AED choice in special population

Women With Epilepsy (WWE) Updated 2018

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How different are women?

- Habitus
- Metabolism
- Co-morbidities
- Psychosocial stigma
- Hormonal status **

Hormones & Epilepsy

Estradiol = Proconvulsant

- Direct excitatory effects at the neuronal membrane
  - Augments N methyl-D-aspartate (NMDA) mediated glutamate receptor activity
  - Decreases inhibition by decreasing GABA synthesis
  - Logothetis et al. showed that IV conjugated estrogen activated epileptiform activity in 11/16 women

Progesterone = Anticonvulsant

- Direct membrane-mediated inhibitory effects
  - Potentiating GABA A-mediated chloride conductance
  - Potentiates the action of the powerful endogenous inhibitory substance adenosine
  - Backstrom et al. found that IV progesterone at sufficient doses was associated with decrease interictal spikes in 4/7 women with partial epilepsy

Hormones & Women With Epilepsy (WWE)

- Issues
  1. Sexuality / Fertility
  2. Catamenial seizures
  3. Pregnancy & Lactation
  4. Menopause

1. WWE & Sexuality/Fertility

WWE & Sexuality

- The majority of women with epilepsy appear to have normal sex lives
- Some women with epilepsy, both the desire and arousal phases may be inhibited by disease or AEDs

WWE & Fertility

Both disease and treatment can alter the menstrual cycle and fertility

Decreased fertility

- Polycystic ovarian disease (PCOS)
- Sexual dysfunction
- Psychosocial effect of epilepsy
- Seizures and AED effects to the fetus

Failure of contraception

- AED and OCP interactions

Polycystic Ovarian Disease (PCOS)

- Syndrome of
  - Hyperandrogenism (raised testosterone levels)
  - Multiple ovarian cysts
  - Anovulatory cycles
  - Hirsutism
  - Obesity (0-50%)
- Failure of the ovarian follicle to complete normal maturation during the menstrual cycle
- Prevalence of PCOS
  - Women without epilepsy around 4-19%
  - WWE: unknown (~ 2x, even not on AED)
  - WWE on valproate, esp. starting age< 20 (more common)

WWE & contraception

AEDs and OCPs

- Lamotrigine level
  - cOCP can decrease LMT levels by 25–70%
  - Progestrogen only pills can increase LMT level by 20-100%

Enzyme-inducing AEDS	Enzyme-inhibiting AEDS	AED with no effect
Barbiturates Carbamazepine Oxcarbazepine Phenytoin Topiramate (>200 mg/day)	Felbamate Valproate	Ethosuximide Gabapentin Lamotrigine Levetiracetam Tiagabine Zonisamide Benzodiazepines Pregabalin vigabatrin

- Nonenzyme-inducing AEDs: all current contraceptive methods are suitable
- OCP decreased from 50-100µg/d of estrogen to < 50 µg/d (due to risk of thrombosis)
- Modern available combined OCPs contain 20–35 µg/d of ethinylestradiol and < 1 mg of progestogen

WWE on enzyme-inducing AEDs / OCPs

- C-OCP starting with 50 µg/d ethinyl oestradiol dosage
  - If breakthrough bleeding occurs
    - Increase the dose of ethinyl oestradiol to 75 or 100 µg/d or
    - Consider giving 3 packs of the pill without a break ("tricycling")
  - Even on a higher-dose COCP with normal cycles, full oral contraceptive efficacy cannot be guaranteed
- Medroxyprogesterone injections are still effective but take q 10 weeks rather than q 12 weeks

WWE on enzyme-inducing AEDs / OCPs

- No contraindications to the use of nonhormonal methods of contraception in women with epilepsy
- The use of the Mirena coil IUDs also effective (acts locally)
- Emergency contraceptive pill can be used after unprotected sexual intercourse; a higher dose may be needed
- Ineffective ***
  - Progesterone only pill
  - Levonorgestrel implants - high failure rate
  - Should always recommend second contraceptive methods

