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:

<table>
<thead>
<tr>
<th>Type of Potential Conflict</th>
<th>Details of Potential Conflict</th>
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<tbody>
<tr>
<td>Grant/Research Support</td>
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<tr>
<td>Consultant</td>
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<td>Speakers' Bureaus</td>
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<td>Financial support</td>
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<td>Other</td>
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3. The material presented in this lecture has no relationship with any of these potential conflicts, OR

4. This talk presents material that is related to one or more of these potential conflicts, and the following objective references are provided as support for this lecture:

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

<table>
<thead>
<tr>
<th>Medication Name</th>
<th>Generic vs Brand name</th>
<th>individual</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>$63 - $68</td>
<td>31 ¢</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>$158 - $435</td>
<td>$1.23 – $5.09</td>
</tr>
<tr>
<td>Perampanel</td>
<td>$610 - $712</td>
<td>N/A</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>$27 - $1011</td>
<td>$8 - 9 ¢</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>$18 - $28</td>
<td>39 - 51 ¢</td>
</tr>
<tr>
<td>Topiramate</td>
<td>$147 - $506</td>
<td>$1.31 - $2.08</td>
</tr>
<tr>
<td>Valproic Acid</td>
<td>$17 - $124</td>
<td>27 ¢ – $2.21</td>
</tr>
<tr>
<td>Valproate ER</td>
<td>$107 - $165</td>
<td>N/A</td>
</tr>
</tbody>
</table>
Why the markup?
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

<table>
<thead>
<tr>
<th>Phase 0</th>
<th>Documentation of pharmacodynamics and pharmacokinetics in humans</th>
<th>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.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 1</td>
<td>Screening for safety.</td>
<td>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.</td>
</tr>
<tr>
<td>Phase 2</td>
<td>Establishing the efficacy of the drug, usually against a placebo.</td>
<td>Testing with 100 – 300 people to see if it is effective and to further evaluate its safety.</td>
</tr>
<tr>
<td>Phase 3</td>
<td>Final confirmation of safety and efficacy.</td>
<td>Testing with 1,000 – 3,000 people to confirm effectiveness, monitor side effects, and compare it to commonly used treatments.</td>
</tr>
<tr>
<td>Phase 4</td>
<td>Safety studies during sales.</td>
<td>Postmarketing studies providing additional information, including the treatment's risks, benefits, and optimal use.</td>
</tr>
</tbody>
</table>
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?!

Big Pharma
Reality
More

Pharmaceutical industry employees
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
Vagus Nerve Stimulator


- 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.
Meta-analysis of studies.

Seizure reduction was 36.2% ± 0.5% in 1178 patients seen ≤ 1 year after surgery.

Seizure reduction was 51.0% ± 0.5% for 1247 patients seen > 1 year postoperatively.

- Tuberous sclerosis seizure reduction 68.1% ± 4.6%
- Lennox-Gastaut syndrome or other epileptic encephalopathies had a reduction of 47.8% ± 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

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

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.

<table>
<thead>
<tr>
<th></th>
<th>6 months</th>
<th>1 year</th>
<th>2 years</th>
<th>5 years</th>
<th>10 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temporal Resection</td>
<td>83% (80-87%)</td>
<td>80% (76-85%)</td>
<td>78% (74-83%)</td>
<td>76% (71-81%)</td>
<td>74% (69-79%)</td>
</tr>
<tr>
<td>Extrateminal Resection</td>
<td>50% (34-74%)</td>
<td></td>
<td></td>
<td></td>
<td>42% (26-66%)</td>
</tr>
<tr>
<td>Brain. 2007 Feb. 130:574-84.</td>
<td>56%</td>
<td>45%</td>
<td>30%</td>
<td></td>
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</tr>
</tbody>
</table>
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

[Chemical structure of THC]

[Image of cannabis leaf]

[Image of CBD oil bottle]
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 18th Amendment**
  - Signed January 16, 1919
  - Took effect on January 16, 1920.
Food and Drug Administration – 1930
- Replaced the Bureau of Chemistry.

The 21st 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
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 Cannabis

$\Delta_9$ Tetrahydrocannabinol (THC)
- Identified in 1990
- Affects $\text{CB}_1$ Receptors on the brain
- Conflicting reports re: anticonvulsant properties
- Psychotropic side effects - rate limiting

Cannabadiol (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”

- 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

<table>
<thead>
<tr>
<th>Seizure syndrome</th>
<th>seizure free</th>
<th>improved control</th>
<th>no change</th>
<th>worse</th>
</tr>
</thead>
<tbody>
<tr>
<td>IS and LGS</td>
<td>13%</td>
<td>79%</td>
<td>8%</td>
<td>0</td>
</tr>
<tr>
<td>Dravet</td>
<td>13%</td>
<td>60%</td>
<td>13%</td>
<td>13%</td>
</tr>
<tr>
<td>Others</td>
<td>15%</td>
<td>69%</td>
<td>10%</td>
<td>6%</td>
</tr>
</tbody>
</table>

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 seizures
  - 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 ≥50%
  - Families that moved to Colorado to obtain medical cannabis - 47% seizure reduction of ≥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?!

Honamand 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.

- 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?