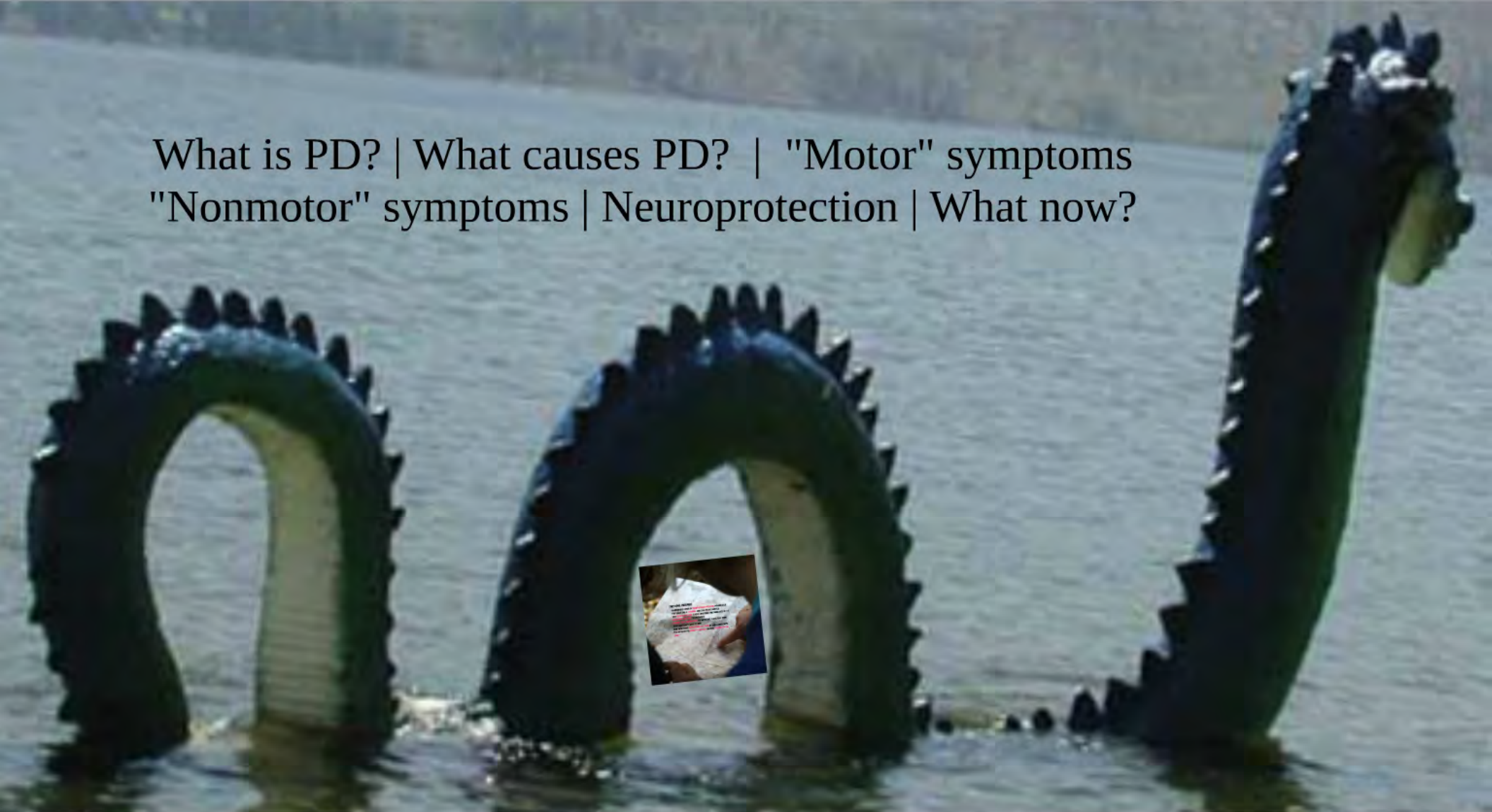


Daryl Wile, MD, MSc, FRCPC (Neurology)
Clinical Assistant Professor, UBC Southern Medical Program
November 3, 2017

OGOPOGO OVERVIEW

What is PD? | What causes PD? | "Motor" symptoms
"Nonmotor" symptoms | Neuroprotection | What now?



TAKE HOME MESSAGES

- PARKINSON'S IS CAUSED BY **MANUFACTURING PROBLEMS** IN BRAIN CELLS THAT CAUSE LOSS OF **DOPAMINE** AND OTHER BRAIN CHEMICALS
- YOUR **BRAIN WORKS HARD** TO KEEP EVERYTHING FUNCTIONING WELL BUT IT **NEEDS GOOD CONDITIONS** TO COMPENSATE
- **EXERCISE, SLEEP AND NUTRITION** ARE IMPORTANT TO GIVE YOUR BRAIN GOOD CONDITIONS TO WORK ITS BEST
- SOME MEDICATIONS **SUPPORT MANUFACTURING** BY ADDING INGREDIENTS
- IT IS IMPORTANT TO **LISTEN TO YOUR BODY** AND FIND **INFORMATION YOU TRUST**

