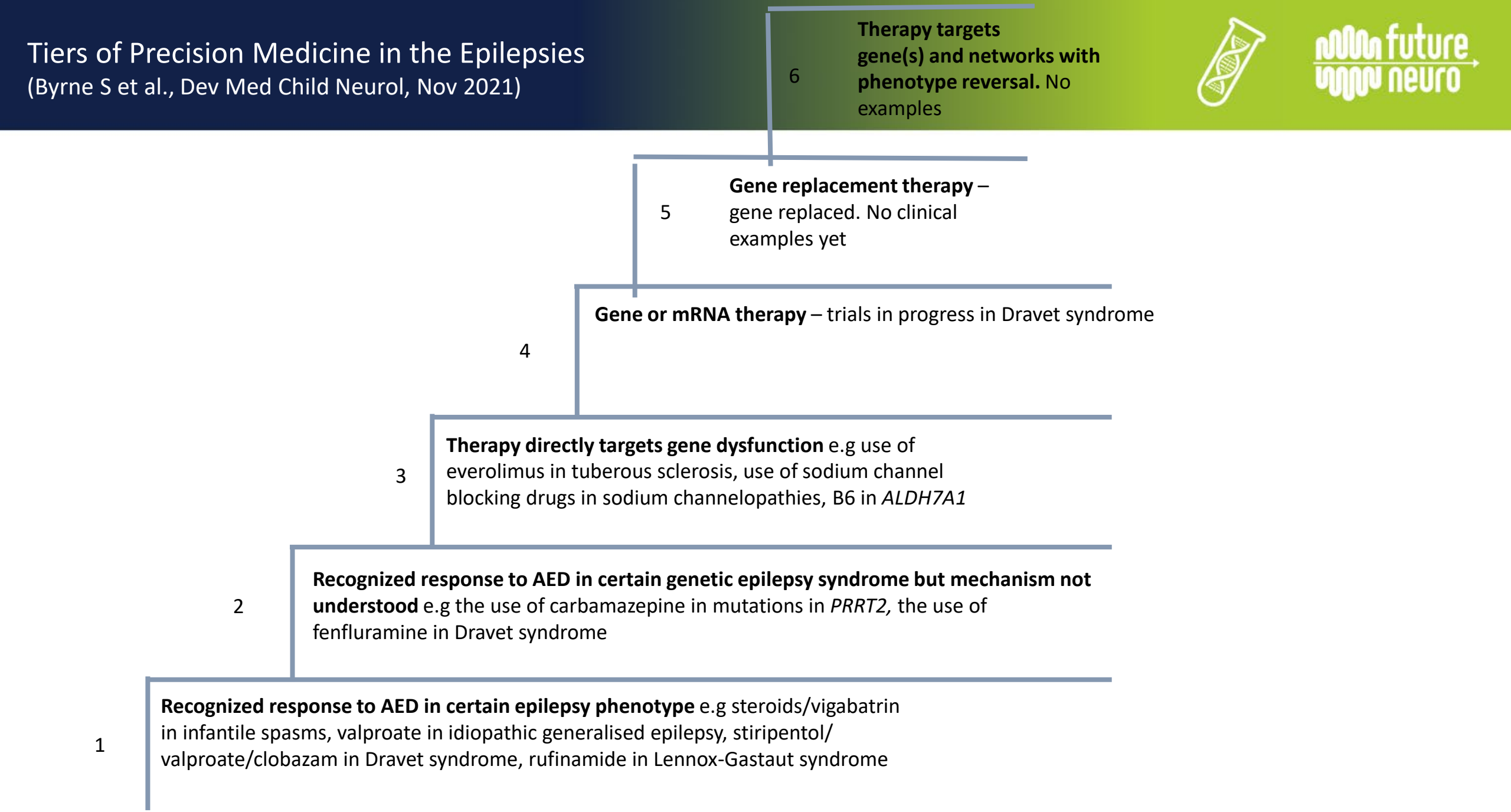
Precision Medicine

- Precision (molecular / genomic) medicine refers to the scientific basis that underpins the personalization of medical care, particularly in the context of treatments *targeted* towards the precise molecular causes of disease.

  - A Roadmap for Precision Medicine in the Epilepsies
    - EpiPM Consortium, Lancet Neurol 2015; 14:1219-1228.

