Nutrition & Parkinsonism

Laurie K Mischley, ND PhD MPH

OHSU Integrative Medicine Symposium
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OHSU

Disclosures

- Advisory Boards: Brian Grant Foundation, Next Frontier Biosciences
- Founder: NeurRx, Social Purpose Corporation
  - ParK-9: Dogs that identify the scent of parkinsonism
  - Parkinson's School (online)
- Owner of PRO-PD scale (free scores available at www.PROPD.org)
- Institutional Affiliations: Bastyr University, National College of Naturopathic Medicine
- Clinical Practice: Seattle Integrative Medicine
- Medial Director of PD Summer School @ Bastyr University

My bias:
Patient-Centered Pragmatic Research

VIEW BY TOPIC VIEW ALL

WPC BLOG

WPC 2019 FOLLOW SUBSCRIBE

CLINICAL SCIENCE · OCTOBER 8, 2018

PATIENT-CENTERED CARE: A PARADIGM WHOSE TIME HAS COME

If you ask a neurologist to describe Parkinson's disease, most will tell you it's a disease defined by tremor, rigidity, slowness, and stooped posture. A few years ago, we surveyed over 1000 people with Parkinson's (PwP) and asked them to describe their symptoms--fatigue, impaired handwriting, loss of smell, memory problems, and muscle pain were the most common.[1]

I have spent the past few years reflecting on the discrepancy between how patients and providers view this disease. I keep coming back to this idea that **PD has been defined by the symptoms that providers can observe, not by the symptoms the patient experiences.** Currently, PD is understood and managed from a *provider-centered paradigm.*

Percent of Patients Reporting Symptom	Symptoms
80-85%	Fatigue, Impaired Handwriting, Hyposmia
70-80%	Memory impairment, Muscle pain, Daytime sleepiness, Slowness, Tremor, Sexual impairment, Balance, Urinary dysfunction, Stooped posture

Conditionally Essential Nutrients in PD

"Humans are parasites of the planet. In order to sur- vive, there are minerals and molecules, ultraviolet waves, and other organisms on which we rely. We need some of Earth's resources to function optimally and in some cases, we need them to function at all. These nutrients on which we rely are considered essential nutrients if they are used by most humans most of the time."

Table 1: Examples of Nutrients Gaining Acceptance as Conditionally Essential in Certain Disease States

CONDITION	NUTRIENT	Phase 1 Defic	Phase 2 Defic	Phase 3 Defic
Parkinson's	Q10	Synthesized by HMG-CoA reductase (commonly inhibited by statins)	SpectaCell FIA 4-fold risk of Q10 defic [11].	TBD: Myalgia? Fatigue? Weakness? Cardiomyopathy?
Parkinson's	Glutathione	Synthesized on demand, not stored.	40% depletion of nigral GSH at diagnosis; GSH defic leads to inflammation, ROS, mitochondrial dysfunction	GSH depletion associated with aging, GSH progression
Parkinson's See also: *Epilepsy* *Mental illness* *Tics* *Addiction* *ADHD* *Migraine* *Alzheimer's* *MS, ALS, HD*	Lithium	Not stored. Typically obtained	Ecological studies from 1970s show municipal supply assoic with body level. Depletion in rainy regions, highest in desert. *To-do: Repeat in WA	Low Li associated with psychosis, depression, aggressive behavior, and suicide. Calls in the literature for more research and Li the water supply of depleted regions have been ignored. *To-do: Study Li repletion among those deficient. Reverse feeding study.

Journal of
Food and Nutrition

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Conditionally Essential Nutrients: The State of the Science

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Does Diet Influence Risk of Developing PD?

- **Increased Risk**
  - Red meat, processed meat
  - Dairy
  - Refined grains
  - Desserts & sweets
  - Well water
  - Pesticides
- **Decreased Risk**
  - Vegetables
  - Legumes
  - Fruit
  - Fish
  - Coffee
  - Tea

PUT THESE DATA TO USE!
Teach those not yet diagnosed.
Practice Prevention.

Diet & PD Symptoms

- **Malnutrition is common in PD**
- Associated with:
  - Constipation
  - Depression
  - Anxiety
  - Cognitive impairment
  - Dystonia

Nutrition and Nonmotor Symptoms of Parkinson's Disease

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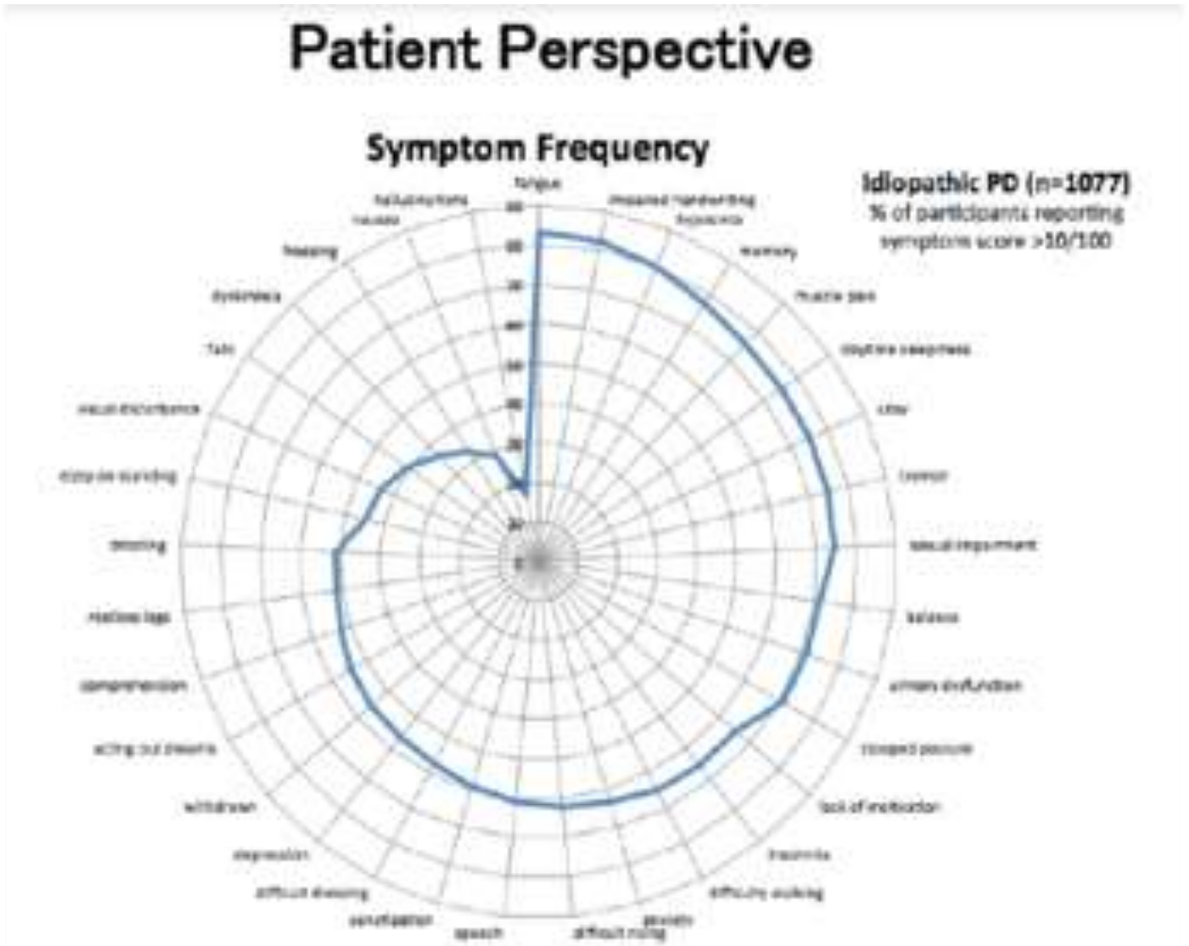
Contents

What About Diet and RATE of Progression?

?