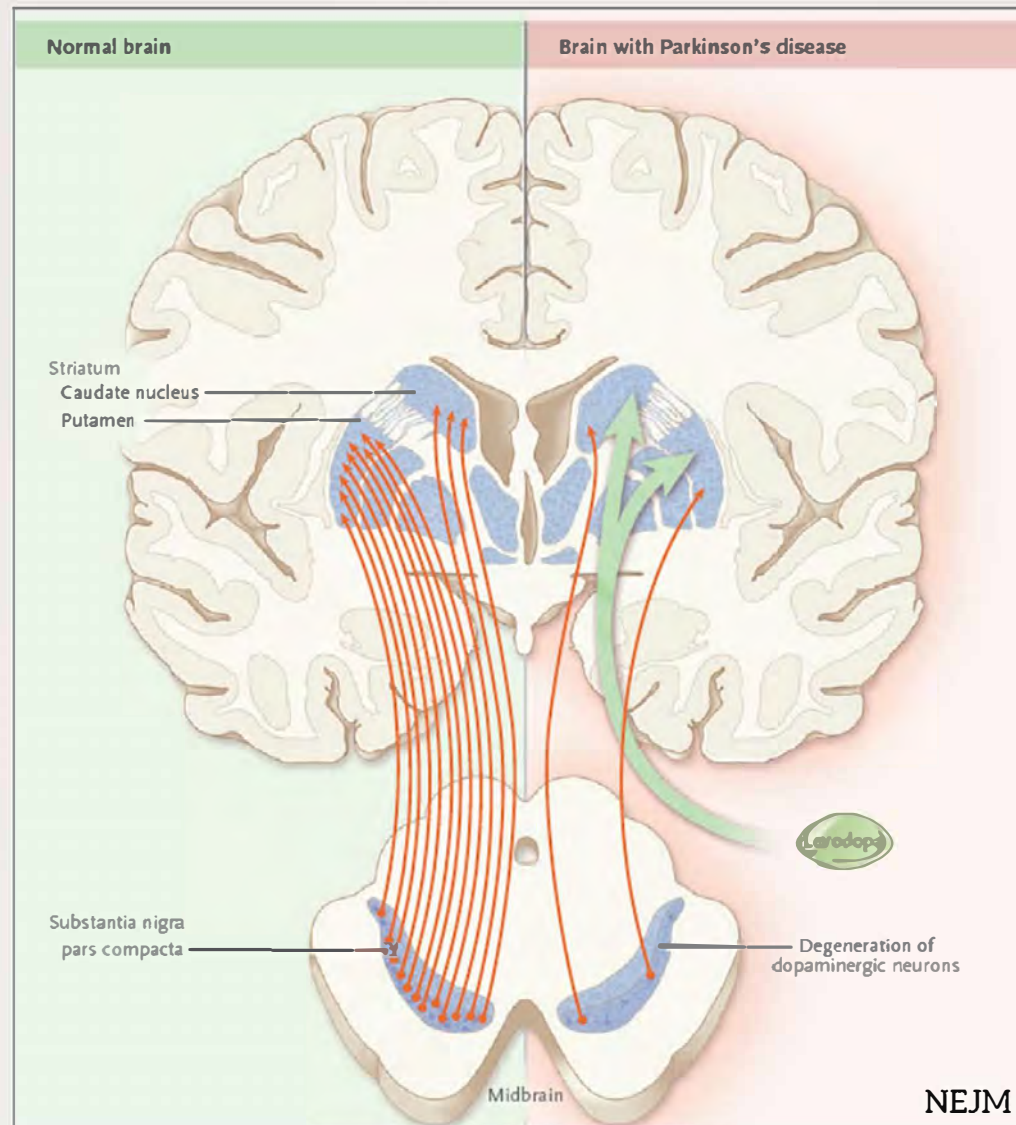
The Rusty Barrel



- A **chronic, progressive neurodegenerative** disorder
- Long underway when symptoms start
- Caused by a combination of genetic and environmental factors
- May be undetected until symptoms are obvious

