Parkinson’s Disease and Prevention
A Public Health Approach

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Preventing Parkinson’s Disease

1ary Prevention

- Prevent PD
- Pathogenesis
- Preserve Health

2ary Prevention

- Prevent Prodromal Symptom Onset
- Stop Symptom Progression
- Prevent parkinsonism/dementia onset

3ary Prevention

- Prevent progression of disease: parkinsonism, dyskinesias, dementia, etc.
- Prevent consequences of PD: Fractures, pneumonia

HEALTH  PRECLINICAL  PRODROMAL PD  PARKINSON’S DISEASE
Primary Prevention

• Remove or mitigate the cause(s) of Parkinson’s disease

• The disease process does not occur

https://cursos.campusvirtualsp.org
What Causes Parkinson’s Disease?
Some Factors Associated with a Higher Risk of Parkinson’s Disease

- Pesticides
- Polychlorinated Biphenyls
- Head Injury
- Chlorinated Solvents
- Male Sex
- Age
- Military Service
- Welding \ Metals?
- Physical Inactivity
- Air Pollution
PRIMARY PREVENTION OF PARKINSON’S DISEASE

PROOF OF PRINCIPLE
Parkinson’s Disease in Pesticide Applicators

• Population:
  • 84,740 Farmers & Spouses in Iowa or N Carolina
  • Obtaining pesticide applicator licenses 1993-1997
  • Enrolled in Agricultural Health Study

• Methods:
  • Prospective follow-up for PD
  • In-home neurologist assessment of 1 PD: 3 matched controls; DNA, blood pesticides; expert consensus diagnosis
  • Detailed histories of pesticide application, PPE use, farm & other occupational toxicant exposures, diet & lifestyle, family history
Parkinson’s Disease in Pesticide Applicators

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• Results:

<table>
<thead>
<tr>
<th>Pesticide</th>
<th>Functional Class</th>
<th>PD Risk (OR)</th>
<th>95%CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paraquat</td>
<td>Herbicide</td>
<td>2.5</td>
<td>1.3-4.7</td>
<td>0.004</td>
</tr>
</tbody>
</table>
Paraquat
1,1’-Dimethyl-4,4’-bipyridinium dichloride

Toxicity:
Redox activity $\rightarrow$ superoxide anions

- Commonly used herbicide
- > 100 crops
- Agricultural, landscaping uses
- Banned in EU 2007
- Use in the US, worldwide has been increasing
Can Parkinson’s Disease Be Prevented?

Example 1: Diet
Risk of Parkinson’s disease associated with the herbicide paraquat is attenuated by high dietary intake of polyunsaturated fatty acids

Kamel et al, 2012

- PD cases and matched controls in AHS PD study
- Diet before PD diagnosis from a food frequency questionnaire

RESULTS:

- Parkinson’s disease inversely associated with high dietary polyunsaturated fatty acids, notably α-linolenic acid: “Healthy diet”

  (OR 0.4, 95% CI 0.2-0.8)

- Association of Parkinson’s disease with paraquat attenuated with healthy diet, stronger in those with low intake of α-linolenic acid

  | Healthy diet, No paraquat | 1.0 (refferent) |
  | Unhealthy diet, No paraquat | 1.4 (0.5-3.9) |
  | Healthy diet, Used paraquat | 1.3 (0.7-2.5) |
  | Unhealthy diet, Used paraquat | 4.5 (1.7-12) |
Can Parkinson’s Disease Be Prevented?

Example 2:
Protective Behaviors
Applicators were asked if they used Personal Protective Equipment (PPE) (masks, gloves, respirators) and washed off immediately after a spill.

Increased Risk of PD Was Not Observed in Farmers Using PPE During Pesticide Application

Furlong, Tanner, Goldman, et al, 2015

1 Adjusted for age, sex, state, smoking

PARAQUAT*

FPE  NO PPE

Furlong, Tanner, Goldman, et al, 2015
What If Adults Just Exercised More?

Estimated Number of People with PD in the U.S.* & the Projected Reduction in PD If Physical Activity in Adults Increases

- Minimum Estimated PD patients
- PD patients if 20% increase in physical activity
- PD patients, if 80% increase in physical activity

* Based on Marras, 2018

Simon et al, 2020
The Dilemma

• Environment may not be cleaned up
• People may not follow health recommendations

Secondary prevention: aim is to correct departures from a state of health.
→ Target people with prodromal Parkinson’s disease
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HEALTH | PRECLINICAL | PRODROMAL PD | PARKINSON’S DISEASE
The challenge:
Efficiently Identifying Prodromal PD
Genes & Parkinson’s Disease

• Total < 20 % PD

• Penetrance reduced: Other genes & environmental factors also important

• Autosomal Dominant. ~ 5% PD
  PARK-SNCA, PARK-LRRK2, PARK-VPS35

• Autosomal Recessive < 5% PD
  PARK-Parkin, PARK-PINK1, PARK-DJ1, PARK-DNAJC6

  Complex phenotypes < 1% PD
  PARK-ATP13A2, PARK-PLA2G6, PARK-FBXO7, PARK-DNAJC6, PARK-SYNJ1