What is Parkinson's?
(According to Patients)

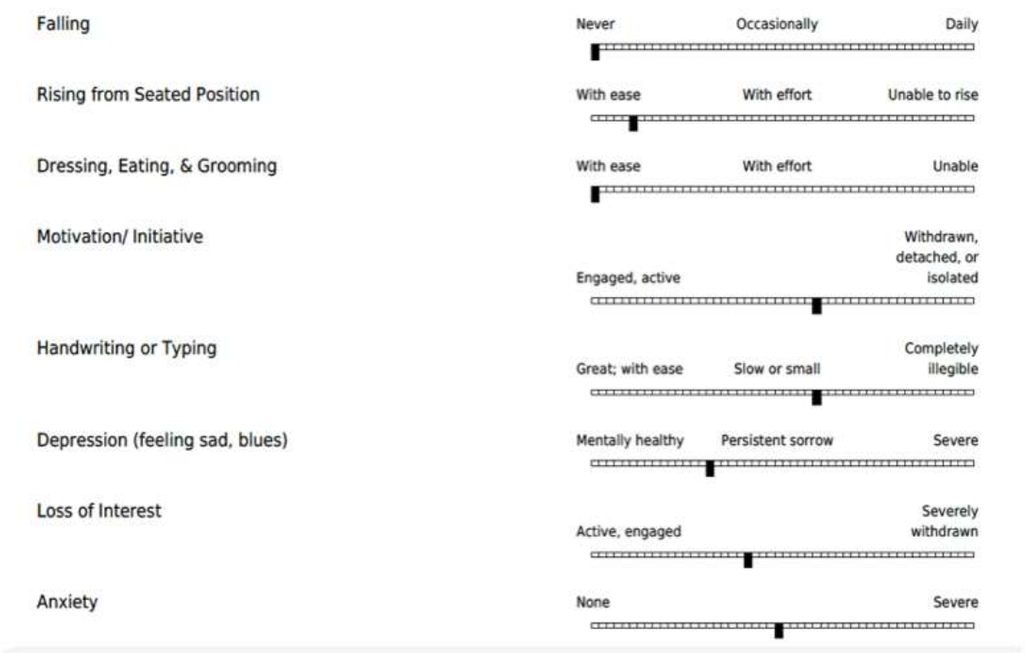
Percent of Patients Reporting Symptom	Symptoms
80-85%	Fatigue, Impaired Handwriting, Hyposmia
70-80%	Memory impairment, Muscle pain, Daytime sleepiness, Slowness, Tremor, Sexual impairment, Balance, Urinary dysfunction, Stooped posture
60-70%	Lack of motivation, Insomnia, Difficulty walking, Anxiety, Difficulty rising, Impaired speech
50-60%	Constipation, Difficulty dressing, Depression, Withdrawn, Acting out dreams, Comprehension, Restless legs, Drooling
40-50%	Dizzy on standing, Visual disturbance, Falls
30-40%	Dyskinesia, Freezing
<30%	Nausea, Hallucinations



Mischley LK 2017

Measuring PD **Progression**

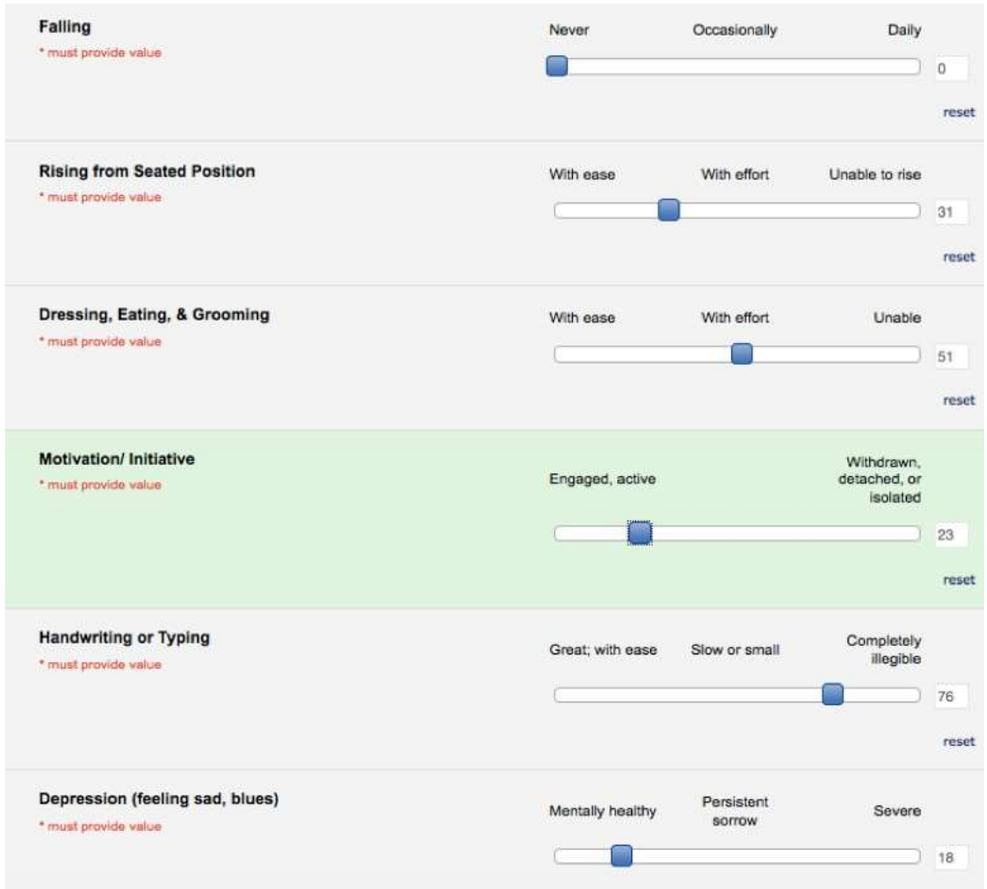
- Ideal scale:
  - Administered remotely
  - Patient-centered
- Correlates with quality of life
- Correlates with established measures of disease severity
- Continuous, stratifiable by symptom, sensitive enough to detect slight change

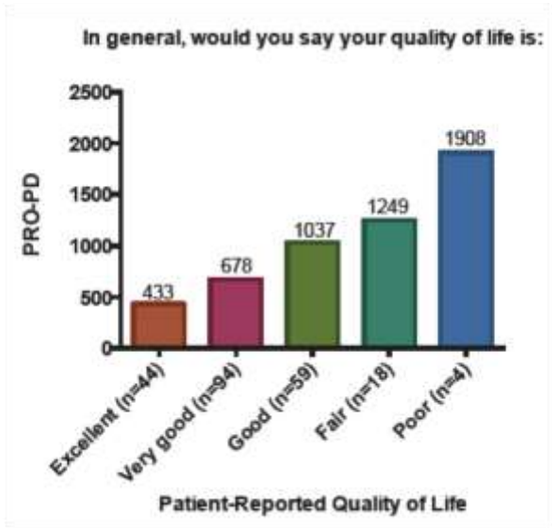


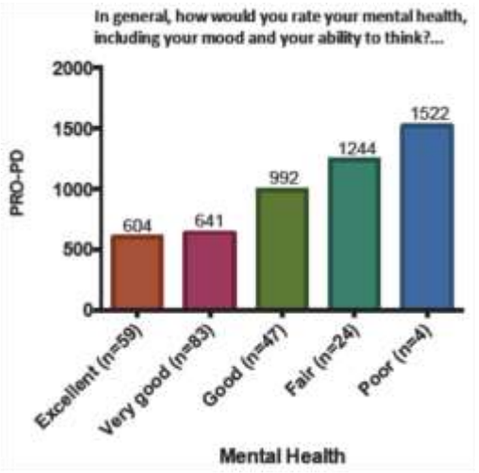
- **www.PROPD.org**

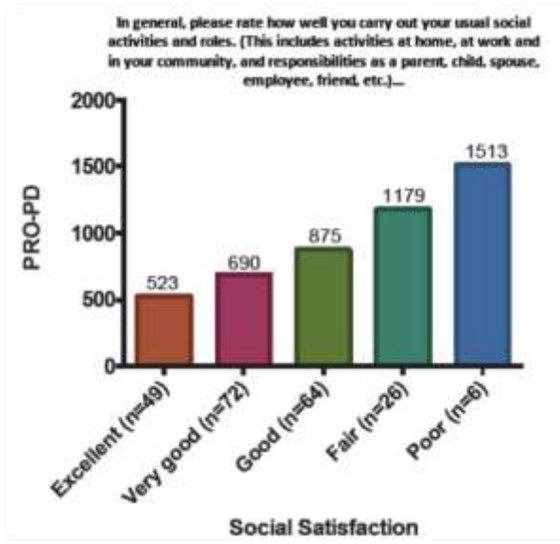
Are Patient-Reported Outcomes Accurate?

