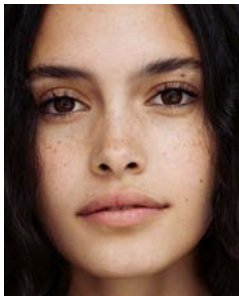## Slide 1

Cosmetic and Sexual Side Effects of Anti-Seizure Medications

Adriana Bermeo-Ovalle, MD
Rush University Medical Center
Chicago, IL.
Southern Epilepsy and EEG Society Meeting
March 2018

Slide 2

Let's talk about:

- Weight management
- Hair loss
- Other cosmetic side effects
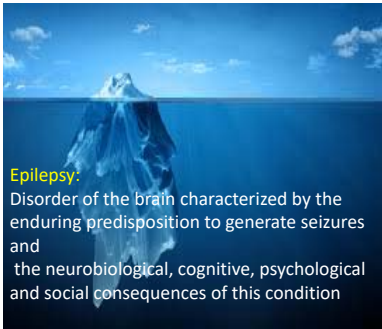- Sexuality and Libido

Slide 3

Epilepsy

- Disclosures: None

Slide 4

Cosmetic Issues in Epilepsy

- Columbia and Yale AED Database Project
- 1903 Patients (>16years old) 2000-2013
- Compared old and New AEDs
- Reports of:
  - Acne
  - Gum thickening
  - Hair loss 1.9%
  - Undesired hair
  - Weight gain 3.6%
- 110 (5.8%) reported these SE, 70 (3.7%) were intolerable
- More in female and tend to be recurrent
- **Pregabaline (9.8%)** and **Valproic acid (21.9%)**

Chen B, Epilepsy and Behavior, 2015

Slide 5

Epilepsy

Seizures

Social limitations
Social Isolation
Cognitive difficulties
Medication side effects
Financial burden
Psychiatric co-morbidities
- Depression
- Anxiety
- Suicidal ideations
Family stress
Access to care
Sexual issues
Cosmetic issues

Epilepsy:
Disorder of the brain characterized by the enduring predisposition to generate seizures and the neurobiological, cognitive, psychological and social consequences of this condition

Slide 6

Cosmetic side effects

- **Third reason for discontinuing AEDs**
  1. General health
  2. Cognitive and behavior
  3. Cosmetic
- Seen by others
- Affect social functioning
- Negatively impact quality of life
- Not dose dependent
- No difference between Mono and Poly therapy

De Kinderen, et al. Seizure 2013

Weight Management   🜨 RUSH

- Global obesity epidemic
- Weight gain and central fat distribution are common among women in midlife.
- Factors include:
  - Decreased estrogen levels
  - Lifestyle
  - Diet
- Central obesity increases risk for:
  - Dysglycemia
  - Dyslipidemia
  - Hypertension
  - Cardiovascular disease
- Weight gain in midlife increases risk of:
  - Cancer
  - Arthritis
  - Mood disorders
  - Sexual dysfunction

Health Risk Increase

Weight gain (Kg)	Disease	Risk Increase
1	Heart disease	3%
	HTN	5%
2-5	HTN	30%
5-8	Type2 DM	100%
	HTN	75%
	Ischemic stroke	25%
11-20	HTN	300%
	Ischemic Stroke	50%
>20	HTN	400%
	Ischemic Stroke	100%

Kapoor E. Mayo Clin Proc 2017

Weight Management WWE   🜨 RUSH

- Anti-seizure meds associated with Weight gain:
  - Valproic acid
    - 2-5Kg in 1 year avg.
  - Pregabalin
  - Vigabatrin
  - ? Carbamazepine
- Anti-seizure meds associated with weight loss:
  - Felbamate
  - Topiramate
  - Zonisamide

Weight gain %	
Valproic acid	13.0/12.6
Pregabalin	8.4/8.4
Vigabatrin	3.1/3.1

Ben-MenCHEM, Epilepsia, 2007

Weight Management in WWE   🜨 RUSH

- Anti-seizure medications may have an effect on weight
- Women 2x more likely to report
- Mechanism: Multiple factors
  - Appetite
  - Genetic underpinning
  - Metabolism
  - Hormonal metabolism
- Influence adherence o treatment
- Limits in physical activity in some but not all populations

Weight gain	Weight neutral	Weight loss
Carbamazepine	Lamotrigine	Felbamate
Gabapentin	Levetiracetam	Topiramate
Pregabalin	Phenytoin	Zonisamide
Valproic acid		
Vigabatrin		

Chukwu, Expert Rev Clin Pharmacol. 2014

Weight Management in WWE   🜨 RUSH

- Dietary treatments for Epilepsy
  - Ketogenic diet
  - Modified Atkins Diet
  - Low Glycemic Index Diet

- Anti-seizure medications side effects
  - Appetite control

Yale-Columbia study   🜨 RUSH

- Weight gain 3.6% of pts
- Was the most common CSE 61.8%
- Intolerable in 3.3%
- Higher incidence in women than men
- Average gain 7.68 Kg or 10.4% weight
- Average time for discontinuation 127 days
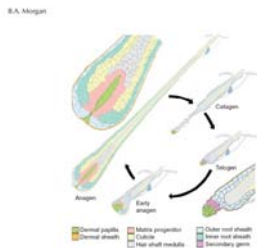- 20% had also other CSE