Tiers of Precision Medicine in the Epilepsies

(Byrne S et al., Dev Med Child Neurol, Nov 2021)



Precision therapy in WWE

- “Teratogens act in a dose-dependent manner on a susceptible genotype. However, the genotypes at risk for ASM-induced teratogenic deficits are unknown”
- “We envision a future in which precision medicine enables a new practice style that puts focus on early detection, prediction, and targeted therapies for WWE”
  - Li Y et al, Ep Behav 2021

Women with epilepsy

- Menarche
- Menstrual cycle
- Contraception
- Folic acid (dose)
- Pregnancy planning
  - Teratogenicity of AEDs
- Pregnancy management
- Delivery
- Breastfeeding
- Menopause

AAN Epilepsy Quality Measures in Clinical Practice – Each Visit

- Seizure type and current seizure frequency
- Epilepsy syndrome and aetiology of epilepsy
- EEG results
- MRI results
- Querying and counselling about AED side effects
- Referral for surgical treatment when appropriate
- Counselling about specific safety issues
- ***Counselling about contraception and pregnancy***
    - Fountain N et al, Neurology 2011.

History of ASM safety in pregnancy

- The fetal trimethadione syndrome
  - Zackai EH et al. J Pediatr 1975
- The fetal hydantoin syndrome
  - Hanson JW, Smith DW. J Pediatr 1975
- The fetal phenobarbitone syndrome
  - Seip M. Acta Paediatr Scand 1976
- The fetal valproate syndrome
  - DiLiberti JH et al, Am J Med Genet 1984
  - ……. And so on

- Meador KJ et al, NEJM, 2009
- Campbell E at al, JNNP, 2014
- Baker GA et al, Neurology 2015
- Christensen J et al, JAMA 2013
- Meador KJ et al, Neurology 2020
- Magne Vegrim H et al, JAMA Neurology, 2022

Prospective pregnancy registers

- The North American AED Pregnancy Registry
- International Registry of Antiepileptic Drugs and Pregnancy – EURAP
- The UK and Ireland Epilepsy and Pregnancy Register
- Australian Register of Antiepileptic Drugs in Pregnancy
- International Lamotrigine Pregnancy Register

Comparison of the major registers

Registry	UK and Ireland Epilepsy and Pregnancy Register [12]	North American Epilepsy and Pregnancy Registry [13]	EURAP [14]
Methodology	National, prospective based in the United Kingdom. Ascertainment is approximately 33% of the population of WWE in pregnancy	National prospective based in United states of America, and Canada.	International (>40 countries) prospective/ retrospective (includes Australian data)
Participation	50% self-enrollment WWE, and rest through physicians, nurses, midwives.	Self-enrollment by WWE	Through a network of physicians who report cases. No self-enrollment.
Inclusion criteria	Women with epilepsy, treated on AEDs or untreated in 1st trimester	Women taking AED for any reason in pregnancy	Pregnancies with AED exposure at conception.
Exclusion criteria	Pre-enrollment knowledge of malformation, or change in 1st trimester AED, or commencing the AED after conception.	If AEDs are switched in first trimester	Change in 1st trimester AED, or outcome not classifiable.
Data collection methods, and follow up	At enrollment and at 3 months after birth, the patient's general practitioner provides follow up on the case.	Telephone interview with patient at 7 months gestation, and then 8–12 weeks after pregnancy further interview, and in 60% of cases data extracted from patient/infants medical records.	Within 12 months of birth, and also followed up during pregnancy at end of each trimester.
Type and level of exposure	Drug and dose (including dose changes recorded). Highest dose recorded taken as dose exposure.	Drug dose and brand	Drug regime and dose
Drug levels	Not systematically recorded	Not systematically recorded	Not systematically recorded
Diagnosis of epilepsy	Physician reported diagnosis of epilepsy, and clinical geneticist reviews medical record to determine if malformation present	Self reported diagnosis. Medical teratologist blinded review of medical record.	Made by patient's physician. Central classification of outcomes based on teratologists assessment of medical reports.

Kinney MO, Craig JJ. Seizure 2017

Overall MCM rate associated with individual ASMs

- Lamotrigine – 2.3 % (UK and Ireland), 2.0 % (North American)
- Carbamazepine – 2.6 % (UK and Ireland), 5.5 % (EURAP)
- Valproate – 9.3 % (North America), 10.3 % (EURAP)
- Levetiracetam – 0.7 % (UK and Ireland), 2.4 % (North America)
- Topiramate – 4.8 % (UK and Ireland), 4.2 % (North America)
- Phenytoin – 6.4 % (EURAP), 3.7 % (UK and Ireland)
- Phenobarbital – 5.5 % (North America), 6.5 % (EURAP)