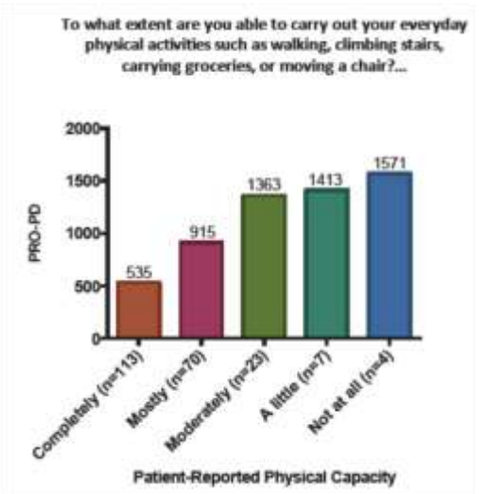
www.CAMCarePD.bastyr.edu





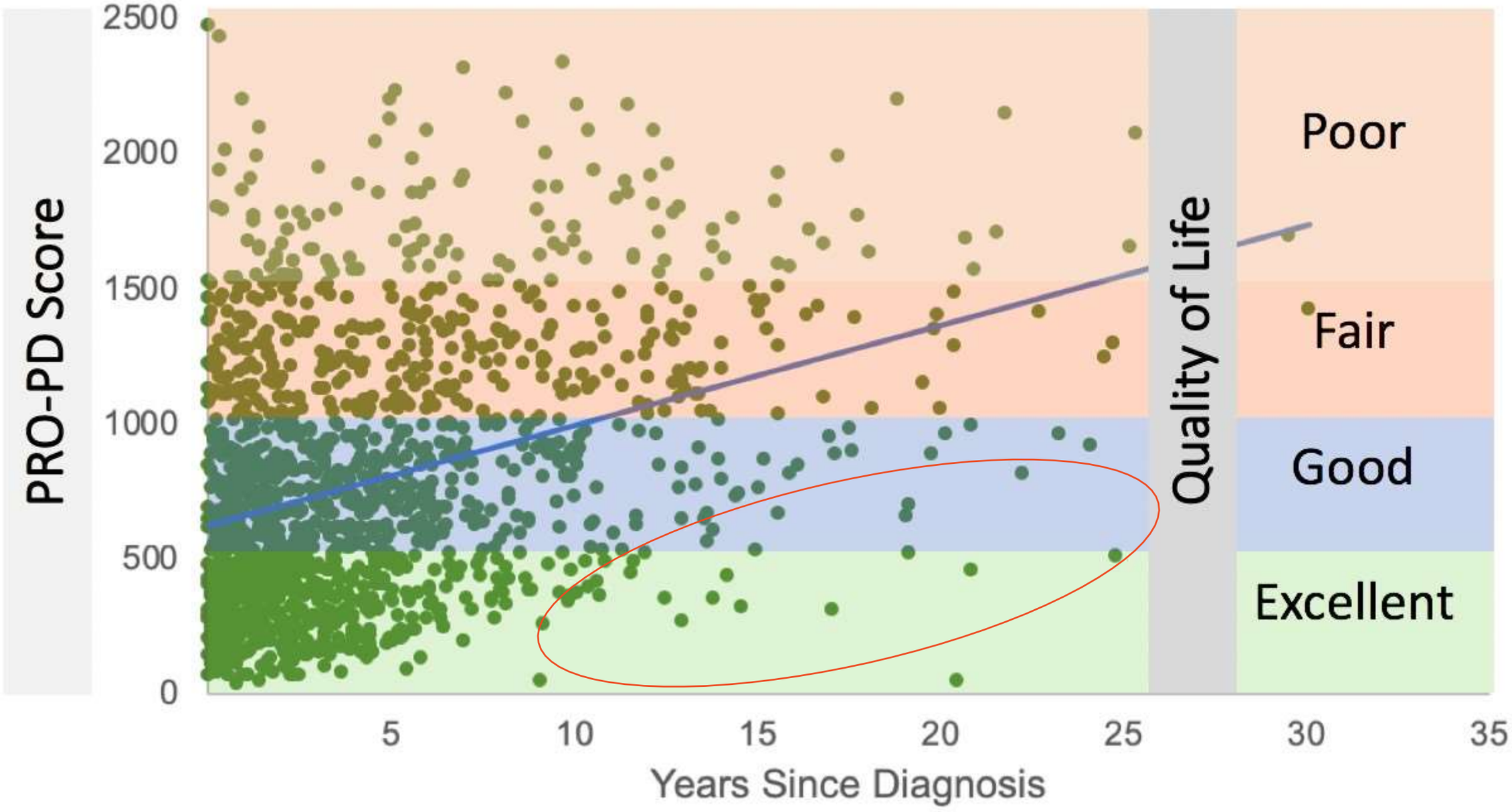






Mischley LK 2016

What are the POSITIVE DEVIANTS doing differently?



Diet: Encourage

- Fresh veggies
- Fresh fruit
- Nuts & seeds
- Non-fried fish
- Olive oil
- Coconut oil
- Wine
- Spices
- Fresh herbs

Diet: Avoid

- Red meat, processed meat
- Dairy
  - Cheese
  - Yogurt
  - Ice cream
- Fried foods
- Soda / Diet soda
- Canned Fruits
- Canned Vegetables

Mischley LK, 2016. Diet & Supps in PD Progression.

https://www.huffingtonpost.com/2014/08/15/french-fries-healthy-fast-food_n_5678580.html

Diary: Why the link with PD?

- 5 studies suggest the more dairy you eat, the more likely you are to be diagnosed with PD
- CAM Care study showed the more dairy people consumed, the worse their symptoms over time.

to foods like mashed potatoes and baked goods.

There may be several mechanisms responsible to explain the association between PD progression and dairy consumption:

(1) Dairy intake lowers uric acid [19]. Uric acid quenches peroxynitrite in the CNS, and low uric acid levels are associated with greater PD incidence and faster PD progression [20].

(2) Diary consumption is associated with insulin resistance [21]. There is a growing body of evidence that PD and other neurodegenerative diseases are a form of "type III diabetes" [22].

(3) Lactose intolerance, occurring when the enzyme, lactase, that digests the milk sugar decreases with age, is especially common in individuals of African, Asian, Hispanic, and Native American decent [23]. Consuming dairy in the absence of sufficient lactase may contribute to intestinal inflammation and intestinal permeability.

(4) Presence of a neurotoxic component or contaminant, for example, pesticides, may be present in dairy [23].

(5) Introduction of bovine microbiota, facilitating seeding of methanogenic organisms, leads to the development of methane-dominant small intestinal bacterial overgrowth (SIBO) and other forms of abnormal intestinal flora [24–26].

Mischley LK 2017

Does it Matter if It's Organic?

"I try to eat organically grown foods when possible."

We surveyed over 1000 PwP. People who responded TRUE had a **PRO-PD score** approximately **75 points lower** than those who don't make the effort (-74.9 (28.1); p=0.008 (-130 to -19.8)).

Data after adjusting for age, gender, income, and years since diagnosis. (Mischley et al 2017)

Mischley LK 2017

Nutraceuticals Associated With Rate of Progression

- Improved Outcomes
  - Coenzyme Q-10
  - Fish oil
- Worse Outcomes
  - Iron supplements
  - (Melatonin seemed to be due to poor sleep, not the melatonin.)

Table 3: Logistic regression model of nutritional supplements and PD progression. Predicted PD severity score, as measured by the PRO-PD, based on the positive report of consistently using of supplements over the previous 6 months. *Adjusted for years since diagnosis, age, and gender. **Adjusted for years since diagnosis, age, gender, and income.

Association between dietary supplements & risk of Parkinson's disease progression					
Nutritional supplement	*n*	Mean change in PRO-PD score (SE)*	*P* value (95% CI)*	Mean change in PRO-PD score (SE)**	*P* value (95% CI)**
Inosine	13	−181.1 (125.6)	0.15 (−427.5 to 65.3)	−107.1 (122.9)	0.384 (−348.4 to 134.2)
Glutathione, oral	43	−126.1 (69)	0.068 (−261.6 to 9.3)	−126.7 (70)	0.07 (−263.9 to 10.5)
DHEA	47	−87.6 (70.8)	0.216 (−226.6 to 51.4)	−72.2 (70.9)	0.309 (−211.3 to 67)
Lithium, low dose	21	−84.9 (100.2)	0.397 (−281.6 to 111.8)	−118.9 (100.4)	0.237 (−315.9 to 78.1)
Low-dose naltrexone	14	−76.1 (120.9)	0.529 (−313.4 to 161.2)	−87.8 (118)	0.457 (−319.3 to 143.8)
CoQ10	286	−70.4 (31.5)	0.026 (−132.2 to −8.6)	−46.6 (31.6)	0.141 (−108.7 to 15.4)
Fish oil	376	−69.5 (29.5)	0.019 (−127.4 to −11.6)	−57.7 (29.6)	0.052 (−115.7 to 0.4)
Quercetin	21	−50.7 (105.9)	0.632 (−258.5 to 157.1)	−60.5 (106.4)	0.569 (−269.3 to 148.2)
Turmeric/curcumin	197	−47.3 (35.6)	0.186 (−117.3 to 22.8)	−49.5 (35.9)	0.168 (−120 to 20.9)
Gingko biloba	30	−47.2 (83.2)	0.57 (−210.5 to 116)	−61.1 (81.2)	0452 (−220.5 to 98.2)
Coconut oil	190	−35.8 (36.4)	0.324 (−107.2 to 35.5)	−52.7 (36.4)	0.147 (−124.1 to 18.6)
Resveratrol	43	−28.5 (70.7)	0.687 (−167.3 to 110.3)	−18.7 (72.7)	0.797 (−161.4 to 124)
Vitamin D	623	−26.1 (29)	0.368 (−83 to 30.8)	−3.6 (29.2)	0.902 (−60.9 to 53.7)
Alpha-lipoic acid	79	−19.1 (53.4)	0.72 (−123.9 to 85.7)	0.05 (54.4)	0.999 (−106.7 to 106.7)
5-Methyltetrahydrofolate (5-MTHF)	27	−17.1 (91.4)	0.852 (−196.4 to 162.2)	−25.1 (95.6)	0.793 (−212.7 to 162.5)
Probiotics	249	−12.3 (32.7)	0.708 (−76.5 to 52)	−12.4 (32.9)	0.706 (−77 to 52)
NADH	14	−9.7 (120.8)	0.936 (−246.7 to 227.3)	−25.2 (122.6)	0.837 (−265.7 to 215.4)

Hindawi
Oxidative Medicine and Cellular Longevity
Volume 2017, Article ID 6405278, 9 pages
https://doi.org/10.1155/2017/6405278

Coenzyme Q10 in PD

- QE3 study vs. Phase I, Phase II, & population studies

Case-control study showed patients with PD were more likely to be deficient in coenzyme Q10.

