



# The Cost of Medicine and other Interests

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# Conflict of Interest Disclosure

Speaker: Jennifer A. Vickers, MD



1. I do not have any potential conflicts of interest to disclose, **OR**
2. I wish to disclose the following potential conflicts of interest:

Type of Potential Conflict	Details of Potential Conflict
Grant/Research Support	
Consultant	
Speakers' Bureaus	
Financial support	
Other	

3. The material presented in this lecture has no relationship with any of these potential conflicts, **OR**
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- 1.
  - 2.
  - 3.



# Objectives

- ▶ Review cost of laboratory testing: Genetic tests, and general lab tests
- ▶ Review cost of medications
- ▶ Review the cost of creating a new medication
- ▶ Alternative therapies
  - ▶ Surgical interventions and their cost.
  - ▶ Dietary therapies
- ▶ Review of Medical Cannabis

# Laboratory tests





# Lab tests

- ▶ Chromosome Microarray testing (AKA Comparative Genomic Hybridization)
  - ▶ Uses oligonucleotides to match up base pairs.
  - ▶ Identifies deletions or duplications on chromosomes
- ▶ Whole Exome testing
  - ▶ A technique for sequencing protein coding genes on the DNA molecule.
  - ▶ Identifies abnormalities involved in protein function.



# Cost of Laboratory Testing

- ▶ Chromosome Microarray (aka Comparative Genomic Hybridization).
  - ▶ Athena – not clearly available
  - ▶ ARUP - \$1,595 for self pay
  - ▶ Baylor Miraca Genetics Lab - \$950 – \$14,075
  - ▶ CD Genomics – refused to give information
  - ▶ Gene Dx DNA Diagnostic Experts - \$1,117 self pay, \$3,000 insurance



# Cost of Laboratory testing

- ▶ Whole exome testing: (Rough estimates)
  - ▶ Athena – self pay \$4,750 for proband, and \$8,500 for proband and parents.
  - ▶ ARUP - \$7,900
  - ▶ Baylor Miraca Genetics Lab - \$7,000 self pay and \$11,950 insurance
  - ▶ CD Genomics – Refused to give information
  - ▶ Gene Dx DNA Diagnostic Experts – Proband \$5,000, Trio \$7,000 for self pay and \$20,060 insurance



# Cost of Laboratory Testing

- ▶ Complete Metabolic Panel - \$46.39
- ▶ CBC with differential - \$27.24
- ▶ Phenytoin (Dilantin) level - \$72.35
- ▶ Valproate (Depakote) level - \$77.51
- ▶ Levetiracetam (Keppra) Level - \$220.06



# Cost of medications



# Cost of Medications

Medication Name tablets	Generic vs Brand name	individual
Carbamazepine	\$63 - \$68	31 ¢
Levetiracetam	\$158 - \$435	\$1.23 – \$5.09
Perampanel	----- - \$712	N/A
Phenobarbital	\$27 - -----	8 - 9 ¢
Phenytoin	\$18 - \$28	39 - 51 ¢
Topiramate	\$147 - \$506	\$1.31 - \$2.08
Valproic Acid	\$17 - \$124	27 ¢ – \$2.21
Valproate ER	\$107 - \$165	N/A

# Why the mark up?



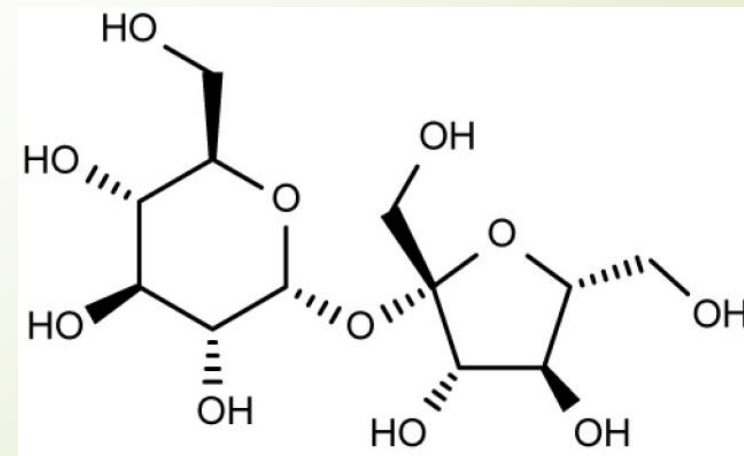
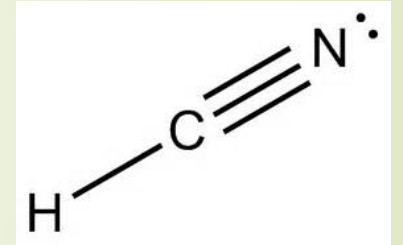
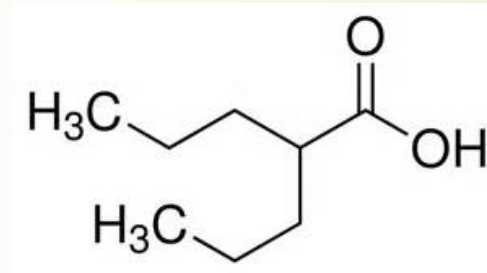
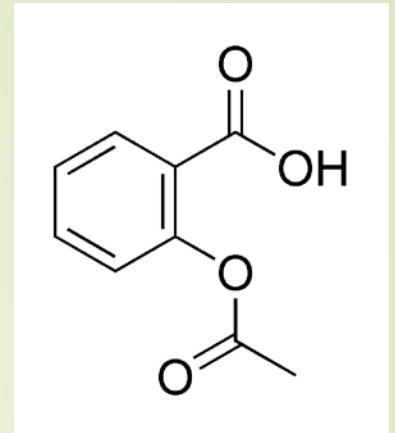
Why is levetiracetam \$5.09 and  
Phenobarbital 8 – 9¢