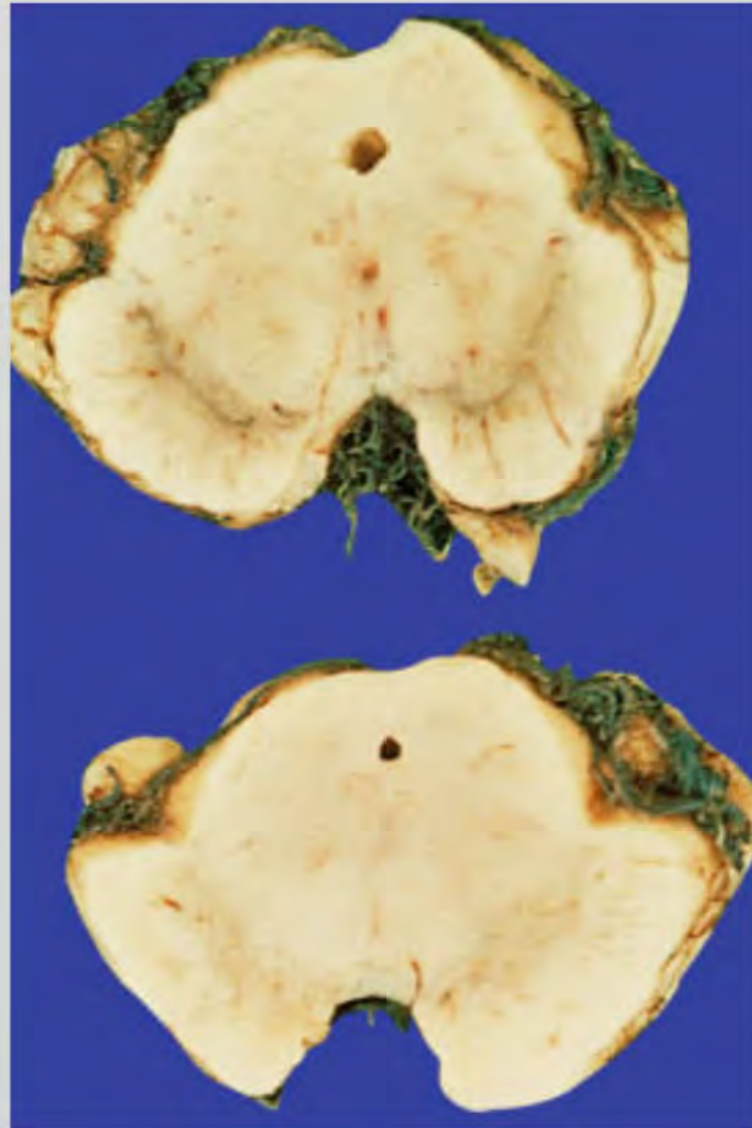


Dopamine deficiency is a SYMPTOM of the disease



LeWitt PA. Levodopa for the Treatment of Parkinson's Disease. The New England Journal of Medicine, 359:2468-2476 (2008)

Which is caused by MANUFACTURING FAILURE

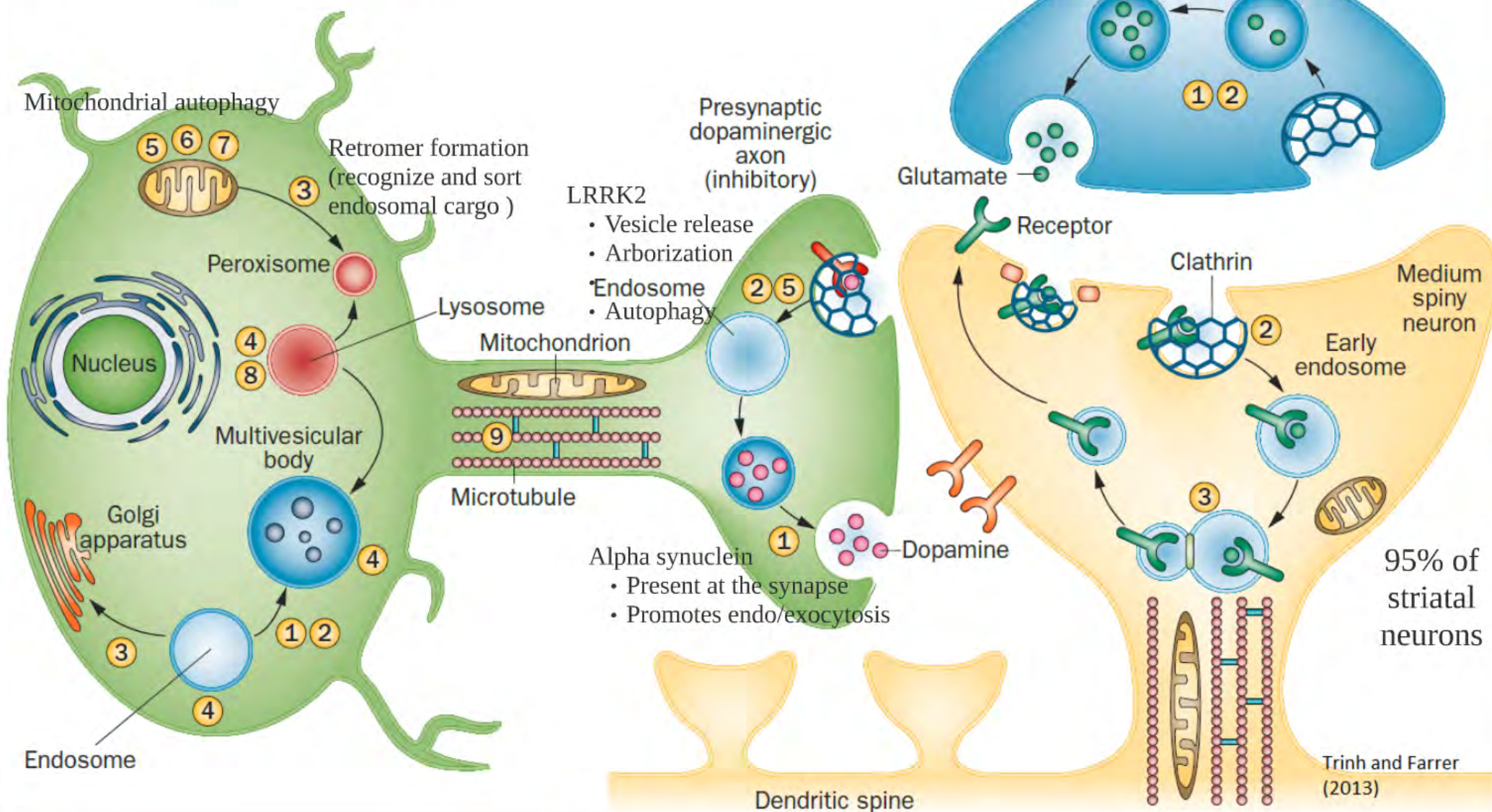


Parkinson's

Insights from Genetic Discoveries



- | | | |
|-----------------------|----------|-----------|
| 1 α -Synuclein | 4 GBA | 7 DJ-1 |
| 2 LRRK2 | 5 Parkin | 8 ATP13A2 |
| 3 VPS35 | 6 PINK1 | 9 MAPT |