• Glucocerebrosidase 5 – 8 % PD

Poewe et al, 2017; Obeso et al, 2017
Preventing Genetic Causes of Parkinson’s Disease

Theoretical Approach:
• Identify gene mutation carriers
• Intervene to block or correct effect of mutation before pathologic process begins

- New treatments at the research stage
- Genetic testing for people with PD available
<table>
<thead>
<tr>
<th>Prodromal Diagnosis</th>
<th>Cases/Controls 2,717/13,585</th>
<th>OR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constipation</td>
<td>477/953</td>
<td>2.8 (2.5,3.1)</td>
</tr>
<tr>
<td>REM Sleep BD</td>
<td>22/37</td>
<td>3 (1.8,5.1)</td>
</tr>
<tr>
<td>Seborrheic dermatitis</td>
<td>110/346</td>
<td>1.6 (1.3,2.0)</td>
</tr>
<tr>
<td>Anosmia</td>
<td>24/64</td>
<td>1.9 (1.2,3.0)</td>
</tr>
<tr>
<td>Neurogenic bladder</td>
<td>45/138</td>
<td>1.6 (1.2,2.3)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>578/1837</td>
<td>1.8 (1.9,2.3)</td>
</tr>
<tr>
<td>Depression</td>
<td>789/2271</td>
<td>2.1 (1.9,2.3)</td>
</tr>
</tbody>
</table>

**Screening for Prodromal PD in the Electronic Medical Record**

Newly diagnosed PD 2004 – 2010 & Matched Controls

Members of Northern California Kaiser Permanente

Future PD diagnosis more common in people seeking health care for certain conditions
PPMI - PRODROMAL PYRAMID

Study Goal: Longitudinally assess cohort of unaffected individuals at high-risk of developing motor features of PD within 3-5 years due to evidence of dopaminergic deficit

Intensive longitudinal in-clinic assessment
N~2000

Prodromal participants assessed with DaTSCAN
N~6000

Establish feasibility of identifying PD prodromal cohort
Identify clinically meaningful outcomes to better identify prodromal PD and to monitor disease progression in prodromal PD

Prodromal Participants for PD (Hyposmia, RBD, Genetic) who also demonstrate evidence of dopaminergic deficit considered highest risk for developing motor features

Remote risk screening; UPSIT, genetic risk score, digital sensor technologies
N~50000

Existing 'at risk' cohorts due to RBD, hyposmia or rare genetic mutations enter at Remote

Generalizable online assessment using PROs (early motor, autonomic, sleep, cognition, depression, anxiety, FmHx, etc)
N~100000

Leverage online scalable screening platforms, such as Fox Insight

PPMI Clinical (Prodromal longitudinal)
PPMI Clinical (Prodromal screening)
PPMI Remote
PPMI Online
What About People Who Have Parkinson’s Disease?

Tertiary Prevention
Preventing Parkinson’s Disease

1. Prevent PD Pathogenesis; Preserve Health
2. Prevent Prodromal Symptom Onset; Stop Prodromal Symptom Progression; Prevent parkinsonism/dementia onset
3. Prevent progression of Parkinson’s disease; Prevent consequences of PD: Fractures, pneumonia

HEALTH PRECLINICAL PRODROMAL PD PARKINSON’S DISEASE
Disease Modifying Therapies for PD: Research Approaches

**Goal:** Halt the disease process.

- **Approach:** Prevent aggregation or promote clearance of misfolded alpha-synuclein.
  
  **Examples:**
  - Monoclonal Antibody Infusion against alpha-synuclein
  - Vaccine development against alpha-synuclein

- **Approach:** Correct abnormal function due to genetic changes; “Personalized medicine”: Patients have identified gene defects

  **Examples:**
  - LRRK2 inhibitors
  - Restore glucocerebrosidase enzyme function
  - Target mitochondrial dysfunction
Preventing the Consequences of PD: Preventing fractures

• People with PD have very high risk of fractures
  • 2- to 4-fold increased risk for fractures
    • ANY fracture: 14 % risk per year (17% in women, 12% in men)
    • HIP fracture: 4% risk per year (4.5% in women, 3.9% in men)
  • Even higher in those > 60
  • These risks far exceed National Osteoporosis Fndn. thresholds for treatment
  • Fractures increase disability, reduce independence, increase mortality

• Yet, people with PD & other forms of parkinsonism have far lower rates of osteoporosis treatment!
This study is done from your home!

- If you are eligible for the study, a nurse will come to your home to give you a short exam.
- You’ll receive a one-time dose of the study treatment (either zoledronic acid or a placebo).

Earn $100 upon enrollment & $50 per year during the study.

Want to learn more about joining TOPAZ?

Ready to join? Visit topaz.eurekaplatform.org and enter invitation code

or call: 1-800-4PD-INFO (1-800-473-4636)
Conclusion

Prevention is possible!

A combination of public health and targeted medical interventions has the potential to significantly reduce Parkinson’s disease burden.
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