2. WWE & Catamenial Seizures

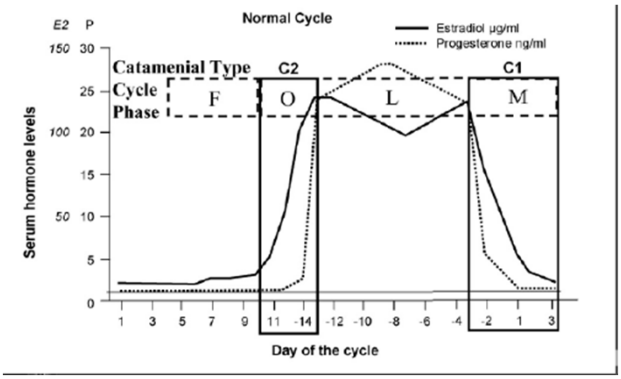
Catamenial Seizures

- Prevalence 10-12% (30% of women with localization-related epilepsy)
- Refer to an increase in seizure frequency around the time of the menses, either just before or during the first few days of menstruation
- Exacerbations primarily related to
  - Changing sex hormone concentrations during the menstrual cycle
    - Positive correlation with serum estradiol/progesterone ratio
    - Ratio is highest during days prior to ovulation & menstruation
    - Ratio is lowest during post-ovulatory (early & midluteal phase)
  - Alterations in AED concentrations, as seen with phenytoin and lamotrigine, throughout the menstrual cycle

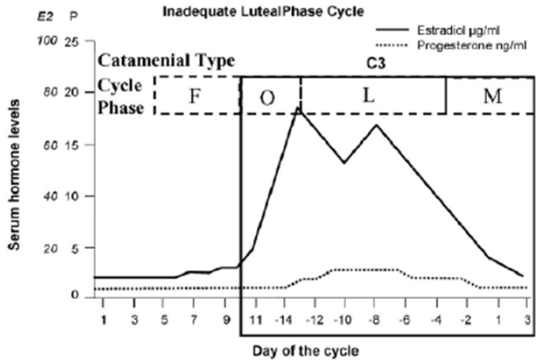
3 Catamenial Seizures Patterns (C1, C2, C3)

- Ovulatory cycles
  - During perimenstrual days (pattern C1)
  - Periovulation (pattern C2)
- Anovulatory cycles
  - Post-ovulation, when luteal phase inadequate (pattern C3)

Ovulatory Cycle



Anovulatory Cycle



Catamenial seizures – Treatment concepts

- ↑ AED dose around time of ↑ seizures
- Avoid cyclic variation by using a continuous OCP
- Supplemental progesterone during luteal phase
- Double-blind, randomized, placebo-controlled trial of cyclic supplemental progesterone currently underway

Catamenial Seizures – Treatment Strategies

- For women already on AEDs
  - Intermittent clobazam on days when ↑ seizures
  - Acetazolamide perimenstrually
  - Progestogens perimenstrually
- For women not already taking AEDs
  - Intermittent perimenstrual clobazam (5-30 mg/d)
  - COCP; depot progestogen therapy; or perimenstrual progestogen

3. WWE & Pregnancy/Lactation

Epilepsy ◄- - - - ► Pregnancy

Effect of pregnancy on epilepsy

- Seizure frequency (due to estrogen/progesterone change)
  - 54-80%: no change
  - 8-46%: increased (various studies)
  - 25%: improved seizure frequency
- Predictor of seizure free during pregnancy
  - Seizure free 9 months before pregnancy (chance = 84-92%)
- Factors that may exacerbate seizures
  - Noncompliance
  - Nausea and vomiting
  - Inappropriate decrease in AED
    - Changes in blood volumes
    - A pregnancy-related fall in plasma drug concentrations (phenytoin, carbamazepine, phenobarbitone, and lamotrigine)
  - Sleep deprivation

Effect of epilepsy on pregnancy

- > 90% of WWE have a normal pregnancy
- Neonatal or perinatal death reported 2-3x higher
  - Wide variability in studies; one study with no increased risk of death
- Maternal mortality: 10X WWE vs. women without epilepsy
- Obstetrical complication: inconclusive
  - Low birth weight
  - Preterm, prematurity
  - Still birth
  - Preeclampsia
  - Bleeding
  - Placental abruption
  - Prolonged hospital stay > 6 days

