Unmet Needs for Parkinson’s Disease Therapeutics

Coalition Against Major Diseases & FDA Workshop
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Disclosures: Consultant for Adamas & Pfizer Pharmaceuticals
Topics

• Why Parkinson’s Disease therapeutics matters
• Therapeutic Gaps
• Bridging the Gaps
  – New approaches
  – Continuing challenges
Global Burden of Parkinson’s Disease Is Expected to Increase As Life Expectancy Increases World Wide

Figure III.2. Life expectancy at birth for the world and major areas, 1950-2100

Consequently, the global burden of Parkinson’s disease is expected to increase.

Change in number of people with Parkinson’s disease in the world’s most populous nations from 2005 to 2030*

*Among individuals over 50 in the world’s ten most populous and Western Europe’s five most populous nations

Source: Dorsey et al, Neurology 2007;68:384-6
Consequences for Society

Costs:

– Direct costs of health care
– Indirect costs:
  • Loss of years worked, lost societal contributions
  • Mental & physical costs
  • Affects person with PD & family members, colleagues, friends
The Current and Projected Economic Burden of Parkinson’s Disease in the United States

Stacey L. Kowal, MSc, Timothy M. Dall, MS, Ritashree Chakrabarti, PhD, Michael V. Storm, BS, and Anjali Jain, MD

FIG. 2. Medical costs of PD over time.

Mov Disord 2013
Can We Reduce the Burden?

Education
Research
Advocacy
Health Services

Better Treatment
History of PD Therapy in the US

1817: Parkinson described Paralysis agitans
Late 1800’s: Belladonna alkaloids as Rx
1950’s: Synthetic anticholinergics as RX
Late 1960’s: L-dopa
1970’s:
  L-dopa + decarboxylase inhibitor (dci)
  Amantadine
  Bromocriptine as adjunct to l-dopa
1980’s:
  Pergolide as adjunct to l-dopa Withdrawn 2007
  Sustained release l-dopa/dci
  Selegiline as adjunct to l-dopa
1990’s:
  1997 Pramipexole (mono, adjunct)
  1997 Ropinirole (mono, adjunct)
  1998 Tolcapone (with l-dopa/dci) Black box hepatic failure
  1999 Entacapone (with l-dopa/dci)
2000’s:
  2004 Apomorphine s.c. (Intermittent hypomobility)
  2006 Rasagiline (mono, adjunct)
  2007 Rotigotine patch Recall 2008
  2006/7 Rivastigmine oral & patch Dementia
2010—...:
  2012 Rotigotine patch Reintroduced
  ?

→ ALL BUT 1 DRUG: SYMPTOMATIC TREATMENT FOR MOTOR SYNDROME
Clinical Knowledge Gaps in Parkinson’s Disease

**CLINICAL COURSE:**
- No diagnostic test
- No predictor of risk (for most)
- No reliable marker of progression
- No reliable predictor of prognosis

**TREATMENT:**
- No way to prevent disease
- No cure
- No way to slow disease progression
- Inadequate Symptomatic Treatment:
  - Motor – imperfect control of symptoms, and with side effects
  - Nonmotor – many and diverse problems, few treatments
Bridging the Gap
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<tr>
<th>Topic Area</th>
<th>Recommendation</th>
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<tr>
<td>Clinical Research</td>
<td>1. Define the features and natural history of prodromal PD including progression, events that underlie phenoconversion to clinically manifest PD, and biomarkers or other determinants of prodromal subtypes with the goal of providing sufficient rationale to initiate proof-of-concept prevention trials that initially target high-risk populations.</td>
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<td>2. Develop effective treatments and companion biomarkers for dopa-resistant features of PD. These features include both motor symptoms, particularly gait and balance problems, such as freezing of gait, and non-motor symptoms, especially cognitive impairment, psychosis, and dysautonomia.</td>
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<td>3. Characterize the long-term progression of PD and understand the mechanisms that underlie the heterogeneity in clinical presentation and rates of progression. Factors related to disease heterogeneity may include clusters of clinical features as well as biological factors such as genotype and biomarkers.</td>
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THE FIRST CHALLENGE: Defining Parkinson’s Disease
At diagnosis of Motor PD:

- 50% neuron loss in the substantia nigra
- 80% striatal dopamine deficit

Prevent Symptom Onset
→ Slow or Stop Progression of motor syndrome

Prevent disease features:
dyskinesias, dementia

Pathogenesis & clinical course of PD only partially understood
The 3rd Challenge: Define Measures of Risk, Onset & Progression in Parkinson’s Disease

**HEALTH**
- Markers of risk
  - Genes
    - Exposure group?
  - Exposure group?

**DISEASE**
- Prodromal
  - Hyposmia
  - ANS
  - RBD
  - Tissue*?
  - Imaging
- Diagnosis
  - Clinical
  - Post-mortem
  - Imaging (adjunct)
  - Tissue*?

**DISEASE OUTCOMES**
- Progression
  - Clinical exam
  - Tissue*?
  - Imaging?

**RELIABLE BIOMARKERS NEEDED!**

* Blood, CSF, skin, GI (ENS), salivary gland, other?
PPMI
The Parkinson’s Progression Markers Initiative: A Prospective Biomarkers Study

OBJECTIVES
- Standardized protocols
- Dataset/sample collection
- Biomarker verification studies
- Identify progression markers

POPULATIONS
- Early Untreated PD
- Matched Controls
- RBD
- Hyposmics
- LRRK2, SNCA PD & Families

Real Time Data Sharing

Imaging & Biologic markers may increase efficiency of clinical trials

Frasier et al, 2010; Marek et al 2011
Overcoming Barriers to Success in Studies of Parkinson’s Disease

Slow enrollment is a major cause of delay and expense

Only about 10% of persons eligible to participate in studies enroll

Can changes in outcomes & study conduct speed things up?
Improve Outcome Measures

Develop Measures Not Dependent on Motor Disease:

- Imaging: brain (DaTScan), other organs
- Physiological measures: Tremor recording, tapping time, EEG spectral analysis
- Global clinical measures: self-reported or examination & interview-based (UPDRS, QOL)
- Other biomarkers: laboratory measurements of body tissues (blood, urine, CSF, saliva, biopsied tissue)

➔ FUTURE: Combinations of measures
Increase Enrollment & Retention In Clinical Trials

Remote Assessment

Randomized Controlled Clinical Trial of “Virtual House Calls” for Parkinson Disease

E. Ray Dorsey, MD, MBA; Vinayak Venkataraman, BS; Matthew J. Grana, BA; Michael T. Bull, BS; Benjamin P. George, MPH; Cynthia M. Boyd, MD, MPH; Christopher A. Beck, PhD; Balaraman Rajan, MBA, MS; Abraham Seidmann, PhD; Kevin M. Biglan, MD, MPH
BIG DATA

- Information from continuous monitoring
- Large numbers of people
- Universal platform
- Can combine w/ other info (imaging, genes)

**Potential Benefits:**

- Identify patterns of disease progression
- Reduce the burden of clinical trial participation
- Identify subgroups more likely to benefit from certain interventions
- Provide new outcome measures?
Linked Clinical Trials: Repurposing

Brundin et al, J PD 2014

Recommendations from LCT committee

- Is it owned?
  - Yes
  - Is it generic?
    - Yes
    - Govt. Philanthropy
      - Govt. Philanthropy
      - Generic companies
        - Is there interest in running a trial from owner?
          - Yes
          - Linked Clinical Trial format
          - Licence agreements
            - Commercial exploitation
            - Govt. Philanthropy
            - Seed funding
          - No
          - Facilitate funding
          - Explore commercial exploitation
            - Govt. Philanthropy
            - Seed funding
    - No
    - Explore commercial exploitation
      - Govt. Philanthropy
      - Seed funding
  - No
  - Is it ownable? E.g. could it be delivered in a novel way?
    - Yes
    - Govt. Philanthropy
      - Seed funding
      - Facilitate funding
    - No
  - Is it commercially viable?
    - Yes
    - Licence agreements
      - Commercial exploitation
      - Govt. Philanthropy
        - Seed funding
    - No
      - Explore commercial exploitation
        - Govt. Philanthropy
        - Seed funding
THANK YOU!