Disclosures

• Off-label therapies will be discussed
• I have a bias against expensive medications and procedures
• I will discuss a medical technology only available in Omaha at CHI
• I will discuss some but not all providers of DBS technology
Origins

- First described in 1817 by James Parkinson: “Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forward, and to pass from a walking to a running pace: the senses and intellects being uninjured.”
- Charcot, 1872: “even a cursory exam demonstrates that their problem relates more to slowness in execution of movement rather than to real weakness. In spite of tremor, a patient is still able to do most things, but he performs them with remarkable slowness. Between the thought and the action there is a considerable time lapse.”
- Gowers, 1888: “The movement of the fingers at the metacarpal-phalangeal joints is similar to that by which Orientals beat their small drums.”

Tremor
Bradykinesia

Gait changes
Stats

- Age of onset:
  - <4% less than 50
  - Likelihood increases with age
- Male to female ratio: **1.5:1**
  - 50 to 59 years old: 3:1
- US prevalence:
  - 680,000 individuals in the US aged ≥45 years with PD in 2010
  - This is **572 per 100,000 over 45**
  - Predicted 930,000 in US by 2020
  - Approaching the number of people with Type I Diabetes in the US
- US incidence: 60,000 new cases a year

Nebraska Parkinson’s disease registry

- Report PD patients within 60 days of diagnosis
  - Demographics
  - Date of diagnosis
- Estimated prevalence of 329.3 per 100,000 in 2004, about 6000 people, highest per-capita of any state at that time
Legend
Parkinson’s Disease Patients
- 0 - 19
- 20 - 67
- 68 - 147
- 148 - 292
- 293 - 600
- 601 - 2815

The registry began collecting data in 1997.

Nebraska
Out-of-State
Total Cases
15,053
574
15,627

Diagnosis of PD based on physician office confirmation or death certificate.

Registry was terminated from Oct. 2004 - Feb. 2006 due to lack of funding.

NEBRASKA
Good Life. Great Mission.
DEPT. OF HEALTH AND HUMAN SERVICES

Prevalence, pred
($10^6$, $10^7$)
- $1.175$
- $1.323$
- $2.085$
- $3.287$
- $13.860$
Pathophysiology of PD
Is PD an Autoimmune Disease?

- Mice with mutations that cause PD in humans do not get PD symptoms unless they get a gut infection when young
- Found reactive T-cells in brains, suggesting that PD may be an autoimmune disease triggered by a gut infection
- New: Microglia are critically involved in the cell-to-cell transfer of alpha-synuclein

Risk Factors: Smoking and Peppers

- Active smokers have 50% lower risk of PD compared to never smokers
- PD risk decreases with increasing duration of smoking and increases again with time since quitting
- People who ate higher levels of edible Solanaceae (nightshade family) had a lower risk of Parkinson's disease in comparison to those who did not eat as much
  - Peppers
  - Tomatoes
  - Eggplant
  - Potatoes
Predictors of PD

- Dream enactment
  - 50% of those with RBD will get PD or dementia within 10 years
- Anosmia
- Constipation
- Depression/Anxiety
- PD personality
  - Low novelty seeking: secondary to low dopamine?
  - High harm avoidance: secondary to depression?
  - Higher levels of Neuroticism, but lower levels of Openness and Extraversion

Diagnosing PD

- Clinical diagnosis: not perfect
- 2016 study: Accuracy of clinical diagnosis performed by movement disorders experts rose from 79.6% on initial assessment to 83.9% of refined diagnosis after follow-up
Diagnosing PD

- Clinical diagnosis with a levodopa trial
- DAT scan
  - FDA approved to distinguish between ET and PD
  - Might be helpful in sorting drug-induced parkinsonism from PD

Normal DaT density
Possible nonparkinsonian syndrome

Abnormal DaT density
Possible parkinsonian syndrome

DaTscan will be distributed in the striata and appear as mirrored comma or crescent shapes if dopamine neurons are intact or not affected. A decrease in DaTscan activity will result in period or oval shapes and reduced image intensity on one or both sides.
MIBG Cardiac SPECT
Measures cardiac sympathetic denervation
80-95% sensitive and specific for PD/DLB