Hair loss   🜨 RUSH

- Average growth 6in per year
- Average loss 50 to 250 strands per day
- Strong familiar influence
- Most hair loss with age 50s-60s
- In women new hair may be finer and thinner

Medical causes
Pregnancy-postpartum
Thyroid disorders
Anemia
Polycystic Ovary Syndrome
Skin conditions
Dramatic weight loss
Too much Vitamin A
Stress

Hair growth — RUSH

- Hair grows in cycles
  - Anagen, Catagen, Telogen
  - Growth, transition and rest
- Medication effect on hair growth
  - Increase in resting phase (Telogen)
  - Dystrophic hair at the expense of growing (Anagen)
- Anti seizure medication changes tend to be reversible

Morgan B. CSH Perspectives in Medicine 2014

Sexuality — RUSH

- Men and Women with Epilepsy have higher rate of sexual dysfunction
  - Hypothalamic dysfunction related to seizures
  - Increased sex hormone-binding globulin level
    - P-450 enzyme inducers and VPA
  - Lower bioactive testosterone level
  - Alteration of serotonin
  - Sexual dysfunction after surgery (may also improve)
    - Temporal
    - Limbic
    - Frontal cortex

Harden C, Seizure 2008

Hair loss in WWE — RUSH

- Second most common reported cosmetic side effect
- Women 4x more likely to report
- When reported almost always intolerable 92%

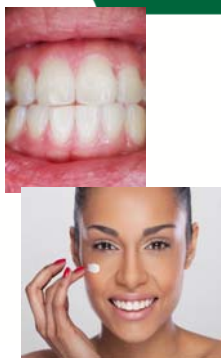| Reported association with hair loss		
Valproic acid	8.9% + CR	
Levetiracetam	0.4%+ CR	2 months-R
Topiramate	1.7%	
Lamotrigine	0.8% + CR	2-3 weeks-R
Pregabalin	0.7%	
Carbamazepine	0.3% +CR	

Sexuality — RUSH

- 20-30%WWE have sexual dysfunction
  - Libido/desire
  - Arousal
  - Orgasm
- Contributing factors
  - Medications (serotoninergic transmission)
    - PHT, PBT, **LTG, TPM**
  - Social fear
  - Depression and anxiety
  - Reduced genital blood flow
  - Right sided epilepsy?

Harden C, Epilepsy and Behavior 2005

Other Cosmetic side effects — RUSH

- Gum Thickening
  - Phenytoin 2.5% (reported up to 50%)
  - All intolerable
  - 51 days
- Acne
  - Felbamate (1.9%) and Lamotrigine (0.6%)
  - All intorelable
  - 34-50 days
- Hirsutism
  - Reported with PHT
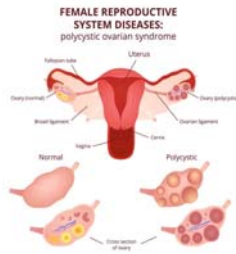 - 68 days

Sexuality — RUSH

- Treatment
  - Multidisciplinary evaluation
  - Tight seizure control
  - Modify AEDs
    - Lamotrigine
    - Oxcarbazepine
  - Monotherapy
  - Androgen therapy
  - Genital vasodilators (Sildenafil)
  - Psychotherapy

Yogarajah, Curr Pharm Des 2017

PCOS

- Reproductive dysfunction in WWE
  - Menstrual disorder
  - Hirsutism
  - Polycystic ovaries
  - Hormonal abnormalities relater to Hypothalamic-Pituitary axis dysfunction
  - Anti-seizure medications
    - P-450 enzyme-inducing meds
    - Valproic acid

FEMALE REPRODUCTIVE SYSTEM DISEASES:
polycystic ovarian syndrome
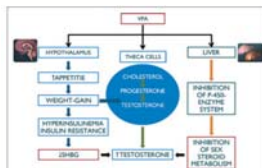

Thank you !

PCOS

Figure 2.
Mechanisms of induced hyperandrogenism by VPA. VPA may induce hyperandrogenism through an indirect effect. VPA has a stimulating effect on the hypothalamus leading to increased appetite and, thereby, weight gain. This weight gain causes insulin resistance and related hyperinsulinemia; by suppressing the synthesis of SHBG, insulin increases free testosterone concentrations. Another hypothesis is that VPA leads to hyperandrogenism through direct effects on the ovary. VPA stimulates androgen biosynthesis in human theca cells in vitro. In addition, VPA has an inhibitory effect on the hepatic P450 enzyme system and, thereby, it may inhibit the metabolism of sex steroids such as T, hence provoking increased androgen levels.
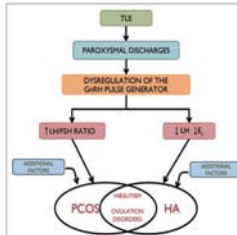Epilepsia © ILAE

Figure 1.
Pathogenic mechanisms by which epilepsy itself may induce reproductive disorders in women. The involvement of temporal lobe regions in epilepsy may cause a propagation of paroxysmal discharges toward the hypothalamus and, thereby, disrupt the activity of the GnRH pulse generator. Increase of the pulse frequency of GnRH secretion and, consequently, of the LH/FSH ratio is associated with PCOS. In contrast, a lower GnRH pulse frequency causes a decrease of LH and E2 levels that is charac-

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Ask!

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