Odds of deficiency in coenzyme Q10 status was significantly greater in PD patients compared to age and gender-matched controls. (OR 4.7-5.4; 95% CI: 1.5-17.7; P=0.003-0.009).

More than 30% of patients with PD were deficient.

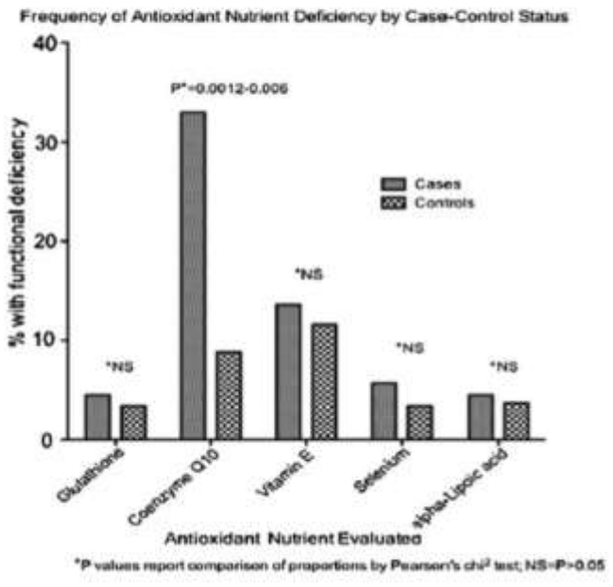
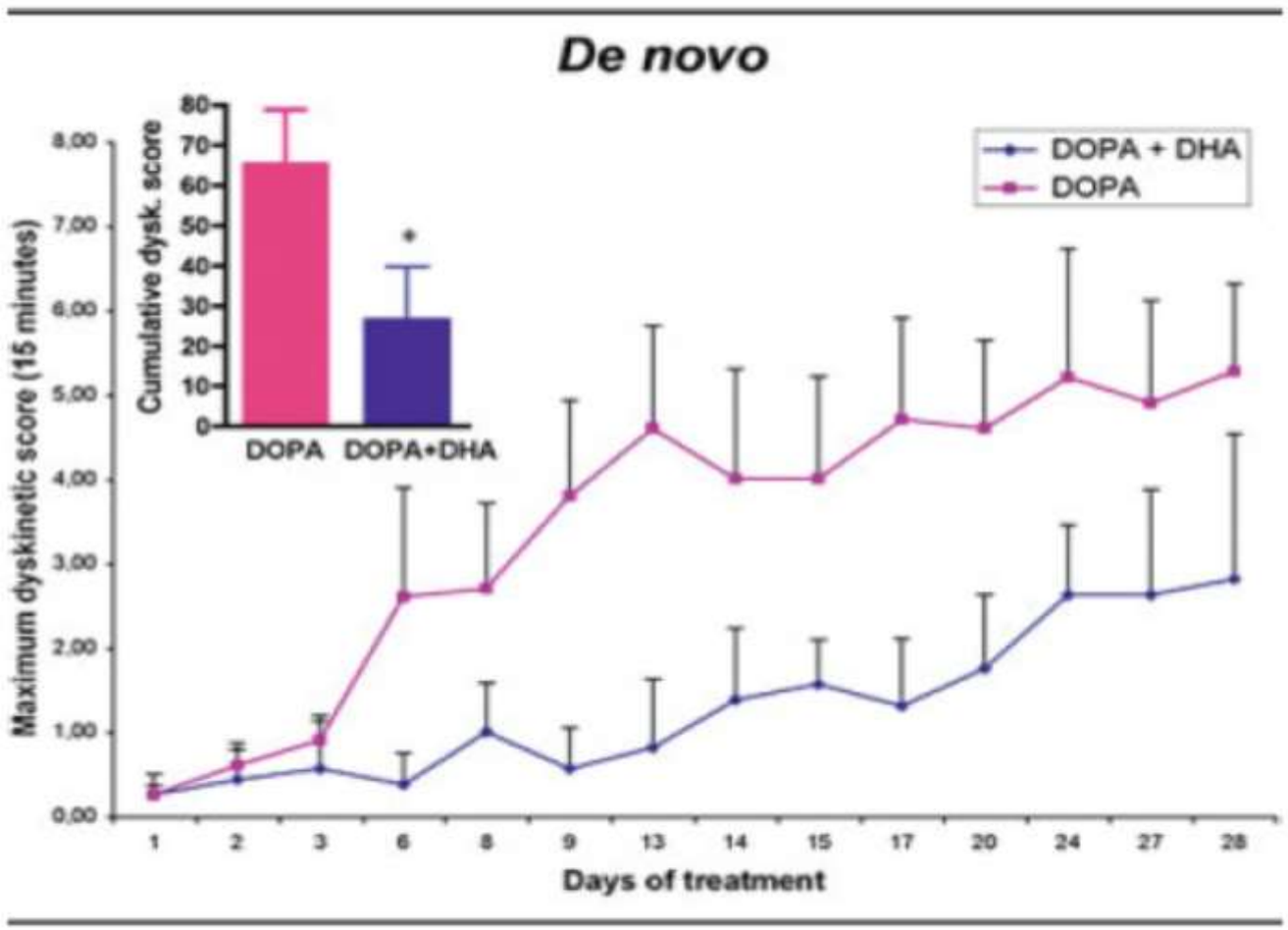


Fig. 1. Frequency of antioxidant deficiency by case–control status.