<table>
<thead>
<tr>
<th>Name of Drug</th>
<th>Stop Taking</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxapine</td>
<td>4 days before</td>
</tr>
<tr>
<td>Benztrapine</td>
<td>3 days before</td>
</tr>
<tr>
<td>Cogentin</td>
<td>3 days before</td>
</tr>
<tr>
<td>Bupropion (Aplenzin, Budeprion, Voxra, Wellbutrin, Zyban)</td>
<td>48 hours before</td>
</tr>
<tr>
<td>Buspirone</td>
<td>15 hours before</td>
</tr>
<tr>
<td>Citalopram</td>
<td>24 hours before</td>
</tr>
<tr>
<td>Cocaine</td>
<td>6 hours before</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>24 hours before</td>
</tr>
<tr>
<td>Methamphetamine</td>
<td>24 hours before</td>
</tr>
<tr>
<td>Methylphenidate (Concerta, Metadate, Methylin, Ritalin)</td>
<td>20 hours before</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>24 hours before</td>
</tr>
<tr>
<td>Selegiline</td>
<td>48 hours before</td>
</tr>
<tr>
<td>Sertraline</td>
<td>3 days before</td>
</tr>
</tbody>
</table>
Transcranial ultrasound

- Li et al: Overall diagnostic accuracy of TCS in differentiating PD from normal controls: pooled sensitivity of 0.83 and a pooled specificity of 0.87

Skin Biopsy

- Medial forearm and back of neck might be the best sites
- Staining for phosphorylated alpha synuclein has yielded 100% specificity and high sensitivity in various studies
- Methodologically tricky; not ready yet for prime time
- Cannot distinguish between the synucleinopathies (DLB, PD, Pure autonomic failure), BUT
- In Multiple Systems Atrophy, the alpha-synuclein was in a different place than in PD: in somatosensory fibers, not autonomic fibers as in PD
Treatment of PD

- **Levodopa**
  - First tried in 1961
  - FDA approved in 1968
  - Carbidopa/levodopa (Sinemet) became available in 1973
    - Carbidopa is a dopa decarboxylase inhibitor
    - Remains the strongest drug for PD 45 years after inception

My treatment approach
Levodopa management

- Titration begins at 0.5 tablets TID
- Empty stomach = 1 hour before or 2 hours after meals
- Sinemet CR for nighttime symptoms: 70% bioavailable
- I add entacapone and/or dopamine agonists once early-wearing off or motor fluctuations develop
- I treat dyskinesias with amantadine or levodopa reduction
- THERE IS NO UPPER LIMIT ON LEVODOPA DOSE PER DAY NO MATTER WHAT EPIC OR THE INSURANCE COMPANIES TELL YOU

Homocysteine

- Levodopa therapy causes elevated homocysteine
- Homocysteine is associated with heart attack and stroke
- Lowering homocysteine in PD with folate/B6/B12 combo supplements may decrease complications such as:
  - Cognitive decline (those with high Hcy levels decline faster)
  - Peripheral neuropathy:
    - “In a comparison between patients with and without neuropathy, the levodopa dose was higher, serum vitamin B12 levels were lower, and homocysteine levels were higher in the patients with neuropathy”
New therapy: Almost the same as old therapy

- Rytary (C/L ER)
- Compared with CL + E, IPX066 demonstrated a lower percent "off" time (24.0% vs. 32.5), lower "off" time (3.8 vs. 5.2 h/day), and higher "on" time without troublesome dyskinesia (11.4 vs. 10.0 h/day)
- So **1.4 hours more on time/day** than Stalevo
### Rytary

<table>
<thead>
<tr>
<th>Total daily dose of levodopa in immediate-release carbidopa-levodopa</th>
<th>RECOMMENDED STARTING DOSAGE of RYTARY (carbidopa / levodopa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>400 mg to 549 mg</td>
<td>RYTARY 23.75 mg / 96 mg 3 caps taken TID</td>
</tr>
<tr>
<td>550 mg to 749 mg</td>
<td>RYTARY 23.75 mg / 96 mg 4 caps taken TID</td>
</tr>
<tr>
<td>750 mg to 949 mg</td>
<td>RYTARY 36.25 mg / 145 mg 3 caps taken TID</td>
</tr>
<tr>
<td>950 mg to 1249 mg</td>
<td>RYTARY 48.75 mg / 195 mg 3 caps taken TID</td>
</tr>
<tr>
<td>≥1250 mg</td>
<td>RYTARY 61.25 mg / 245 mg 3 caps taken TID</td>
</tr>
</tbody>
</table>

TID: three times daily.