WWE & Planning on pregnancy

- If a patient has been seizure free for at least 2– 3 years with no risk factors for seizure recurrence, consider withdrawing AEDs 6 months prior to planned conception
- Potential preconceiving
  - Adequate seizure control
  - Switching of AED (choose the lowest risk of teratogenicity)
  - Minimally effective dose
  - Minimal peak drug concentration, more frequent dosing
  - Monitor blood level and prenatal diagnosis
  - Avoid polytherapy (prefer to monotherapy)
  - Folic supplement
- NB: in unplanned pregnancy
  - Not recommend to abruptly stop AED (high risk for status and SUDEP)

FDA: Pregnancy category

Categories	Human	Animal	AEDs
A	/	-	
B	NA	/	
C	NA	X	Benefit > Risk
D	X	-	Benefit > Risk
X	X	X	Risk > Benefit

Pregnancy categories

C	C	D	X
AZA, acetazolamide BRV, brivaracetam CLB, clobazam CZP, clonazepam OXC, oxcarbazepine PER, perampanel PGB, pregabalin RUF, rufinamide TGB, tiagabine LAC, lacosamide	VGB, vigabatrin ZNS, zonisamide LTG, lamotrigine (IR) LVT, levetiracetam ESL, eslicarbazepine ESM, ethosuximide EZG, ezogabine; FBM, felbamate GBP, gabapentin	CBZ, carbamazepine LTG, lamotrigine (XR) Diazepam Lorazepam PB, phenobarbital PHT, phenytoin TPM, topiramate	VPA, valproic acid

NB: in polytherapy, the malformation rate of topiramate increases to 14.1% vs. 2.4% as monotherapy

Pregnancy & Anticonvulsants

- Fetal malformation
  - Major: cleft lip, cleft palate, VSD, NTD
  - Minor: hypertelorism, epicanthal fold, board nasal bridge, elongated phillrum, distal digital& nail bed hypoplasia
- Major congenital malformations (MCM)
  - 4-14% WWE vs 1-4% non-epilepsy (2-3X)
  - First trimester on AEDs risk ~3%
  - Valproate (~7-10%)
    - 1-2% NTD (10-20x) with dose related
    - ≤1000 mg/day OR ~ 1
    - ≤1500 mg/day OR = 3.7
    - >1500 mg/day OR = 10.9
  - Polytherapy (15%)

Epilepsia 2004
.J Neurol Neurosurg Psychiatry 2001

Articles

Comparative risk of major congenital malformations with eight different antiepileptic drugs: a prospective cohort study of the EURAP registry

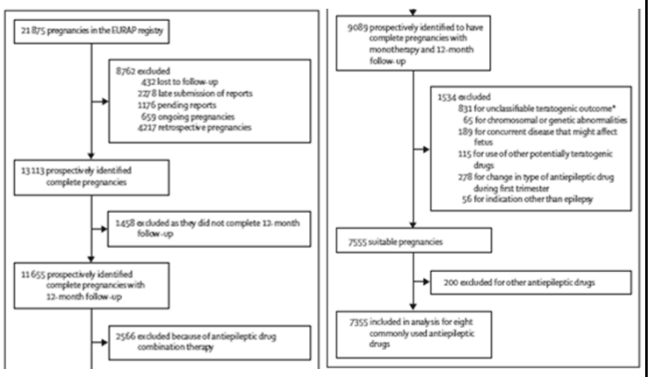
Torbjörn Tomson, Dina Battino*, Erminio Bonizzoni, John Craig, Dick Lindhout, Emilio Perucca, Anne Sabers, Sanjeev V Thomas, Frank Vajda, for the EURAP Study Group†*

www.thelancet.com/neurology Published online April 18, 2018 http://dx.doi.org/10.1016/S1474-4422(18)30107-8

Aim & Method

- A longitudinal, prospective cohort study, EURAP international registry
- 42 countries, 1999-2016, n 7,355 pregnancies
- Compare the occurrence of major congenital malformations (MCM) following prenatal exposure
- 8 most commonly used AED in monotherapy
- Risk at different dose range
- Timing: each trimester, at birth, 1-year after birth

www.thelancet.com/neurology Published online April 18, 2018 http://dx.doi.org/10.1016/S1474-4422(18)30107-8



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Prevalence of major congenital malformations in offspring exposed prenatally to 1 of 8 different antiepileptic monotherapy (7,355 pregnancies)