MCM Data summaries – dose response

Registry	MCM rate following antiepileptic drug exposure				
	Valproate	Carbamazepine	Lamotrigine	Levetiracetam	Topiramate
UK and Ireland Registry	82/1200 (6.7% CI 5.5-8.3%)	43/1657 (2.6% CI 1.9-3.5%)	49/2098 (2.3% CI 1.8-3.1%)	2/304 (0.7% CI 0.2-2.5%)	3/70 (4.3% CI 1.7-13.3%)
EURAP	Dose <700 mg 24/431 (5.6% CI 3.6-8.2%) Dose ≥700 to <1500 mg 50/480 (10.4% CI 7.81-13.5%) Dose ≥1500 mg 24/99 (24.2% CI 16.2-33.9%)	Dose <400 mg 5/148 (3.4% CI 1.1-7.7%) Dose ≥400 to <1000 mg: 56/1047 (5.3% CI 4.1-6.9%) Dose ≥1000 mg 18/207 (8.7% CI 5.2-13.4%)	Dose <300 mg 17/836 (2.0% CI 1.2-3.2%) Dose ≥300 mg 20/444 (4.5% CI 2.8-6.9%)	N/A	N/A
Australian registry of AEDs in pregnancy	35/253 (13.8% CI 1.7-10.6%)	19/346 (5.5% CI 0.6-4.4%)	14/307 (4.6% CI 0.5-3.8%)	2/82 (2.4% CI 0.2-3.8%)	1/42 (2.4% CI 0.1-6.1%)
International lamotrigine pregnancy registry	N/A	N/A	35/1558 (2.2% CI 1.6-3.1%)	N/A	N/A
North American Antiepileptic drug pregnancy register	30/323 (9.3% CI 6.4-13.0%)	31/1033 (3.0% CI 2.1-4.2%)	31/1562 (2.0% CI 1.4-2.8%)	11/450 (2.4% CI 1.2-4.3%)	15/359 (4.2% CI 2.4-6.8%)

Polytherapy MCM rate (UK and Ireland)

Polytherapy regimen	Number of informative exposures	Number of MCMs	MCM rate (95% CI)	Odds ratio (95% CI)	p Value
Lamotrigine + other	594	19	3.2% (2.1-4.9%)	N/A	N/A
Lamotrigine + valproate	227	16	7.1% (4.4-11.1%)	2.3 (1.2-4.5)	0.017
Carbamazepine + other	491	24	4.9% (3.3-7.2%)	N/A	N/A
Carbamazepine + valproate	122	11	9.0% (5.1-15.4%)	1.9 (0.9-4.1)	0.08
Topiramate + other	204	10	4.9% (2.7-8.8%)	N/A	N/A
Topiramate + valproate	38	10	26.3% (15.0-42.0%)	6.9 (2.6-18.1)	0.0001
Levetiracetam + other	424	18	4.3% (2.7-6.6%)	N/A	N/A
Levetiracetam + valproate	57	1	1.8% (0.3-9.3%)	0.4 (0.05-3.1)	0.38

Clobazam and clonazepam

- Relatively infrequently used drugs with few available data
- We mainly use clobazam (a versatile treatment option)
- Some concern in Indian Register study
- Not replicated elsewhere
- Clobazam a versatile drug – short, intermediate, and longer term

Lacosamide in Pregnancy

- Lacosamide (Vimpat^{R}) used in both focal and generalised epilepsy
- (I have had good anecdotal experience with this drug in pregnancy in my practice)

- Embryotox Center of Clinical Teratology and Drug Safety in Pregnancy between 2004 and 2019
- 55 prospectively and 10 retrospectively ascertained pregnancies
- No reported birth defects or miscarrages reported
  - Hoeltzenbein M et al, Seizure, April 2023

Sodium valproate and WWE

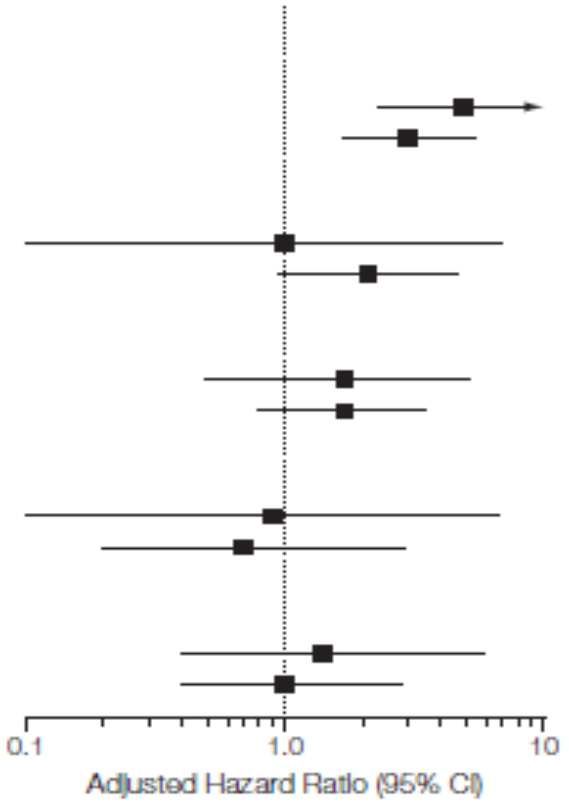
- The most teratogenic ASM
- Only used under specialist supervision