**Prices and coupons for 120 tablets of carbidopa / levodopa 25mg/100mg**

<table>
<thead>
<tr>
<th>Store</th>
<th>Price</th>
<th>Get Coupon</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hy Vee</td>
<td>$20.94</td>
<td>GET FREE COUPON</td>
</tr>
</tbody>
</table>

With free coupon

<table>
<thead>
<tr>
<th>Store</th>
<th>Price</th>
<th>Get Coupon</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hy Vee</td>
<td>$1,035</td>
<td>GET FREE COUPON</td>
</tr>
<tr>
<td></td>
<td>$859.41</td>
<td>GET FREE COUPON</td>
</tr>
</tbody>
</table>

(*est retail price with free coupon)*

### Dyskinesias

[Image of a person with dyskinesias symptoms]

*Supplement to Arch Neurol. 2010;66(11):114-115. © AMA.*
Dyskinesias

• The 5-year risk of dyskinesias was 50% in patients with disease onset between 40–59 years of age as compared to 16% in those with disease onset after 70 years.

• Dyskinesias develop at a mean daily dose of 387 mg.

• Genetic polymorphism of the dopamine receptor D2 gene \( \rightarrow \) reduced risk of dyskinesias.

• Reduced by:
  • Reducing daily levodopa dose
  • Amantadine reduces the duration of LID by 60%
  • Dopamine agonists/COMT inhibitors
  • DBS

New therapy: Almost the same as old therapy

• Amantadine CR (Gocovri)

• Amantadine ER reduced on-time with troublesome dyskinesias by about 1.5 hours per day, from a baseline of about 4.6 hours.
Pimavanserin (Nuplazid)

- Approved by the FDA in 2016
- First-in-class atypical antipsychotic that does not induce clinically significant antagonism of dopaminergic, adrenergic, histaminergic, or muscarinic receptors
- First FDA-approved drug indicated for the treatment of the hallucinations and delusions in PD-associated psychosis.

<table>
<thead>
<tr>
<th>Dosage</th>
<th>Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>25 mg</td>
<td>$16.22 from 100 oral tablet</td>
</tr>
<tr>
<td>17 mg</td>
<td>$2,909.73 from 60 oral tablet</td>
</tr>
</tbody>
</table>

Psychosis in PD
Deep Brain Stimulation = “Deep Brain Deactivation”

- Can get DBS now after just four years into diagnosis
- Rechargeable Batteries
  - Last 15 years instead of 3-5 years
- Easier to get MRI-scans now
- Many companies working on feedback loops for auto-adjustment

Vercise™ DBS System Stimulation Control

16 independent current sources for customizable stimulation:
Fine control of stimulation position and shape

Fine adjustment of stimulation between contacts gives you the ability to quickly locate and confine stimulation to the desired area.

Results from different clinical investigations are not directly comparable. Information provided for educational purposes only.

Focused Ultrasound Thalamotomy: FDA approved for PD tremor in 2018

Future therapy for dyskinesias

- Dyskinesias involve the serotonergic system and mGluR5 glutamate receptors
- **Eltoprazine**
  - partial 5-HT1A/5-HT1B receptor agonist
- **Buspirone (phase III)**
  - We now know this is a 5HT1A agonist
- **Dipraglurant** (although a relative, mavoglurant, failed)
  - mGluR5 negative allosteric modulator
- **IRL790**
  - “Psychomotor stabilizer” targeting D3 receptors; may treat dyskinesias and psychosis
Neuroprotection in PD

• BDNF or GDNF
  • Multiple failed trials:
    • Recombinant protein administration into the brain (infusion, injection)
    • Adeno-associated virus vector delivery
  • Stem cells most promising recent attempt

Forced exercise

1 hour/ day
3 times a week
8 weeks

30%
Neuroprotection in PD

Nilotinib (Tasigna)

Tyrosine kinase inhibitor similar to Gleevec (imatinib), treatment for CML

Modulates dopamine levels and metabolism, as well as prevents the formation of toxic alpha-synuclein aggregates

In Phase II trials

May affect inflammation and oxidative stress

33% reduction in PD incidence among persons with high serum urate level