	Dose range (mg/day)	Number of pregnancies exposed	Number of major congenital malformation events	Prevalence of major congenital malformation events (95% CI)
Lamotrigine	25–1300	2514	74	2·9% (2·3–3·7)
Carbamazepine	50–2400	1957	107	5·5% (4·5–6·6)
Valproate	100–3000	1381	142	10·3% (8·8–12·0)
Levetiracetam	250–4000	599	17	2·8% (1·7–4·5)
Oxcarbazepine	75–4500	333	10	3·0% (1·4–5·4)
Phenobarbital	15–300	294	19	6·5% (4·2–9·9)
Topiramate	25–500	152	6	3·9% (1·5–8·4)
Phenytoin	30–730	125	8	6·4% (2·8–12·2)

• Lamotrigine, levetiracetam, and oxcarbazepine = unexposed to antiepileptic drugs

• NB: topiramate and phenytoin = small sample size

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Association between prevalence of major congenital malformations and exposure to 1 of the 4 monotherapies in which a dose response was detectable

	Number of pregnancies exposed	Number of major congenital malformation events	Prevalence of major congenital malformation events (95% CI)	p value
Lamotrigine				
≤325 mg/day	1870	46	2·5% (1·8–3·3)	0·0145
>325 mg/day	644	28	4·3% (2·9–6·2)	..
Carbamazepine				
≤700 mg/day	1276	58	4·5% (3·5–5·8)	0·0140
>700 mg/day	681	49	7·2% (5·4–9·4)	..
Valproate				
≤650 mg/day	600	38	6·3% (4·5–8·6)	<0·0001
>650 to ≤1450 mg/day	666	75	11·3% (9·0–13·9)	..
>1450 mg/day	115	29	25·2% (17·6–34·2)	..
Phenobarbital				
≤80 mg/day	73	2	2·7% (0·3–9·5)	0·0390
>80 to ≤130 mg/day	161	10	6·2% (3·0–11·1)	..
>130 mg/day	60	7	11·7% (4·8–22·6)	..

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	Odds ratio (95% CI)	Adjusted p value†
Drug comparisons with lamotrigine ≤325 mg/day		
Valproate (>1450 mg/day)	13·52 (7·73–23·64)	0·0002
Phenobarbital (>130 mg/day)	5·81 (2·40–14·08)	0·0002
Valproate (>650 mg/day to ≤1450 mg/day)	4·72 (3·11–7·18)	0·0002
Valproate (≤650 mg/day)	2·70 (1·67–4·38)	0·0002
Carbamazepine (>700 mg/day)	2·68 (1·71–4·19)	0·0002
Phenobarbital (>80 mg/day to ≤130 mg/day)	2·46 (1·16–5·23)	0·0196
Phenytoin (≥30 mg/day to 730 mg/day)	1·93 (0·78–4·75)	0·1554
Carbamazepine (≤700 mg/day)	1·71 (1·12–2·61)	0·0143
Lamotrigine (>325 mg/day)	1·68 (1·01–2·80)	0·0463
Topiramate (≥25 mg/day to 500 mg/day)	1·67 (0·69–4·04)	0·2524
Oxcarbazepine (≥75 mg/day to 4500 mg/day)	1·13 (0·55–2·31)	0·7358
Levetiracetam (≥250 mg/day to 4000 mg/day)	1·11 (0·62–2·00)	0·7282
Phenobarbital (≤80 mg/day)	1·07 (0·25–4·60)	0·923

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	Odds ratio (95% CI)	Adjusted p value†
Within-drug comparisons		
Phenobarbital (>130 mg/day *vs* ≤80 mg/day)	5·41 (1·05–27·89)	0·0436
Valproate (>1450 mg/day *vs* ≤650 mg/day)	5·00 (2·79–8·97)	0·0002
Valproate (>1450 mg/day *vs* >650 mg/day to ≤1450 mg/day)	2·86 (1·67–4·89)	0·0002
Phenobarbital (>130 mg/day *vs* >80 mg/day to ≤130 mg/day)	2·36 (0·81–6·86)	0·1135
Phenobarbital (>80 mg/day to ≤130 mg/day *vs* ≤80 mg/day)	2·29 (0·47–11·05)	0·3028
Valproate (>650 mg/day to ≤1450 mg/day *vs* ≤650 mg/day)	1·75 (1·12–2·73)	0·0147
Lamotrigine (>325 mg/day *vs* ≤325 mg/day)	1·68 (1·01–2·80)	0·0463
Carbamazepine (>700 mg/day *vs* ≤700 mg/day)	1·56 (1·03–2·37)	0·0352