Mischley LK et al. 2012. J Neurol Sci

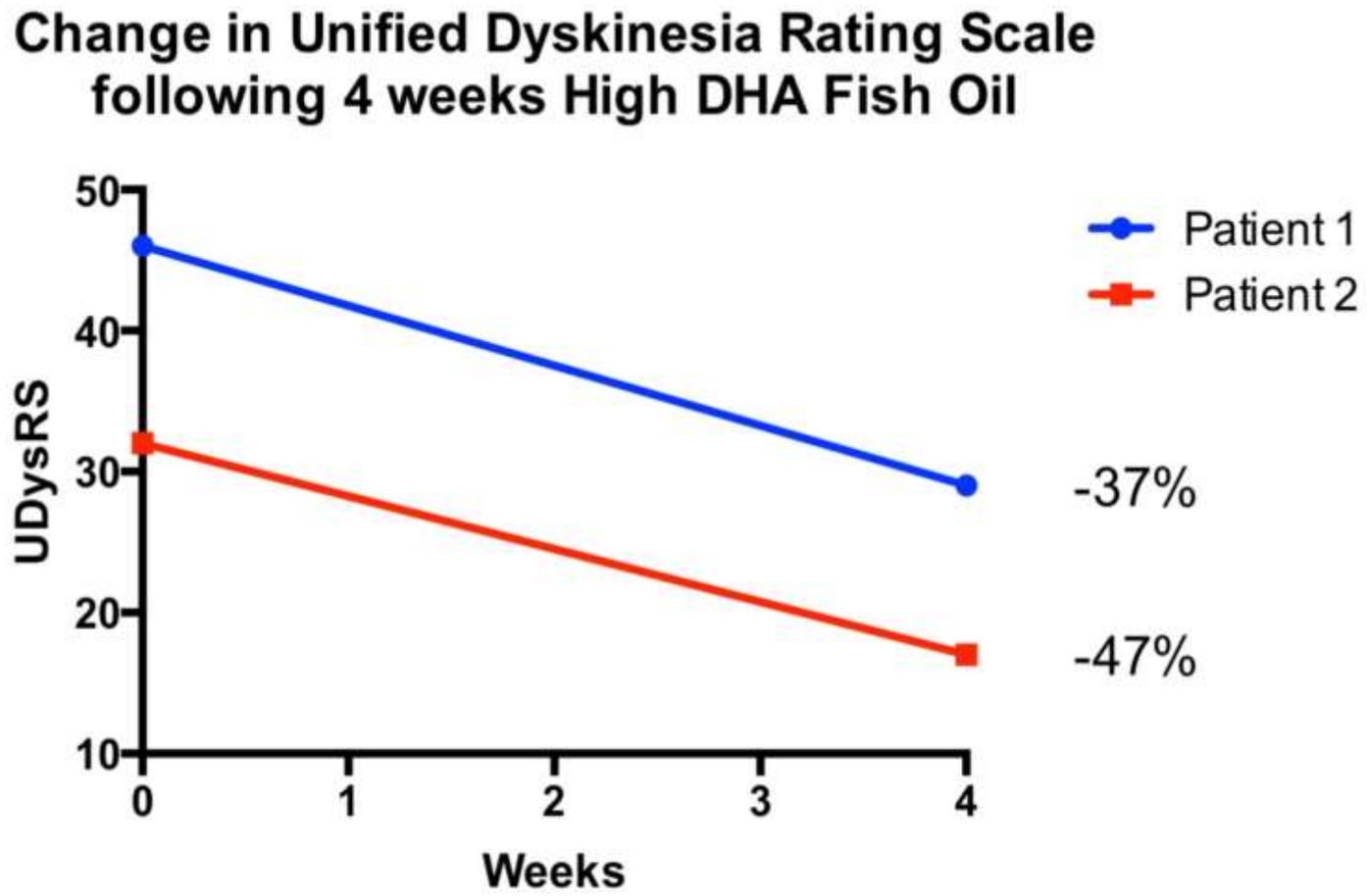
Fish Oil

Reduces dyskinesia in primate model



Samadi P, et al. Ann Neurol 2006;59:282–288

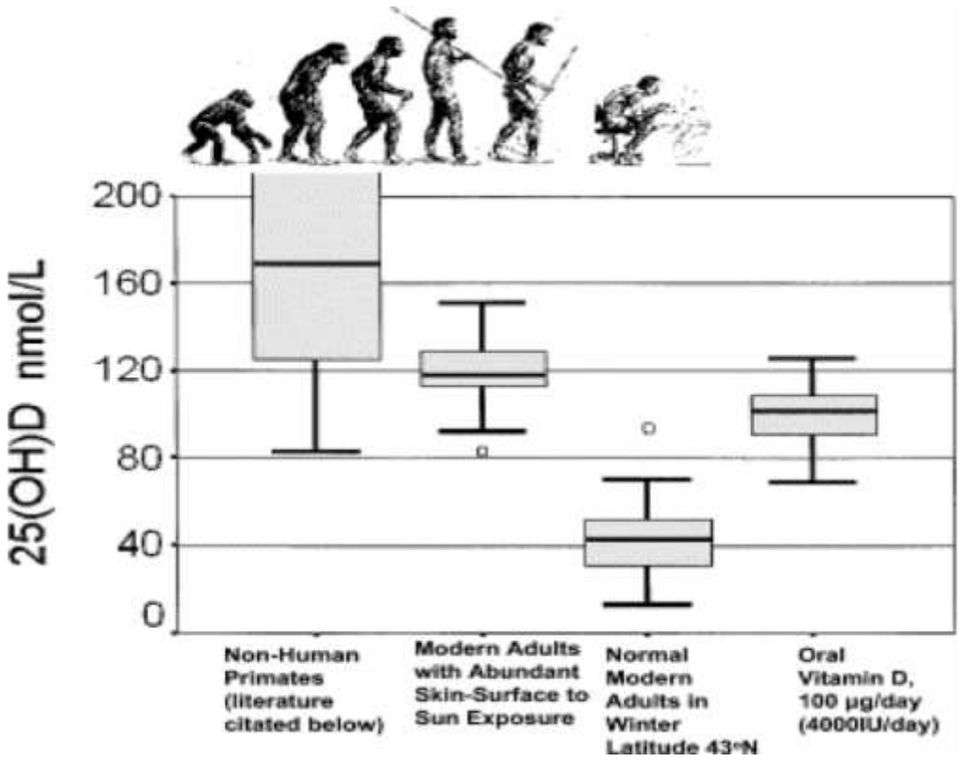
Does fish oil reduce dyskinesia in humans?



Mischley 2013

Vitamin D in PD

- Associated with:
  - Slower bowel transit time
  - Elevated hsCRP
  - Impaired balance, muscle weakness
  - Depression
  - Risk of dementia
  - Required dose depends on: obesity, time outdoors, coverage of skin.
  - Potentially toxic (Toxicity occurs ~ 300 ng/ml (Jones 2008).)



Veith, 2004

Assessing Lithium Status

DOCTOR'S DATA INC

Toxic & Essential Elements; Hair

ESSENTIAL AND OTHER ELEMENTS				
		RESULT µg/g	REFERENCE INTERVAL	PERCENTILE 2.5th 16th 50th 84th 97.5th
Calcium	(Ca)	724	200 - 750	
Magnesium	(Mg)	38	25 - 75	
Sodium	(Na)	12	20 - 180	
Potassium	(K)	13	9 - 80	
Copper	(Cu)	26	11 - 30	
Zinc	(Zn)	210	130 - 200	
Manganese	(Mn)	0.19	0.08 - 0.50	
Chromium	(Cr)	0.50	0.40 - 0.70	
Vanadium	(V)	0.052	0.018 - 0.065	
Molybdenum	(Mo)	0.050	0.025 - 0.060	
Boron	(B)	0.82	0.40 - 3.0	
Iodine	(I)	0.68	0.25 - 1.8	
Lithium	(Li)	< 0.004	0.007 - 0.020	
Phosphorus	(P)	181	150 - 220	
Selenium	(Se)	1.2	0.70 - 1.2	
Strontium	(Sr)	1.9	0.30 - 3.5	
Sulfur	(S)	50200	44000 - 50000	
Cobalt	(Co)	0.009	0.004 - 0.020	
Iron	(Fe)	8.1	7.0 - 16	
Germanium	(Ge)	0.031	0.030 - 0.040	
Rubidium	(Rb)	0.013	0.011 - 0.12	
Zirconium	(Zr)	0.064	0.020 - 0.44	

Homocysteine-Lowering Nutrients

Biochim Biophys Acta. 2016 Sep;1860(9):1989-97. doi: 10.1016/j.bbagen.2016.06.018. Epub 2016 Jun 16.

L-DOPA-induced hyperhomocysteinemia in Parkinson's disease: Elephant in the room.

Paul R[1], Borah A[2].

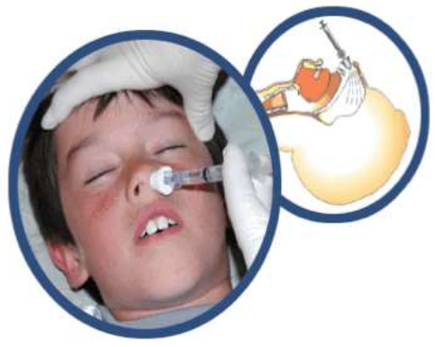
- Levodopa use raises homocysteine levels.
  - Due to interference with folic acid, B12, etc.
- Elevated homocysteine can be neurotoxic. Associated with:
  - Dementia, l-dopa-related behavior abnormalities
  - PD Progression (accelerates neurodegeneration)

Glutathione

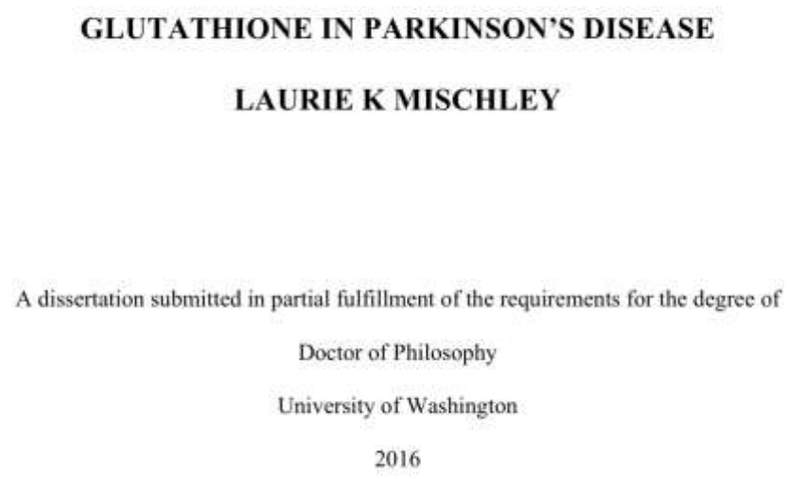
Neurosci Lett. 1982 Dec 13;33(3):305-10.

Parkinson's disease: a disorder due to nigral glutathione deficiency?