Modified from Trinh J, Farrer M. Advances in the genetics of Parkinson disease. Nat. Rev. Neurol. 9, 445–454 (2013)

Broken down
factory equipment

Too much junk

Problems with sorting

Problems with transport



Years {

Symptoms emerge



Brain can no longer compensate



Cells die off



Cells stop working well



Environmental
stressors

Modifiable
Risk / protective
factors



Genetic
risk

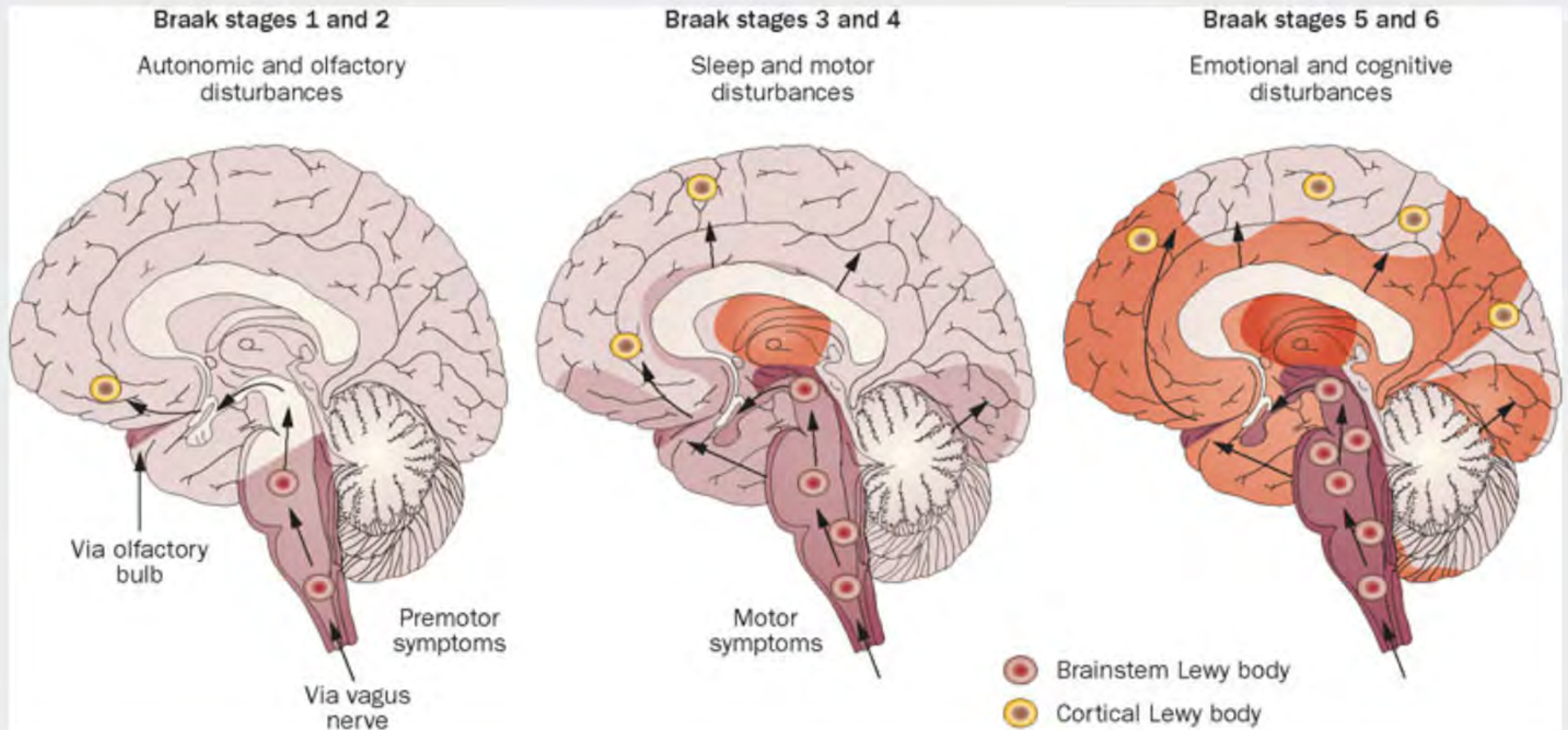
1

3

4

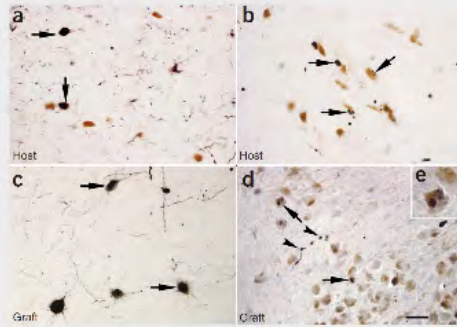
6

Nondopaminergic deficit



Doty RL. Olfactory dysfunction in Parkinson disease. *Nature Reviews Neurology* 8, 329–339 (2012)

Lewy Bodies spread



Grafted cells "catch" PD / Lewy bodies (Kordower 2008)