- 10% risk of major congenital malformation
- 30% + risk of learning difficulties
- 4-5 incidence of autism / autistic spectrum disorders

Prenatal valproate exposure and risk of autistic spectrum disorders and childhood autism

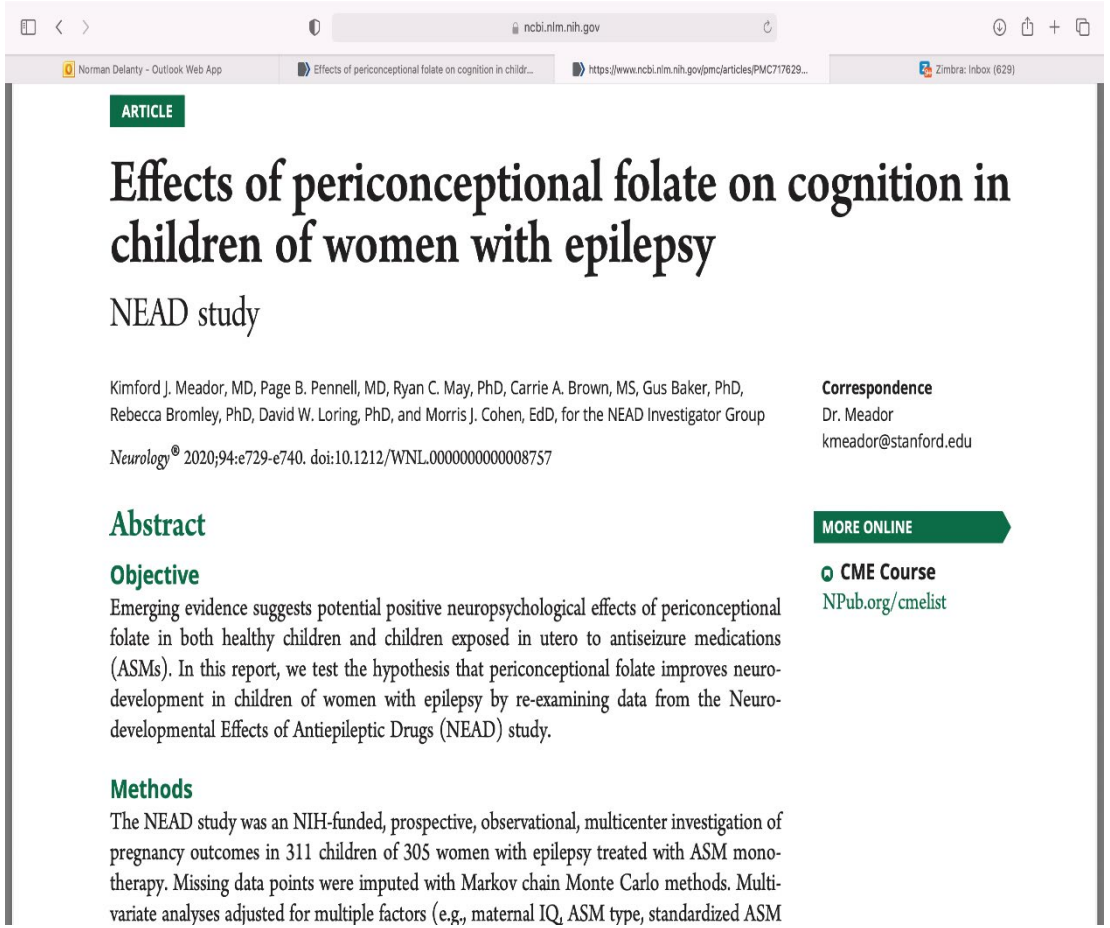
Figure 2. Autism Spectrum Disorder and Childhood Autism in Offspring of Mothers Who Used Antiepileptic Drugs as Monotherapy During Pregnancy Compared With Offspring of Women Who Did Not Use the Individual Antiepileptic Drug