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	Odds ratio (95% CI)	Adjusted p value†
Other antiepileptic drug comparisons		
Valproate (>650 mg/day to ≤1450 mg/day) *vs* lamotrigine (>325 mg/day)	2·81 (1·70–4·65)	0·0002
Valproate (>650 mg/day to ≤1450 mg/day) *vs* carbamazepine (≤700 mg/day)	2·76 (1·82–4·19)	0·0002
Valproate (≤650 mg/day) *vs* levetiracetam (250–4000 mg/day)	2·43 (1·30–4·55)	0·0069
Carbamazepine (>700 mg/day) *vs* levetiracetam (250–4000 mg/day)	2·41 (1·33–4·38)	0·0055
Valproate (≤650 mg/day) *vs* oxcarbazepine (75–4500 mg/day)	2·39 (1·13–5·08)	0·0235
Carbamazepine (>700 mg/day) *vs* oxcarbazepine (75–4500 mg/day)	2·37 (1·17–4·80)	0·0169
Valproate (≤650 mg/day) *vs* carbamazepine (≤700 mg/day)	1·58 (0·98–2·55)	0·0626
Lamotrigine (>325 mg/day) *vs* levetiracetam (250–4000 mg/day)	1·51 (0·79–2·88)	0·2077
Lamotrigine (>325 mg/day) *vs* oxcarbazepine (75–4500 mg/day)	1·49 (0·70–3·17)	0·3051
Oxcarbazepine (75–4500 mg/day) *vs* levetiracetam (250–4000 mg/day)	1·02 (0·45–2·30)	0·9644
Carbamazepine (>700 mg/day) *vs* valproate (≤650 mg/day)	0·99 (0·60–1·65)	0·9708
Oxcarbazepine (75–4500 mg/day) *vs* carbamazepine (≤700 mg/day)	0·66 (0·33–1·32)	0·2393
Levetiracetam (250–4000 mg/day) *vs* carbamazepine (≤700 mg/day)	0·65 (0·36–1·16)	0·1412
Lamotrigine (>325 mg/day) *vs* carbamazepine (>700 mg/day)	0·63 (0·38–1·05)	0·0766
Lamotrigine (>325 mg/day) *vs* valproate (≤650 mg/day)	0·62 (0·36–1·09)	0·0959

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	Odds ratio (95% CI)	Adjusted p value†
(Continued from previous page)		
Non-drug covariates		
Parental history of major congenital malformations	2·98 (1·52–5·87)	0·0023
Southeast Asia *vs* Europe	2·43 (1·48–3·99)	0·0009
Americas *vs* Europe	1·51 (0·62–3·70)	0·3673
Sex (boys *vs* girls)	1·33 (1·07–1·67)	0·0142
Folic acid (appropriate use *vs* no use or inappropriate use)	1·26 (0·99–1·60)	0·0579
Maternal age at conception‡	1·01 (0·98–1·03)	0·5166
Western Pacific *vs* Europe	0·94 (0·63–1·40)	0·7440
Generalised tonic-clonic seizures during first trimester	0·91 (0·58–1·43)	0·6890
Undetermined or unclassifiable *vs* localisation-related epilepsy	0·76 (0·51–1·14)	0·1893
Parity 1 *vs* 0	0·75 (0·58–0·98)	0·0329
Idiopathic generalised epilepsy *vs* Localisation-related epilepsy	0·74 (0·56–0·98)	0·0383
Parity ≥2 *vs* 0	0·72 (0·46–1·13)	0·1574

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	Total (7355)	CBZ (1,957)	LMT (2,514)	LEV (599)	OXC (333)	PB (294)	PHT (125)	TPM (152)	VPA (1,381)
No MCM	95%	95%	97%	97%	97%	94%	94%	96%	90%
MCM	5%	3%	3%	3%	6%	6%	6%	4%	10%
• Cardiac	1	1	1	1	1	3	4	2	2
• Cleft lip/palate	<1	<1	1	<1	<1	<1	0	0	1
• Hypospadias	1	1	<1	<1	0	<1	0	1	2
• NTD	<1	<1	<1	0	0	1	1	0	1
• Polydactyly	<1	<1	0	<1	<1	1	0	0	1
• GI	<1	<1	<1	<1	0	0	0	0	<1
• Renal	<1	1	1	1	0	<1	0	0	1
• Other	1	2	<1	0	1	1	2	1	2
• Multiple MCM	<1	<1	<1	0	0	0	0	0	1