Perry TL, Godin DV, Hansen S.



- Reduced glutathione (GSH) is the primary antioxidant of the central nervous system (CNS).
- ~40% deficiency of brain GSH in early PD.
  - Depletion comes before mitochondrial dysfunction,
  - Protein aggregation, Lewy body formation, or
  - Cell Death, loss of dopamine.
- Augmentation strategies have been explored since the 80's.



GLUTATHIONE IN PARKINSON'S DISEASE

LAURIE K MISCHLEY

A dissertation submitted in partial fulfillment of the requirements for the degree of

Doctor of Philosophy

University of Washington

2016

npJ | Parkinson's Disease

www.nature. com/npjparkd

ARTICLE OPEN

Central nervous system uptake of intranasal glutathione in Parkinson's disease

Laurie K Mischley[1,2,3], Kevin E Conley[1], Eric G Shankland[1], Terrance J Kavanagh[4], Michael E Rosenfeld[2], John E Duda[5,6], Collin C White[4], Timothy K Wilbur[1], Prysilla U De La Torre[1,3] and Jeannie M Padowski[7,8]

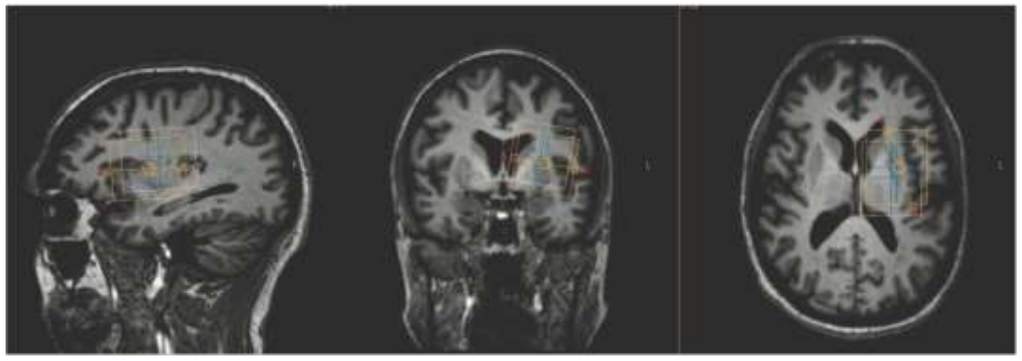
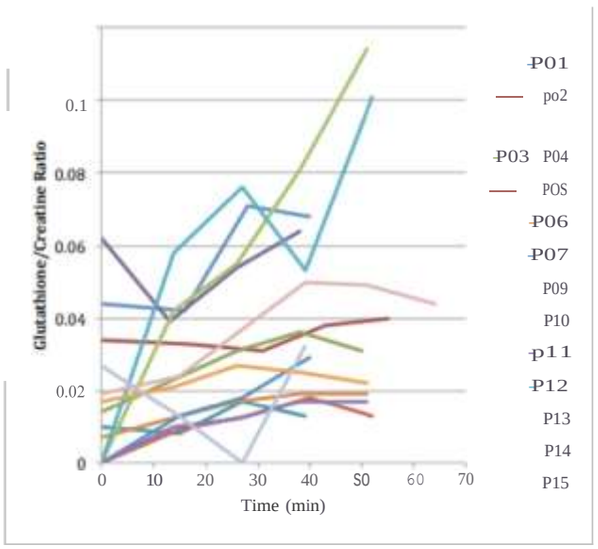
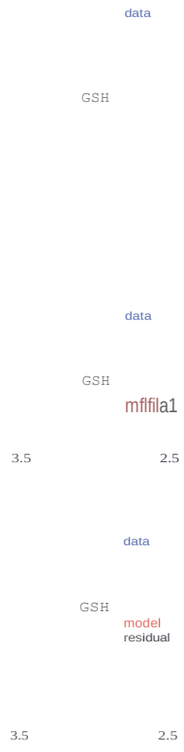


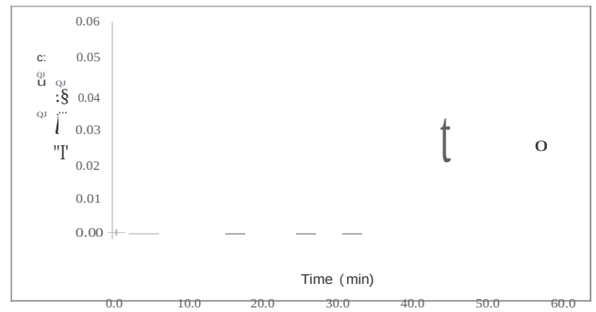
Figure 4. Volume of interest. For all participants, glutathione (GSH) was administered into the left nostril, and a voxel was placed over a 4 x 4 x 5-cm region centered on the left dorsal putamen at the level of the lentiform nucleus.

Individual Results





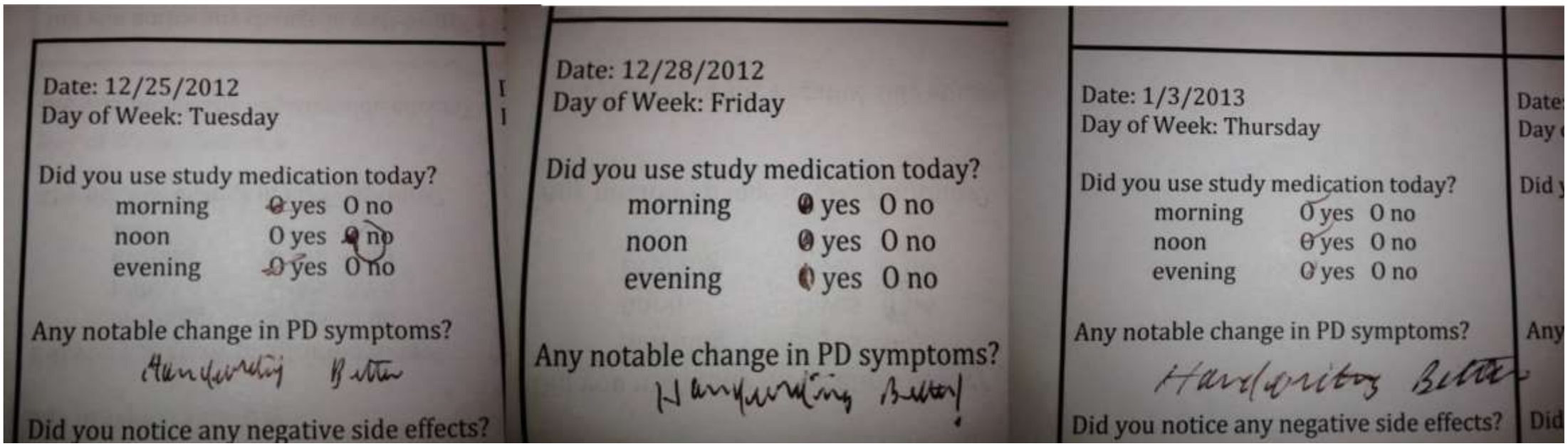
OPJ Parkinson's Disease



Mean mid-point of scan time as min post-dose (SE)	Subjects (=15)	GSH:Cr Mean (SD)	Min	Max	Mean change relative to baseline (SEM)
0 [Baseline]	9	0.026 (0.018)	0.007	0.06.2	
7.6 (0.3)	14	0.025 (0.016)	0.008	0.058	0.00800
20 (0.37)	13	0.036 (0.02.2)	0.012	0.076	0.0194
32 (0.36)	14	0.038 (0.021)	0.013	0.081	0.0221
45 (0.47)	9	0.045 (0.037)	0.013	0.114	0.0350
57	1	0.049	0.049	0.049	0.025

Phase I & II Studies (in)GSH in PD

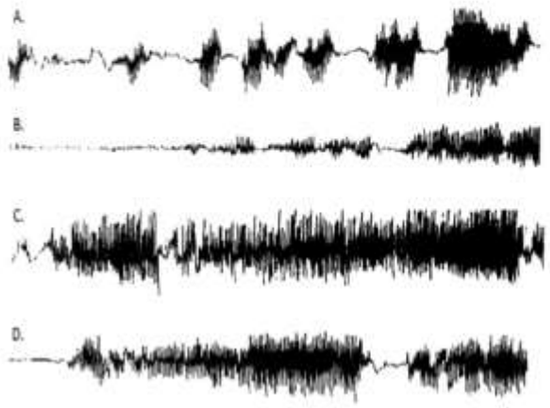
- Safe & tolerable.
- Observed motor improvement in both; an appropriately-powered Phase III study is required to determine whether (in)GSH is better than placebo.