# Cost of New Drug Creation

## 3 step process

- Step 1: Preclinical evaluations:
  - New chemical entities (NCEs) are identified.
  - The NCEs are assessed for:
    - Chemical make-up
    - Stability
    - Solubility
    - Pharmacodynamics
    - Pharmacokinetics.



## Step 2: FDA Regulatory Requirements must be fulfilled

- ▶ Animal pharmacology and toxicology studies.
- ▶ Manufacturing information: Can the medication be reliably made in large quantities and remain stable?
- ▶ Clinical protocols must be submitted.
- ▶ Information about the investigator needs to be reviewed.



# Step 3: Clinical Trials

Phase	Aim	Notes
Phase 0	Documentation of pharmacodynamics and pharmacokinetics in humans	Single subtherapeutic doses of the study drug are given to 10 – 15 subjects. The trial documents: absorption, distribution, metabolism, and excretion of the drug, and the drug's interactions within the body. Confirmation that these are as expected.
Phase 1	Screening for safety.	Testing of 20 – 80 people to evaluate safety, determine safe dosage ranges, and begin to identify side effects. Phase 1 trials are not expected to identify all side effects.
Phase 2	Establishing the efficacy of the drug, usually against a placebo.	Testing with 100 – 300 people to see if it is effective and to further evaluate its safety.
Phase 3	Final confirmation of safety and efficacy.	Testing with 1,000 – 3,000 people to confirm effectiveness, monitor side effects, and compare it to commonly used treatments.
Phase 4	Safety studies during sales.	Postmarketing studies providing additional information, including the treatment's risks, benefits, and optimal use.

# Final Valuation

- ▶ The full cost from discovery to market is complex and controversial. Complicating factors include:
- ▶ High attrition rates
  - ▶ Of 5,000 – 10,000 NCEs, 250 will be tested in laboratory animals.
  - ▶ Of the 250 compounds tested on animals 10 will qualify for human testing.
  - ▶ Of the 10 that make Phase 1 clinical trials, 2 will make it to market.
- ▶ Long timelines:
  - ▶ Most drugs take 8 - 10 years to go through the entire process.
- ▶ Large capital expenditures:
  - ▶ 2003 – estimated cost 800 million dollars
  - ▶ 2006 – estimated cost 1 billion dollars.
  - ▶ 2010 – estimated cost 1.2 billion dollars.
  - ▶ 2013 – estimated cost 5 billion dollars.





Where does all that money go?!