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Folic and vitamin K supplement

- Folic
  - Pre-pregnancy 1 month (or anytime for potential case) – throughout pregnancy
    - No risk: 0.4-0.8 mg/d
    - High risk: 4 mg/d
- Vitamin K
  - Pregnancy women on enzyme inducing agent
    - Mother: oral vitamin K 10-20 mg/d last month
    - Child: Vitamin K 1 mg IM, IV at birth

Post-partum

- 1-2% of women with active epilepsy will have a tonic–clonic seizure during labor (within 24 hour)
- If AED dose increased during pregnancy, gradually reduce it to preconception dose over the few weeks following delivery, to reduce the risk of maternal drug toxicity
- Genetic seizures: IGE → 9-12% of the child would have IGE
- Intrauterine exposure to valproate resulted in children with IQ scores ~ 6-9 points lower than those exposed to other AED (lamotrigine, phenytoin, or carbamazepine)

Breastfeeding and AEDs

- Benefit of breastfeeding
  - Psychological benefits for mother and child (bonding)
  - Reduced infant mortality
  - Fewer infectious disease
  - Decreased risk of immunologically mediated disorders (type 1 DM)
- Current recommendations all support breastfeeding
  - The total amount of drug transferred to infants via breast milk is usually much smaller than the amount transferred via the placenta during pregnancy.
  - However, as drug elimination mechanisms are not fully developed in early infancy, repeated administration of a drug such as lamotrigine via breast milk may lead to accumulation in the infant.
  - Some side effects
    - Lethargy (esp. benzodiazepines, barbiturates)
    - Lamotrigine : increased risk of toxicity, monitor level in breastfed infants if mother taking high dosage

4. WWE & Menopause

Epilepsy & Menopause

- Epilepsy can alter timing of menopause
  - Partial epilepsy → premature menopause
- During menopause seizure frequency
  - Worsens in ~ 40% (later improved after complete menopause)
  - Improves in ~30%
  - No change in ~ 30%
- Multicenter, randomized, placebo-controlled trial in postmenopausal women with epilepsy demonstrated ↑ seizure frequency in a dose-dependent fashion with HRT (Prempro, conjugated equine estrogens plus medroxyprogesterone acetate), esp. Hx of catamenial epilepsy

Epilepsy & menopause & Bone health

- WWE at ↑ risk of fractures, osteoporosis, and osteomalacia
- ~10% of WWE have premature bone demineralization, especially if using AEDs that induce the hepatic cytochrome P450 enzyme system
- Etiologies (multifactorial)
  - Adverse effects of AEDs on bone metabolism, vitamin D, bone turnover
  - Trauma of seizures
  - Subtle effects of AEDs on coordination
- Most effective therapy for AED-induced osteoporosis has not been established

Risk factors for early osteopenia and secondary osteoporosis

- Inadequate nutrition, esp. deficient calcium intake
- Weight < 127 lb
- Inadequate weight-bearing exercise
- Neuromuscular impairment
- Institutionalized or wheelchair/bed-bound status
- Treatment with phenobarbital, primidone, phenytoin, carbamazepine or valproate
- Smoking
- Excessive alcohol intake
- Prolonged steroid therapy
- Menopause
- Fair complexion, or Asian or Northern European ancestry

- Recommendation
  - Screening with bone scans of the spine or hip should be obtained in at-risk women and be repeated every 2 years or if a fracture occurs
  - Women should be counseled about adequate calcium intake, and a dietary history should be obtained
  - Supplementation with calcium and vitamin D

Summary

Men ≠ Women

MWE ≠ WWE

Summary

- Being a woman with epilepsy is not the same as being a man with epilepsy.
- Epilepsy affects sexual development, menstrual cycle, aspects of contraception, fertility, and reproduction in ways that are unique to women
- Selecting AEDs in WWE: based on evidence-based

Thank You