Mischley LK. Phase I Study of Intranasal glutathione for PD. 2015

Glutathione Augmentation Trials in PD

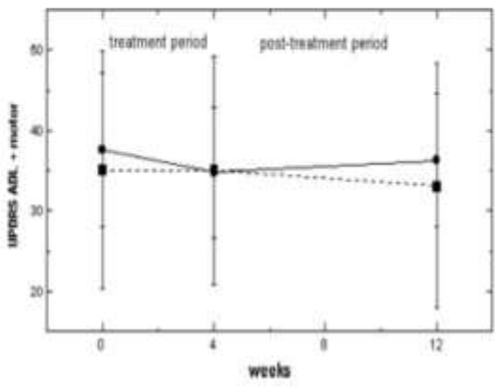
Sechi 1996
IV GSH 2x/d 30 d



Tremor measured by accelerometer.

A. pre-treatment
B. After IV GSH
C. Washout
D. 25/100 c/levodopa 3x/d for 30 d.

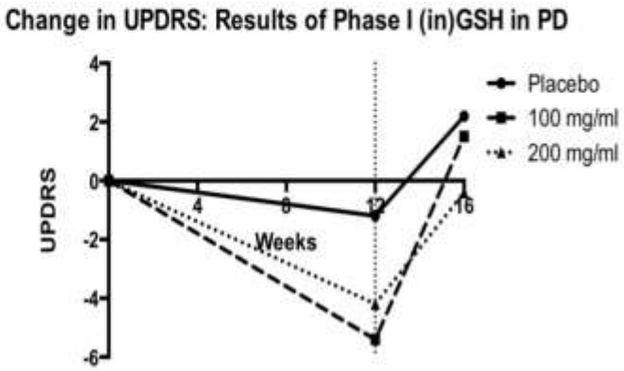
Hauser 2009
IV GSH 3x/wk 4 wks



Dashed line: placebo
Solid line: 1400 mg GSH

Pilot suggestive of mild symptomatic effect.

Mischley 2013
(in)GSH 3x/d 3 mo

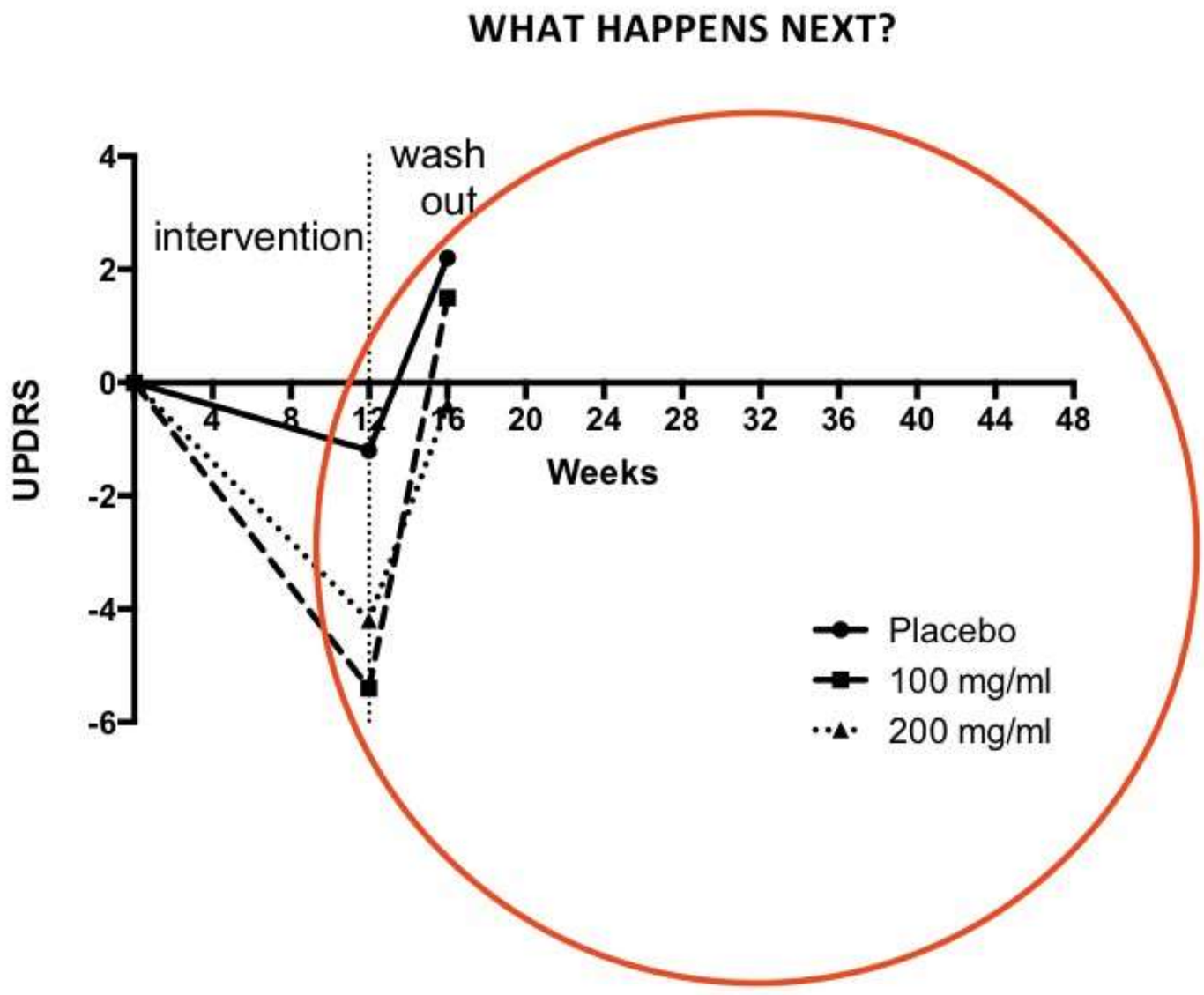


Both (in)GSH treatment arms had improvement in symptoms in the safety & tolerability study.

Mischley 2015
(in)GSH 3x/d 3 mo

Phase IIb- (in)GSH treatment arms **& placebo** has improvement in symptoms.

Intranasal Glutathione Research



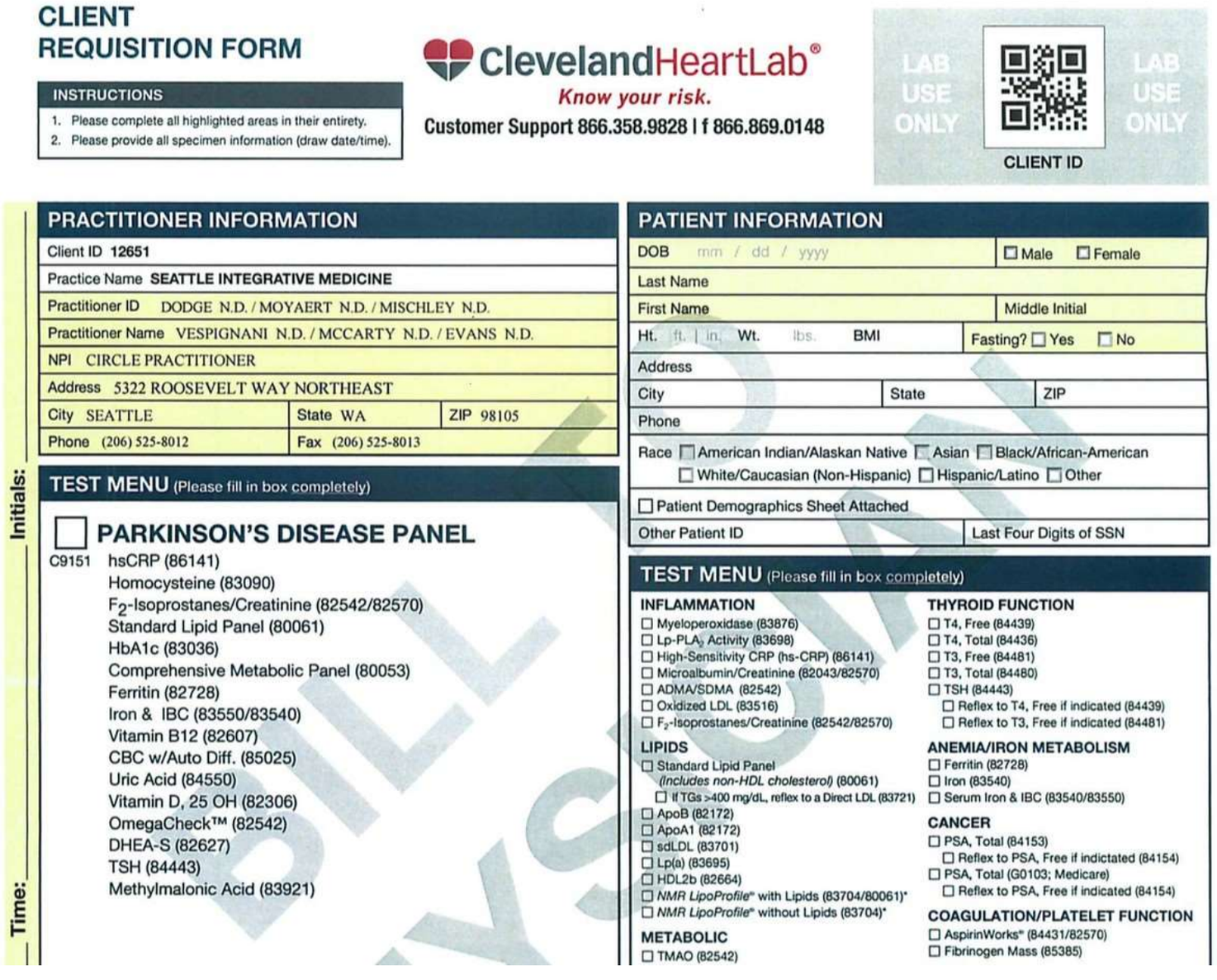
Next steps:
Are motor improvements sustained?
Does (in)GSH affect rate of progression?