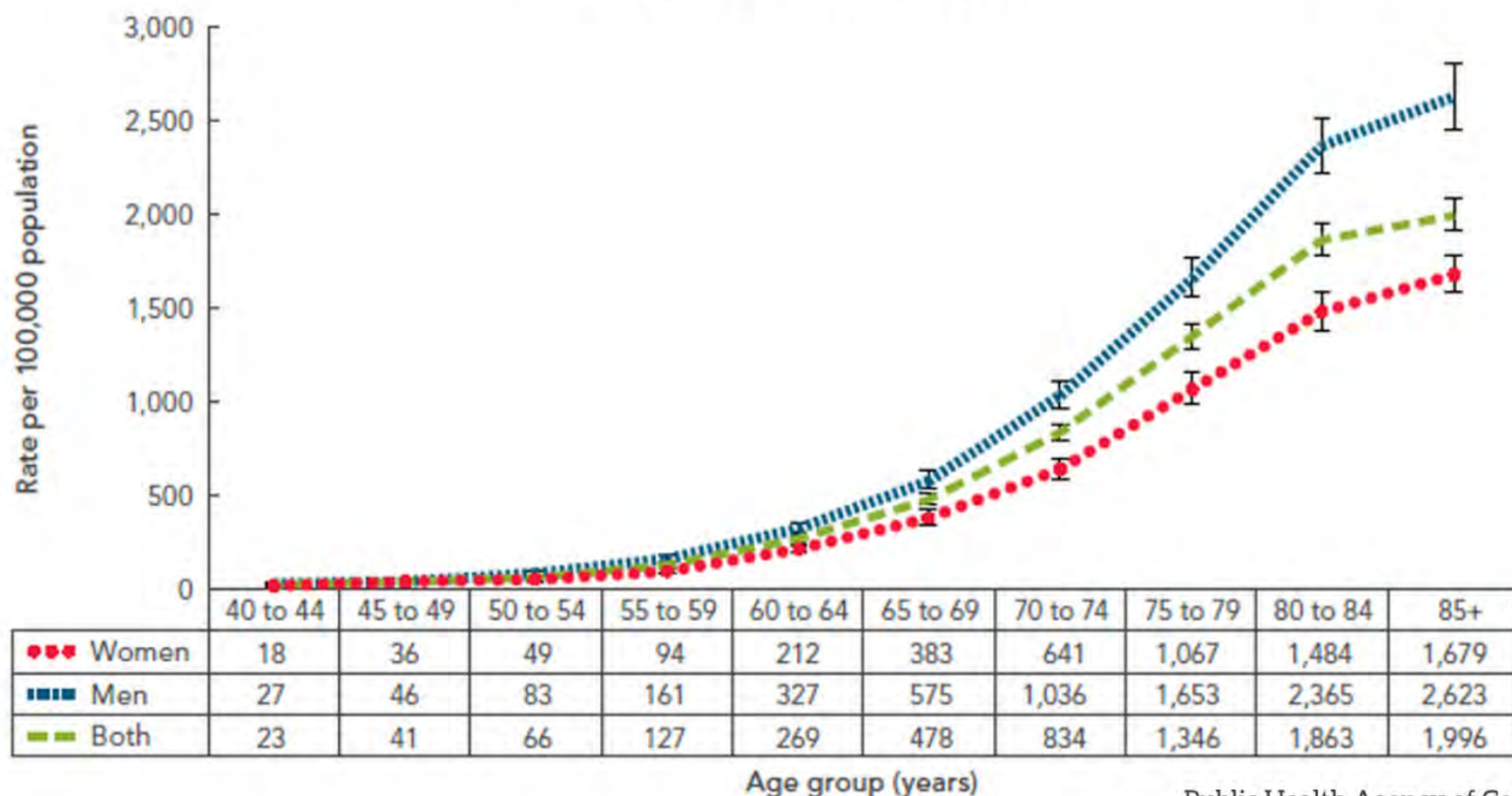


Danish 20 year study suggests the gut is an "entry point" to the brain (Svensson, 2015)

Kordower JH et al. Lewy body-like pathology in long-term embryonic nigral transplants in Parkinson's disease. *Nature Medicine*, 14(5):504-506 (2008)
Svensson E et al. Vagotomy and subsequent risk of Parkinson's disease. *Annals of Neurology*, Online Ahead of Print (June 2015)

Prevalence in British Columbia

Figure 3-2: Prevalence of parkinsonism*, by sex and age group, British Columbia, 2009/2010, BC Administrative Data Project [1]



Public Health Agency of Canada

BC MOH estimate: \$112 million direct costs (2012/2013)
 BC prevalence ~12500 | BC Interior ~2300

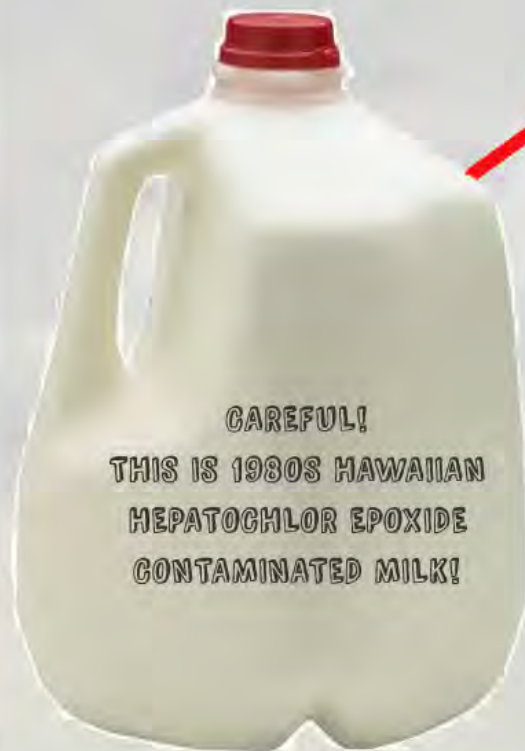
Environmental Risk and Protective Factors

HIGHER RISK

- Pesticides
- Head injuries
- Rural living
- Well water drinking

LOWER RISK

- Nicotine
- Coffee
- Anti-inflammatories
- Exercise



CAREFUL!
THIS IS 1980S HAWAIIAN
HEPATOCHLOR EPOXIDE
CONTAMINATED MILK!