	No. Unexposed	No. Exposed	Adjusted Hazard Ratio (95% CI)
Valproate			
Total	655 107	388	
Childhood autism	2058	7	4.9 (2.3-10.3)
Autism spectrum disorder	5423	12	3.0 (1.7-5.4)
Oxcarbazepine			
Total	655 205	321	
Childhood autism	2064	1	1.0 (0.1-6.9)
Autism spectrum disorder	5427	7	2.1 (0.96-4.6)
Lamotrigine			
Total	654 747	647	
Childhood autism	2062	4	1.7 (0.5-5.2)
Autism spectrum disorder	5426	8	1.7 (0.8-3.5)
Clonazepam			
Total	655 233	269	
Childhood autism	2063	2	0.9 (0.1-6.7)
Autism spectrum disorder	5431	3	0.7 (0.2-2.9)
Carbamazepine			
Total	655 153	386	
Childhood autism	2065	2	1.4 (0.4-5.8)
Autism spectrum disorder	5433	4	1.0 (0.4-2.8)



Christensen J et al.
JAMA 2013;**309**:1696-1703

Folic acid supplementation



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Norman Delanty - Outlook Web App | Effects of periconceptional folate on cognition in childr... | https://www.ncbi.nlm.nih.gov/pmc/articles/PMC717629... | Zimbra: Inbox (629)

ARTICLE

Effects of periconceptional folate on cognition in children of women with epilepsy

NEAD study

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Neurology® 2020;94:e729-e740. doi:10.1212/WNL.0000000000008757

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Abstract

Objective

Emerging evidence suggests potential positive neuropsychological effects of periconceptional folate in both healthy children and children exposed in utero to antiseizure medications (ASMs). In this report, we test the hypothesis that periconceptional folate improves neurodevelopment in children of women with epilepsy by re-examining data from the Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) study.

Methods

The NEAD study was an NIH-funded, prospective, observational, multicenter investigation of pregnancy outcomes in 311 children of 305 women with epilepsy treated with ASM monotherapy. Missing data points were imputed with Markov chain Monte Carlo methods. Multivariate analyses adjusted for multiple factors (e.g., maternal IQ, ASM type, standardized ASM

- Periconceptional folate was associated with higher FSIQ at both 3 and 6 years of age.
- Other positive effects noted, including tests of executive functioning at 6 years of age, and tests of receptive language at 3 years
- Dose effect was not clear

Cancer Risk in Children of Mothers with Epilepsy and High-Dose Folic Acid use During Pregnancy

- Magne Vegrim H et al, JAMA Neurology, September 2022

- Study population of 3,379,171 mother-child pairs
- Of these, 27,784 (0.8%) children of mothers with epilepsy

- Median age of child at analysis 7.3 years, 48.6% female and 51.4% male
- 5,934 (21.4%) children exposed to high dose folic acid
- 1.4% exposed to high dose folic acid in mothers without epilepsy

Results – Main Analysis

- Incidence of cancer in children whose mothers took high dose folic acid was 42.5 per 100,000 person-years (n=18)
- Incidence of cancer in children whose mothers did not take high dose folic acid was 18.4 per 100,000 person-years (n=29)
- Hazard ratio for children exposed to high dose FA was 2.7 (C.I 1.2 – 6.2) compared to those children not so exposed
- Absolute risk of childhood cancer was 1.5% (CI 0.5% - 3.5%)

- Maternal epilepsy itself was not associated with risk of childhood cancer

What to do? / Discussion

- Prospectively advise 0.4 / 0.8 mg per day
- Higher doses (5 mg) in women who had had a previous child with a neural tube defect
  - Change from 5.0 to 0.8 mg after first trimester of pregnancy
- Discuss gently with women already on as they are seen, and reduce to 0.8 mg daily
- Change to 0.8 mg in any women who are currently pregnant
- Await further studies / further guidelines from professional bodies
- I was in contact with Clonmel Healthcare re a 0.8 mg tablet

Practical Approach to Management

- Pre-pregnancy planned review of ASMs and epilepsy control
- Folic acid 0.8 mg (now) and general lifestyle and dietary advice
- Communication between neurology and maternity services and liaison with an epilepsy nurse specialists / advanced nurse practitioner
- Careful monitoring during pregnancy
- Baseline monitoring of drug levels pre-pregnancy / first trimester
- Adjustment of dose in later pregnancy / individualise
- Post-partum neurology check up at about 6 weeks

TAKE HOME POINTS

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  - Rebecca Bromley
- Shared joint care is important to reduce adverse outcomes, including adverse maternal outcomes

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Questions / discussion