Slowing Progression of Parkinson’s Disease: How do you measure that?

Part I: The Challenge

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Parkinson’s disease

- bradykinesia (slowness)
- rigidity (stiffness)
- rest tremor
- postural instability (falls)
How measure PD progression? Depending on disease stage:

- **At-risk / prodromal PD**
  - Conversion to PD
  - Surrogate biomarker (DAT scan Δ)

- **Early / untreated PD**
  - Δ in clinical scale (e.g., UPDRS)
  - Time to need for DA treatment

- **Moderate / treated PD**
  - Δ in clinical scale (e.g., UPDRS)
  - Time to clinical milestone (~falls)
How measure PD progression?
Depending on disease stage:

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Dopamine (DA) signaling facilitates movement
Antiparkinsonian drugs boost DA signaling

1. DA precursor
   L-dopa

2. DA mimics
   DA agonists

3. DA breakdown blockers
   MAO-B/COMT inhibitors

L-dopa → DA → MAO-B
MAO-B/COMT inhibitors
L-dopa → MAO-B/COMT inhibitors

DA synthesis

MAO-B

L-dopa → DA

**Figure 2.** Changes in Total Scores on the Unified Parkinson’s Disease Rating Scale (UPDRS) from Baseline through Evaluation at Week 42.
urate

( trioxy-purine )
Translational potential of urate in PD

• **Convergent epi and clinical data**
  
  identify urate as a *predictor of*
  
  *both risk and the rate of PD*

• **Biological plausibility**
  
  of neuroprotection by urate
  
  • Major antioxidant
  
  • Protects neurons in cell models

• **Therapeutic potential** for neuroprotection
  
  • Urate pathway highly amenable to
    
    pharmacological manipulation
  
  • Inosine, a urate precursor, can
    
    elevate urate in humans
Serum urate is a predictor of progression in PD (pooled cohorts of DATATOP and PRECEPT)

Risk of reaching primary progression endpoint for each quintile of serum urate at baseline

PD Progression Rate (HR for disability @ 2 years)

SURE-PD subjects at baseline

Placebo

Ino (low)

Ino (higher)

n = 1,578 (men & women)

PD Progression Rate

0

1

0.91

0.86

0.71

0.58

Serum Urate

(increasing quintiles)

1

2

3

4

5

MassGeneral Institute for Neurodegenerative Disease
Safety of URate Elevation in PD

SURE-PD

A randomized, double-blind, placebo-controlled, dose-ranging trial of oral inosine to assess safety and ability to elevate CSF urate in early PD

Michael J. Fox Foundation for Parkinson’s Research

MGH, HSPH and the Univ Rochester
UPping URate Safely in PD

UpUrS-PD

A randomized, double-blind, placebo-controlled, dose-ranging trial of oral inosine to assess safety and ability to elevate CSF urate in early PD

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MGH, HSPH and the Univ Rochester
Charlie Sherpiddy
Charlie Sherpiddy – SURE-PD Ambassador
Keys to Clinical Trial Success

- Idea you believe in
- Determination
- Excellent mascot
- Skilled statistician from the outset
Comparison of the Agonist Pramipexole With Levodopa on Motor Complications of PD (CALM-PD) Trial

**Figure 3.** Mean (SE) total (parts I+II+III), motor, activities of daily living, and mental Unified Parkinson’s Disease Rating Scale scores during the course of the trial by treatment assignment.