TIME

Drinking Milk Is Linked to Parkinson's Disease: Study

Alice Park @aliceparkny Dec 9, 2015



A new study finds an intriguing link between contaminants found in milk and the risk of developing the brain disorder

Studies have found a connection between the consumption of dairy products and a higher risk of developing Parkinson disease, the neurodegenerative disorder that affects motor neurons in the brain. While researchers speculated that chemicals found in cows' milk might be responsible, there was little evidence to detail how dairy products like milk and cheese might be affecting people's risk of the disease.



Now, scientists may have uncovered a promising clue. Reporting in the journal *Neurology*, Robert Abbott, from Shiga University of Medical Science in Japan, and his colleagues took advantage of an environmental scandal in Hawaii in the 1980s to investigate the connection. At the time, an organochlorine pesticide used by pineapple farmers made its way into the milk supply when cows were fed a gruel made in part from the pineapple debris. Coincidentally, there was also a study of heart disease among Japanese-American men begun then that involved more than 8,000 men who were followed from mid-life to death. All provided detailed information about what they ate, including how much milk they drank, and some agreed to donate their brains for research upon death.

MORE: Diabetes Drugs May Offer Hope for Parkinson's Disease Treatment

Abbott and his team studied 449 brains and recorded the density of neurons in specific areas of the brain known to be affected by Parkinson's. They found that men who reported drinking more than two glasses of milk a day (16 oz) showed the thinnest nerve networks in these areas, suggesting compromised function of these nerves, compared to men who drank little or no milk. The milk drinkers also had residues of specific organochlorines called heptachlor epoxide.

Alice Park, "Drinking Milk Is Linked to Parkinson's Disease: Study", TIME magazine, Accessed online, <http://time.com/4143358/milk-parkinsons-disease-pesticides/> (2015)



20
Pe
Inte
Min



2010

Pesticide Sales in British Columbia

Integrated Pest Management Program

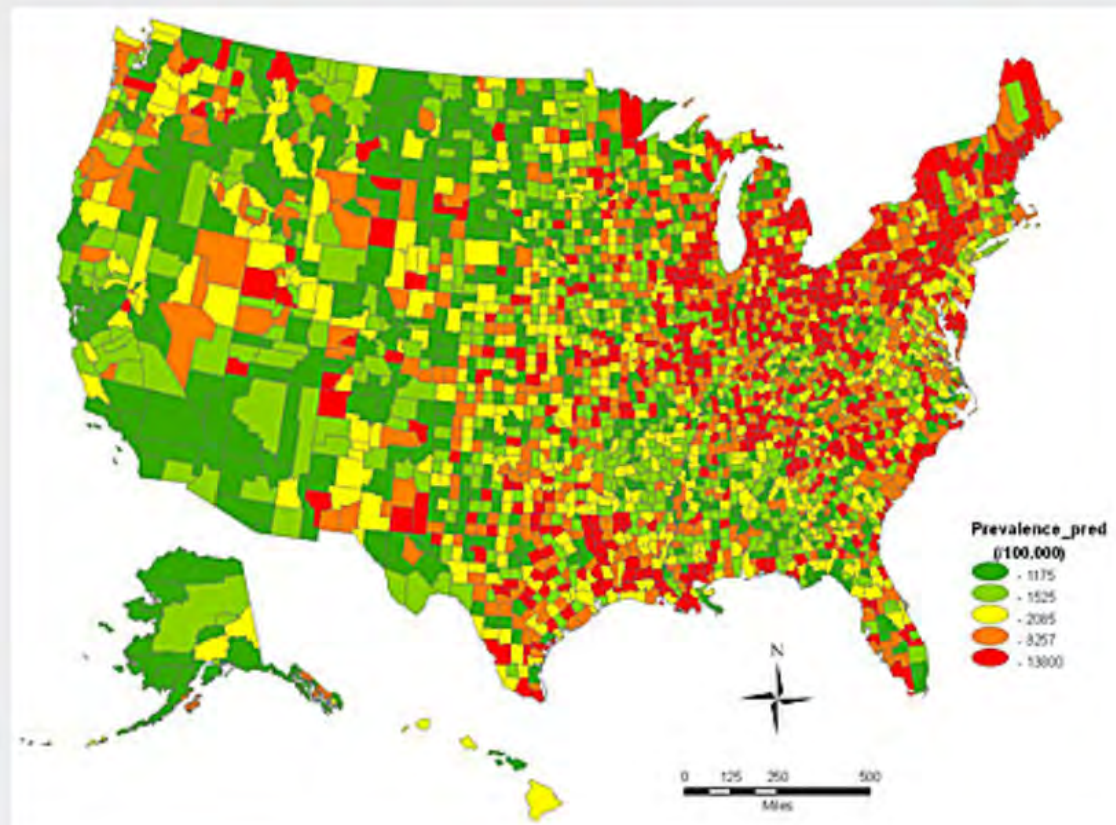
Ministry of Environment



Ministry of
Environment

Table 4: Quantity of selected active ingredients of interest sold (in kilograms)