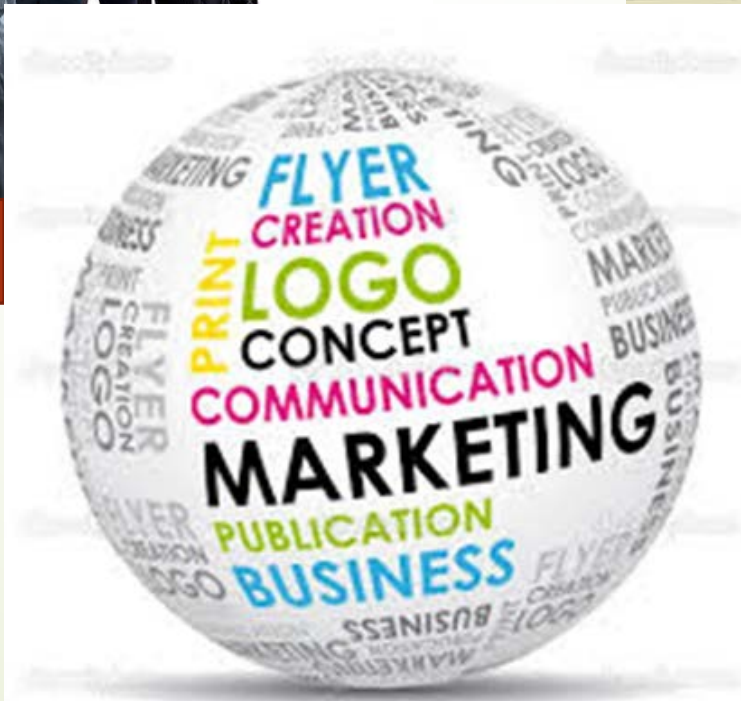
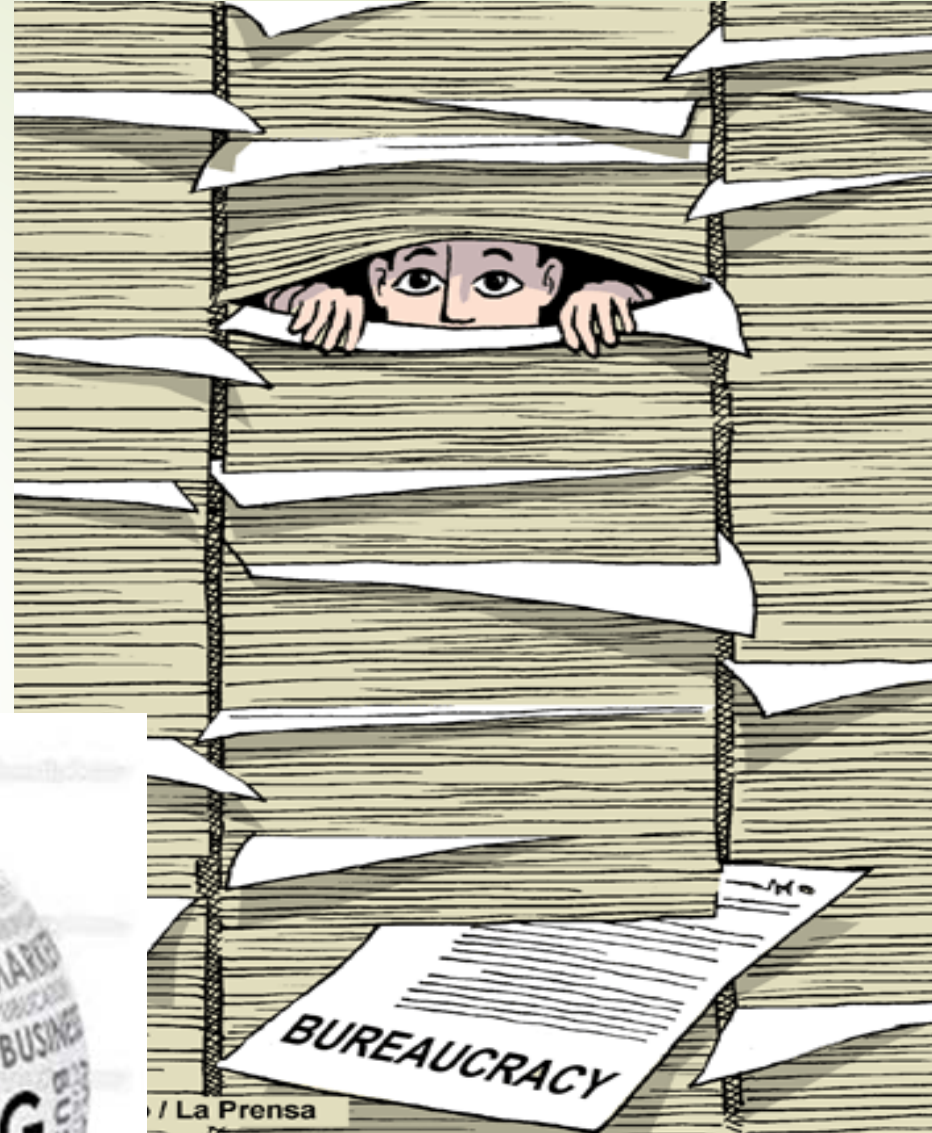
# Reality



More



Pharmaceutical industry employees





DEWEY, CHEETUM, AND HOWE  
Attorneys at Law




# Another “dose” of reality

- ▶ \$100,000,000 price tag for development of drug X.
  - ▶ 10,000,000 patients have a disorder potentially treatable by drug X.
    - ▶ Cost of drug - \$10 per pill.
    - ▶ Metoprolol 7 - 20¢ per tablet
  - ▶ 10,000 patients have a disorder potentially treatable by drug X.
    - ▶ Cost of drug - \$10,000 per pill
    - ▶ Rituximab - \$4,078 per 10 mg (1000 mg every 2 weeks for Rheumatoid Arthritis)
- ▶ Duration of the need for medication will affect cost.