+ product development work

LKMischley 2018

How to Test for Nutritional Deficiencies

- Blood
- Urine
- Hair
- Stool
- Breath
- MRS



CLIENT REQUISITION FORM

ClevelandHeartLab®
Know your risk.
Customer Support 866.358.9828 | f 866.869.0148

LAB USE ONLY — CLIENT ID — LAB USE ONLY

INSTRUCTIONS
1. Please complete all highlighted areas in their entirety.
2. Please provide all specimen information (draw date/time).

PRACTITIONER INFORMATION

Client ID **12651**		
Practice Name **SEATTLE INTEGRATIVE MEDICINE**		
Practitioner ID DODGE N.D. / MOYAERT N.D. / MISCHLEY N.D.		
Practitioner Name VESPIGNANI N.D. / MCCARTY N.D. / EVANS N.D.		
NPI CIRCLE PRACTITIONER		
Address 5322 ROOSEVELT WAY NORTHEAST		
City SEATTLE	State WA	ZIP 98105
Phone (206) 525-8012	Fax (206) 525-8013	

PATIENT INFORMATION

DOB mm / dd / yyyy ☐ Male ☐ Female
Last Name
First Name | Middle Initial
Ht. ft. | in. Wt. lbs. BMI | Fasting? ☐ Yes ☐ No
Address
City | State | ZIP
Phone
Race ☐ American Indian/Alaskan Native ☐ Asian ☐ Black/African-American ☐ White/Caucasian (Non-Hispanic) ☐ Hispanic/Latino ☐ Other
☐ Patient Demographics Sheet Attached
Other Patient ID | Last Four Digits of SSN

Initials:
Time:

TEST MENU (Please fill in box completely)

☐ **PARKINSON'S DISEASE PANEL**

C9151 hsCRP (86141)
Homocysteine (83090)
F_2-Isoprostanes/Creatinine (82542/82570)
Standard Lipid Panel (80061)
HbA1c (83036)
Comprehensive Metabolic Panel (80053)
Ferritin (82728)
Iron & IBC (83550/83540)
Vitamin B12 (82607)
CBC w/Auto Diff. (85025)
Uric Acid (84550)
Vitamin D, 25 OH (82306)
OmegaCheck™ (82542)
DHEA-S (82627)
TSH (84443)
Methylmalonic Acid (83921)

TEST MENU (Please fill in box completely)

INFLAMMATION
☐ Myeloperoxidase (83876)
☐ Lp-PLA_2 Activity (83698)
☐ High-Sensitivity CRP (hs-CRP) (86141)
☐ Microalbumin/Creatinine (82043/82570)
☐ ADMA/SDMA (82542)
☐ Oxidized LDL (83516)
☐ F_2-Isoprostanes/Creatinine (82542/82570)

LIPIDS
☐ Standard Lipid Panel *(Includes non-HDL cholesterol)* (80061)
☐ If TGs >400 mg/dL, reflex to a Direct LDL (83721)
☐ ApoB (82172)
☐ ApoA1 (82172)
☐ sdLDL (83701)
☐ Lp(a) (83695)
☐ HDL2b (82664)
☐ *NMR LipoProfile®* with Lipids (83704/80061)*
☐ *NMR LipoProfile®* without Lipids (83704)*

METABOLIC
☐ TMAO (82542)

THYROID FUNCTION
☐ T4, Free (84439)
☐ T4, Total (84436)
☐ T3, Free (84481)
☐ T3, Total (84480)
☐ TSH (84443)
☐ Reflex to T4, Free if indicated (84439)
☐ Reflex to T3, Free if indicated (84481)

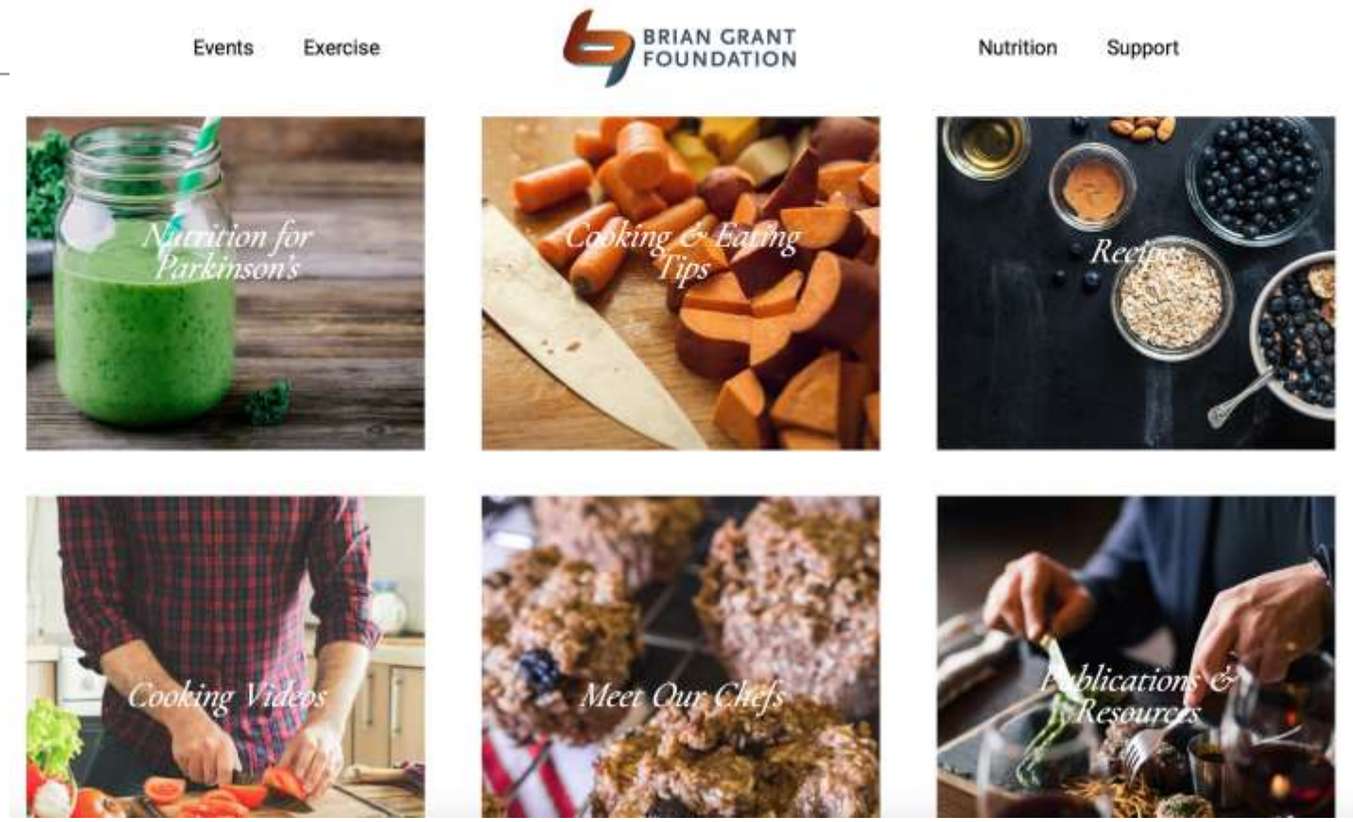
ANEMIA/IRON METABOLISM
☐ Ferritin (82728)
☐ Iron (83540)
☐ Serum Iron & IBC (83540/83550)

CANCER
☐ PSA, Total (84153)
☐ Reflex to PSA, Free if indictated (84154)
☐ PSA, Total (G0103; Medicare)
☐ Reflex to PSA, Free if indicated (84154)

COAGULATION/PLATELET FUNCTION
☐ AspirinWorks® (84431/82570)
☐ Fibrinogen Mass (85385)

Nutrition Resources

https://www.hindawi.com/journals/omcl/2017/6405278/



PARKINSON'S SCHOOL

An Online Course for Patients and Providers

Thank You!

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