Active ingredient	Pesticide type	Primary sector(s) of use	Quantity sold in 2010 (kg)	Quantity sold in 2003 (kg)	% change since 2003
2,4-D	Herbicide	Turf, ind. vegetation	27,943	19,425	+44%
Acetamiprid	Insecticide	Agriculture	219	119	+84%
Aluminum phosphide	Fumigant	Fumigation	2,879	196	+1369%
Atrazine	Herbicide	Agriculture	43	11,535	-99%
Azinphos-methyl	Insecticide	Agriculture	2532	6,499	-61%
Brodifacoum	Rodenticide	Structural	0.57	0.42	+36%
Bromadiolone	Rodenticide	Structural	1.25	0.53	+136%
Carbaryl	Insecticide	Agriculture	18,677	12,363	+51%
Carbofuran	Insecticide	Agriculture	236	484	-51%
Chlorothalonil	Fungicide	Agriculture, turf	50,768	33,505	+52%
Chlorpyrifos	Insecticide	Agriculture	4,235	4,561	-7%
Cypermethrin	Insecticide	Agriculture	333	199	+67%
Deltamethrin	Insecticide	Agriculture	956	71	+1247%
Diazinon	Insecticide	Agriculture	28,518	27,074	+5%
Dichlobenil	Herbicide	Agriculture	6,338	6,645	-5%
Endosulfan	Insecticide	Agriculture	2,101	4,729	-56%
Glyphosate	Herbicide	Agriculture, ind. vegetation, forestry	260,326	126,269	+106%
Imidacloprid	Insecticide	Agriculture	1,297	425	+205%
MCPA	Herbicide	Agriculture	24,470	23,568	+4%
Metam-sodium	Soil fumigant	Agriculture	4,601	28,582	-84%
Methomyl	Insecticide	Agriculture	2,278	338	+574%
Methyl Bromide	Fumigant	Fumigation	3,296	9,948	-67%
Oxamyl	Soil fumigant	Agriculture	1,068	698	+53%
Paraquat	Herbicide	Agriculture	8,052	5,418	+49%
Permethrin	Insecticide	Agriculture	1,485	2,055	-28%
Quintozene	Fungicide	Turf, agriculture	9,873	8,848	+12%
Strychnine	Rodenticide	Agriculture	28.1	47.0	-40%
Thiacloprid	Insecticide	Agriculture	118	0	N/A



Parkinson's Disease Motor Symptoms

Tremor

Rigidity (Stiffness)

Akinesia (Slowness)

Postural instability (Falls)