# Other options for treatment





# Other therapeutic options for epilepsy treatment

- ▶ Dietary therapy
- ▶ Vagus Nerve Stimulator
- ▶ Responsive Nerve Stimulator
- ▶ Temporal lobectomy
- ▶ Corpus callosotomy

# Dietary therapies

- Requires a team approach
  - Dietician
  - Physician
  - Nurse
  - Foods and possibly formula
  - Scale
  - Routine blood tests



  
**KEEP  
CALM  
AND ASK A  
REGISTERED  
DIETITIAN**



# Vagus Nerve Stimulator

Acta Neurol Belg. 1999 Dec;99(4):275-80.



- Average implantation cost \$20,000
- **Cost-benefit of vagus nerve stimulation for refractory epilepsy.**
  - Mean seizure frequency: ↓ from 14 seizures/month (2 - 40) to 9 seizures/month (0 - 30) ( $p = 0.0003$ ).
  - Yearly related direct medical costs per patient: ↓ \$6,682 (\$829 - \$21,888 USD) to \$3,635 (\$684 - \$12,486 USD) ( $p = 0.0046$ ).
  - Mean number of days of hospital admissions: ↓ from 16 days/year (0 - 60) to 4 days/year (0 - 30) ( $p = 0.0029$ ).
- Downside:
  - Responder rate is ~40%.
  - Unable to test effectiveness in advance.



# Vagus Nerve Stimulator

**J Neurosurg 115:1248–1255, 2011**

- ▶ Meta-analysis of studies.
- ▶ Seizure reduction was  $36.2\% \pm 0.5\%$  in 1178 patients seen  $\leq 1$  year after surgery
- ▶ Seizure reduction was  $51.0\% \pm 0.5\%$  for 1247 patients seen  $> 1$  year postoperatively.
  - ▶ Tuberos sclerosis seizure reduction  $68.1\% \pm 4.6\%$
  - ▶ Lennox-Gastaut syndrome or other epileptic encephalopathies had a reduction of  $47.8\% \pm 1.9\%$ .

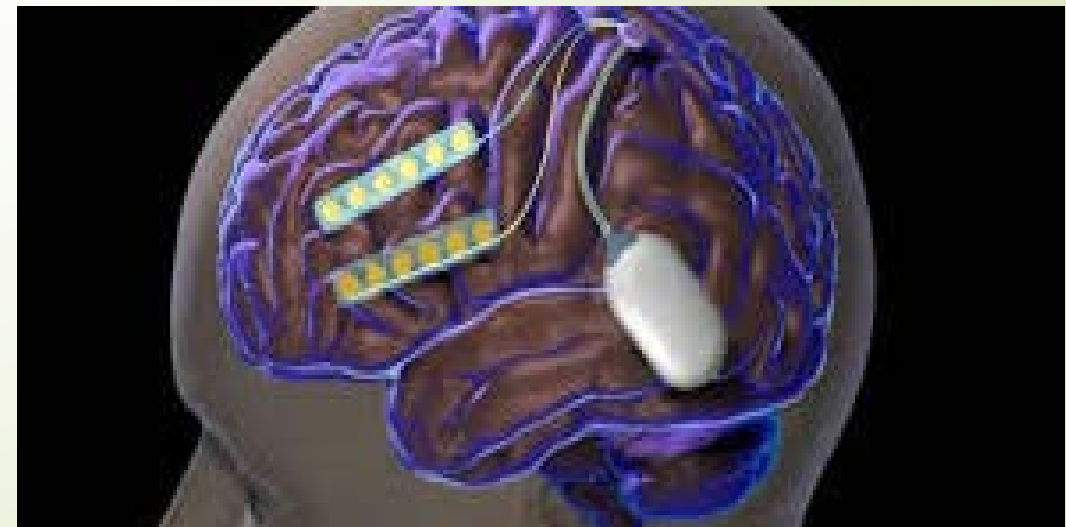
# Responsive cortical stimulation for the treatment of medically intractable partial epilepsy.


[Neurology](#). 2011 Sep 27;77(13):1295-304

## Mean % change in seizure freq. during the blinded eval. per., intent-to-treat population

Blinded evaluation period	Treatment (n 97)	Sham(n 94)	p Value
Mean%change from preimplant period			
<b>Entire BEP (n 191)</b>	37.9% (46.7%, 27.7%)	17.3% (29.9%, 2.3%)	0.012
<b>Month 1 (3rd month postop)</b>	34.2% (44.1%, 22.6%)	25.2% (37.1%, 11.1%)	0.279
<b>Month 2 (4th month postop)</b>	38.1% (47.3%, 27.3%)	17.2% (30.5%, 1.3%)	0.016
<b>Month 3 (5th month postop)</b>	41.5% (52.0%, 28.7%)	9.4% (29.5%, 16.4%)	0.008

Abbreviations: BEP blinded evaluation period





# Responsive Neuro-Stimulator (RNS)

- ▶ Average cost \$35,000 to \$40,000
- ▶ Seizure frequency decrease ranged from 40 – 70%.
- ▶ Downside:
  - ▶ Only 1 or 2 seizure foci
  - ▶ Battery only lasts 3 – 5 years
  - ▶ Limited number of institutions available (NM without any)



# Resective Surgery

- ▶ Video EEG monitoring
    - ▶ Determine localization
    - ▶ Determine events are seizures
  - ▶ Magneto-Encephalography
  - ▶ Positron Emission Tomography
  - ▶ Intracranial monitoring
  - ▶ Wada Testing
  - ▶ Surgery
- ▶ Cost is highly variable dependent on:
    - ▶ The institution involved.
    - ▶ The number of studies needed.

# Extra-temporal Surgical Resection outcome

J Neurosurg. 2006 Apr;104(4):513-24 and e-medicine review

- ▶ 372 (93%) underwent temporal and 27 (7%) had extratemporal resection
- ▶ Engle Class 1 surgery outcome:
  - ▶ Seizure free or no more than a few early, nondisabling seizures
  - ▶ or seizures upon drug withdrawal only
- ▶ 55% of seizure recurrences occurred within 6 months of surgery
- ▶ 93% of seizure recurrences occurred within 2 years after surgery.

	6 months	1 year	2 years	5 years	10 years
Temporal Resection	83% (80-87%)	80% (76-85%)	78% (74-83%)	76% (71-81%)	74% (69-79%)
Extratemporal Resection	50% (34-74%)				42% (26-66%)
	Brain. 2007 Feb. 130:574-84.	56%	45%	30%	



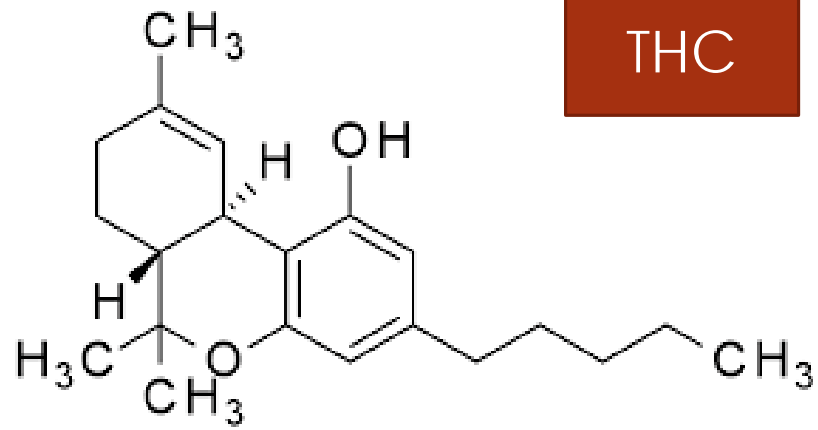
# Corpus callosotomy

- ▶ Corpus callosotomy is a palliative procedure to limit or modify tonic/atonic seizures
- ▶ The seizures still occur as partial seizures, but they do not result in falls.
- ▶ 80% average reduction in tonic/atonic seizures resulting in falls
- ▶ 50% reduction in generalized tonic and tonic-clonic seizures
- ▶ 50% atypical absence seizures
- ▶ Overall, success rates are similar between children and adults
- ▶ Effects are sustained long term.





# Medical Cannabis



THC





# History



- Initially used in China 5,000 BC
  - Malaria
  - Constipation
  - Rheumatic pain
  - Absentmindedness
  - "female disorders"
  - Mixed with wine and resin it was used as an analgesic in surgery
- Uses in ancient India and Africa:
  - "Quickens the mind"
  - Lowers fever
  - Induce sleep
  - Cures dysentery
  - Appetite stimulation
  - Improve digestion
  - Relieve headaches
  - Cures venereal disease



# History

- ▶ WB O'Shaughnessy - The first western physician to take an interest in cannabis as a medicine.
  - ▶ A professor at the Medical College of Calcutta, India.
  - ▶ Observed its use in India.
- ▶ He gave cannabis to animals, to ensure it was safe
- ▶ Began to using it with patients suffering from:
  - ▶ rabies
  - ▶ rheumatism
  - ▶ epilepsy
  - ▶ tetanus
- ▶ In his report in 1839 he wrote:
  - ▶ "A tincture of hemp" (a solution of cannabis in alcohol, taken orally) is an "impressive analgesic."
  - ▶ "An anticonvulsant remedy of the greatest value."

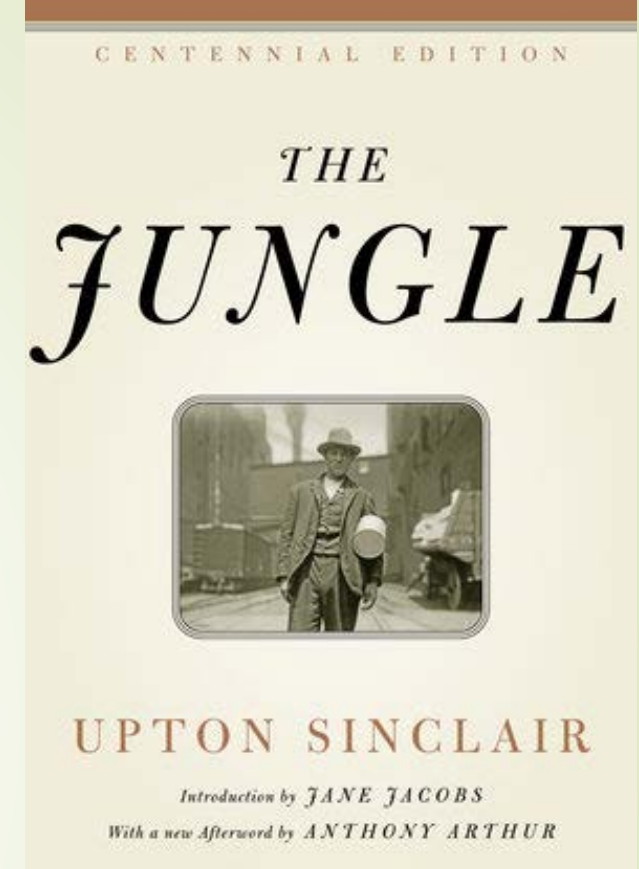
# The corner drug store in the late 1800s

- Marijuana
- Cocaine
- Heroin
- Morphine
- Alcohol



# Series of laws

- ▶ Pure Food and Drug Act of 1906
  - ▶ Signed into law by Theodore Roosevelt
  - ▶ Limited interstate food and drug transport
  - ▶ Identified 10 substances deemed addictive or dangerous.
  - ▶ Validated what was in the drugs.
  - ▶ Enforced by the Bureau of Chemistry.
- ▶ Federal Meat Inspection Act of 1906
  - ▶ Demanded truth in labeling
  - ▶ Monitored sanitation practices
- ▶ The 18<sup>th</sup> Amendment
  - ▶ Signed January 16, 1919
  - ▶ Took effect on January 16, 1920.



- Food and Drug Administration – 1930

- Replaced the Bureau of Chemistry.

- The 21<sup>st</sup> Amendment –

- Repealed - Dec. 5, 1933

- Food, Drug, and Cosmetic Act (1938)

- Johnson's Mild Combination Treatment for Cancer

- Banbar treatment for Diabetes

- Elixer Sulfanilamide

- Signed by FD Roosevelt



- Kefauver-Harris Drug Amendments

- Thalidomide – 1962

- Comprehensive Drug Abuse Prevention and Control Act of 1970:

- Broke drugs into 5 categories based on

- Potential for abuse

- Medical use

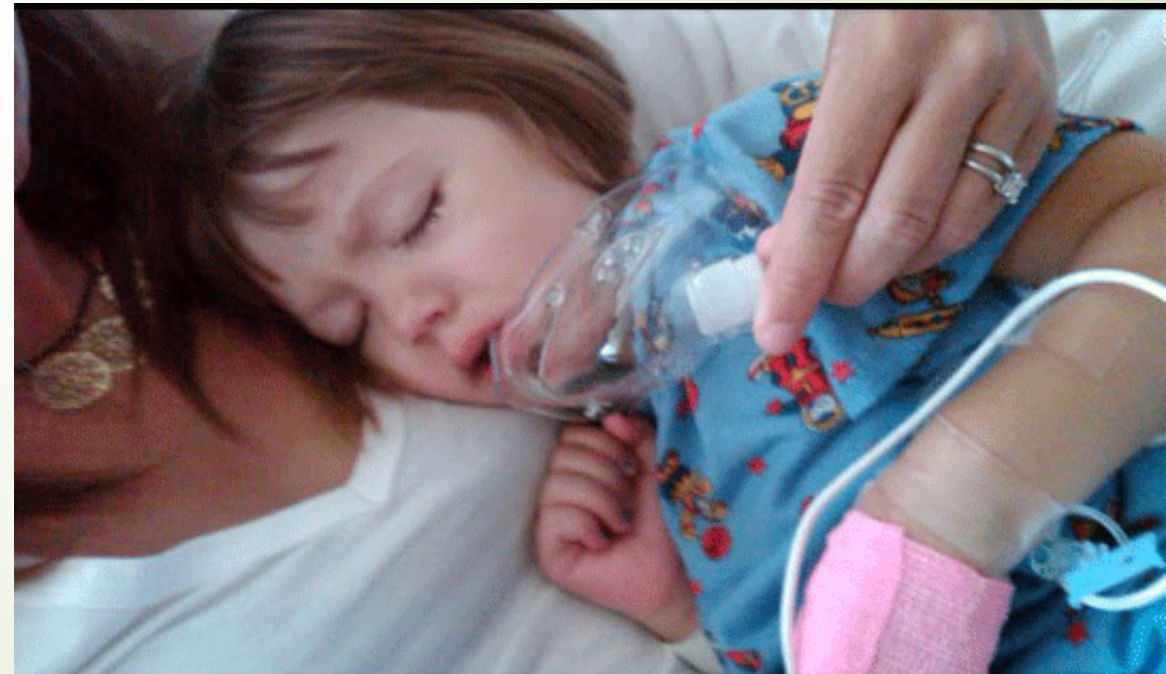
- Safety



U.S. Food and Drug Administration  
Protecting and Promoting *Your* Health

# Here we are today!

- ▶ Charlotte Figi
  - ▶ Onset of seizures at 3 months of age.
  - ▶ Diagnosed with SCN1A mutation – Dravet Syndrome.
  - ▶ Lost skills and by age 5 years was:
    - ▶ G-Tube dependent
    - ▶ Struggled to walk and talk
    - ▶ Full assist with ADLs
    - ▶ 50 GTC seizures daily.





Mom heard about Medical Cannabis

She researched the literature

CBD Oil seemed to be effective

Found two brothers who were developing high CBD strain of Cannabis.



# 20 months after beginning “Charlottes Web”

- Only 2 – 3 nocturnal seizures per month
- Eating and drinking by mouth independently
- Sleeping soundly through the night
- Autistic behaviors have improved.
- Walking and talking again.





# Two main branches to Cannabidiol

## $\Delta_9$ Tetrahydrocannabinol (THC)

- Identified in 1990
- Affects CB<sub>1</sub> Receptors on the brain
- Conflicting reports re: anticonvulsant properties
- Psychotropic side effects – rate limiting

## Cannabidiol (CBD)

- Believed to affect multiple receptors
- Does not have clear toxic side effects
- Does not possess psychotropic effects
- More consistently anticonvulsant.
- Seems to possess anxiolytic effects
- Although it doesn't have psychotropic effects, it is still classified as a class one medication



# Studies



## Cunha JM et al, Pharmacology 1980;21:175-85

- ▶ Phase 2 trial
- ▶ 15 patients all with intractable FOE
- ▶ 8 randomized to 200 – 300 mg CBD oil daily and 7 placebo
- ▶ Duration 4.5 months
- ▶ 4 “almost seizure free”, 3 “partial improvement, 1 “worse”.
- ▶ Placebo arm – 1 “almost seizure free”

## Ames & Cridland, South African Med Journ. 1985;69:14

- ▶ 12 patients with DD and intractable seizures
- ▶ 6 subjects - 200 mg cannabidiol and 6 subjects - sunflower oil.
- ▶ test duration - 3 weeks
- ▶ Seizure activity - unchanged.
- ▶ Those on cannabis had mild drowsiness

# Further studies

## Porter & Jacobson, Epilepsy and Behavior 2013; 29:574-577

- ▶ 24 question online survey
- ▶ offered on Facebook support group
- ▶ 150 parents supporting Medical cannabis
- ▶ 20 responses received.
  - ▶ 13 w/ Dravet syndrome
  - ▶ 4 w/ Doose syndrome
  - ▶ 1 w/ Lennox Gastaut syndrome
- ▶ 2nd survey with same questions regarding Stiripentol.

## Hussain SA et al, Epilepsy and Behavior 2015;47:138-141

- ▶ Online survey
- ▶ Multiple online forums targeting groups involved with Infantile Spasms and Lennox Gastaut syndrome
- ▶ 200 unique responses received 117 met criteria
  - ▶ 45 w/ infantile spasms
  - ▶ 24 w/ Lennox Gastaut syndrome
  - ▶ 15 w/ Dravet syndrome
  - ▶ 5 w/ Doose syndrome
  - ▶ 44 unknown

# Study results

## Porter & Jacobson

Seizure syndrome	seizure free	improved control	no change	worse
IS and LGS	13%	79%	8%	0
Dravet	13%	60%	13%	13%
others	15%	69%	10%	6%

Adverse effects: increased appetite, wt gain, and drowsiness

Positive effects: Improved sleep, increased alertness, better mood

## Hussain SA et al

- 16 of 19 reported seizure reduction
  - 2 of 16 report child is seizure free
  - 8 > 80% reduction
  - 3 > 50% reduction
  - 3 > 25% reduction
- 3 of 19 report no change
- Adverse effects: drowsiness and fatigue
- Positive effects: better mood, increased alertness, better sleep, and decreased self-stimulation.



# Parental reporting of response to oral cannabis extracts for treatment of refractory epilepsy

Press, CA, Knupp, KG, and Chapman, KE. *Epilepsy and Behavior* 2015;45:49 - 52

- ▶ Retrospective chart review - 75 patients
  - ▶ 34 had moved to Colorado to obtain medical cannabis
- ▶ 43 (57%) reported at least some improvement in seizures
- ▶ 25 (33%) reported a >50% reduction in seizures
- ▶ Seizure syndromes:
  - ▶ one with STXBPA1 mutation had worsening of seizure
  - ▶ one with ESES didn't have any change.
  - ▶ 3/13 (23%) w/ Dravet syndrome >50% response
  - ▶ 0/3 (0%) w/ Doose syndrome
  - ▶ 8/9 (89%) w/ Lennox Gastaut syndrome >50% response

# Press CA et al - conclusions

- ▶ 33% reported seizure reduction of more than 50% in response to Cannabis extracts
  - ▶ Colorado residents – 22% seizure reduction of  $\geq 50\%$
  - ▶ Families that moved to Colorado to obtain medical cannabis - 47% seizure reduction of  $\geq 50\%$ .
  - ▶ Four FDA medications and placebo improvement rates:
    - ▶ Clobazam – 31.6%
    - ▶ Perampanel – 26.4%
    - ▶ Esclicarbazepine – 20%
    - ▶ Ezogabine 21%
  - ▶ EEG activity did not improve



# PROBLEMS!!!!

- Significant patient/parent bias
- CBD vs THC and combination ratios unknown
  - Is it really CBD or THC?
  - Who is checking what is in the bottle?
- Cannabis is still a Class 1 medication.







# One other problem

## Affect on developing brains?!

Honarmand K et al, Neurology  
2011;76:1153-60


- ▶ 2 groups of pts with MS
  - ▶ Cannabis users - 25
  - ▶ Non-cannabis users - 25
- ▶ Battery of neuropsych testing
  - ▶ Working memory
  - ▶ Processing speed
  - ▶ Executive functions
  - ▶ Visuospatial perception
- ▶ Cannabis users did significantly worse compared to non-users.

Pavisian B et al, Neurology  
2014;82:1879-87.

- ▶ 2 groups of patients with MS
  - ▶ Cannabis users - 20
  - ▶ Non-cannabis users - 19
- ▶ Underwent functional MRI with neuropsych testing
- ▶ Cannabis users did worse.
- ▶ fMRI showed:
  - ▶ Disorderly pattern of cerebral activation in cannabis users
  - ▶ Attempt to compensate with increased task complexity?



# Conclusion:

- Medical Cannabis – Probably has a place in treating epilepsy
  - Intriguing response in patients with Dravet and Lennox Gastaut syndrome
  - Further testing should be done
  - Will it be greater than any other treatment previously seen?
  - What will be the cost?
- 

Questions?