Soft voice

Less expressive face

Poor handwriting

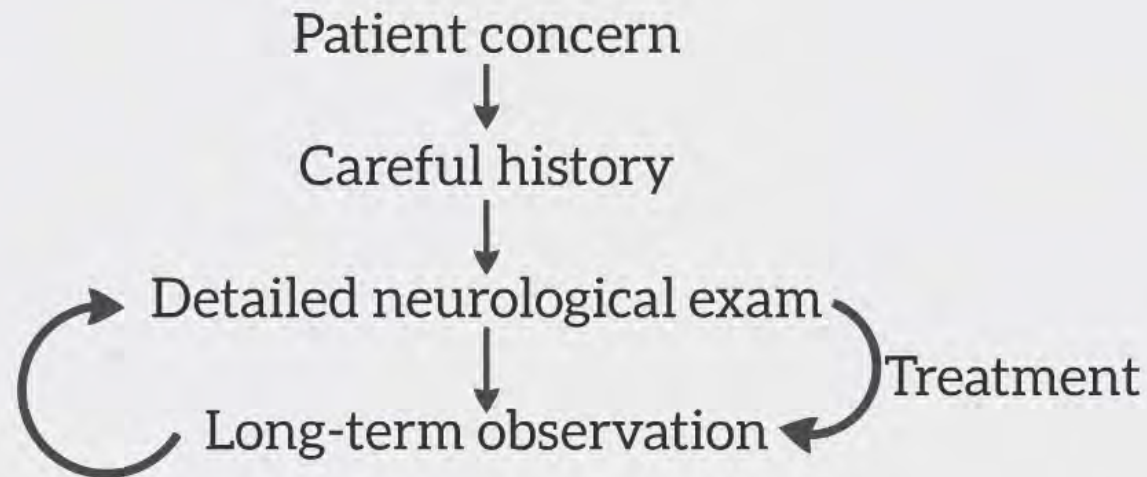
Trouble with everyday hand use


Trouble turning in bed

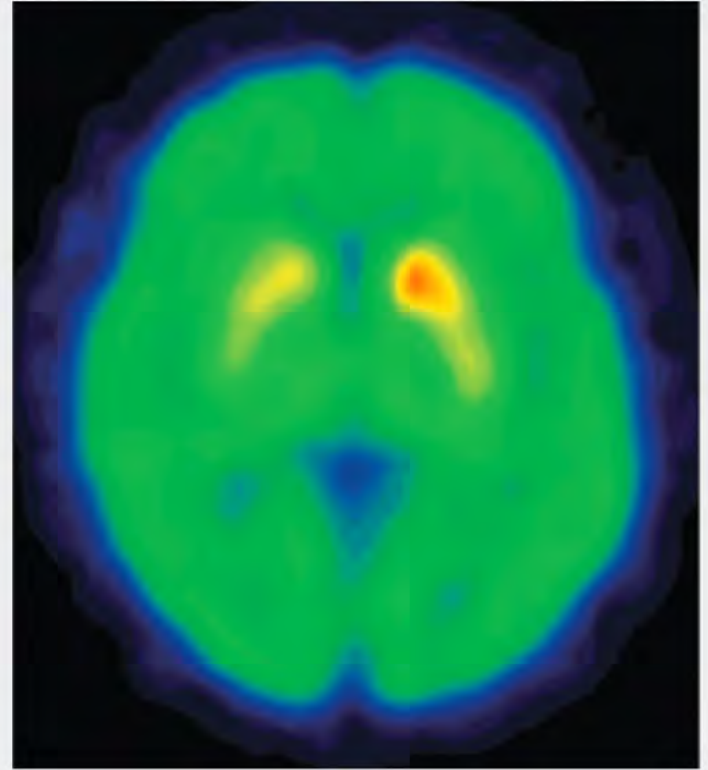
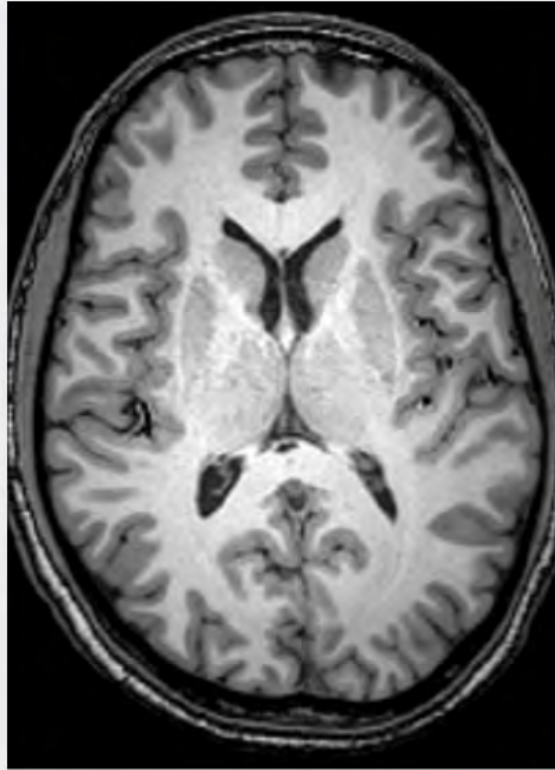
Trouble standing from low seats



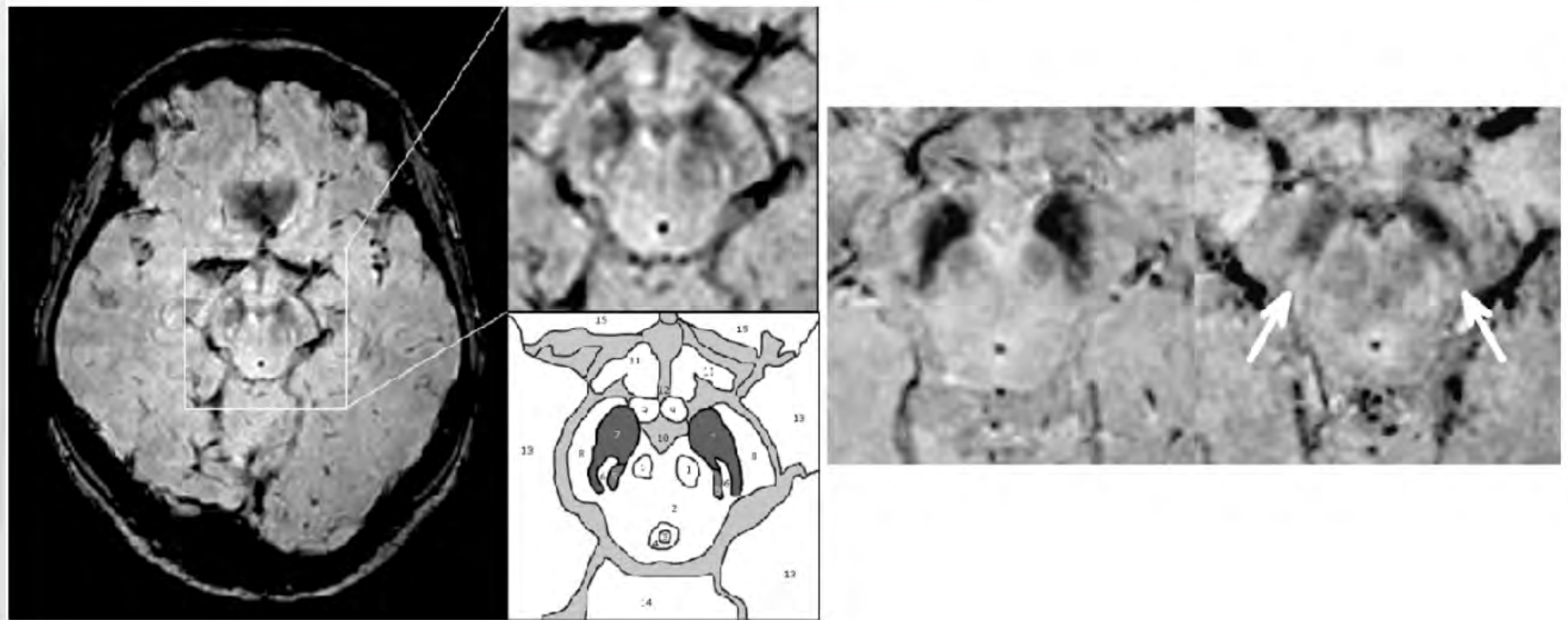
"Parkinsonism"



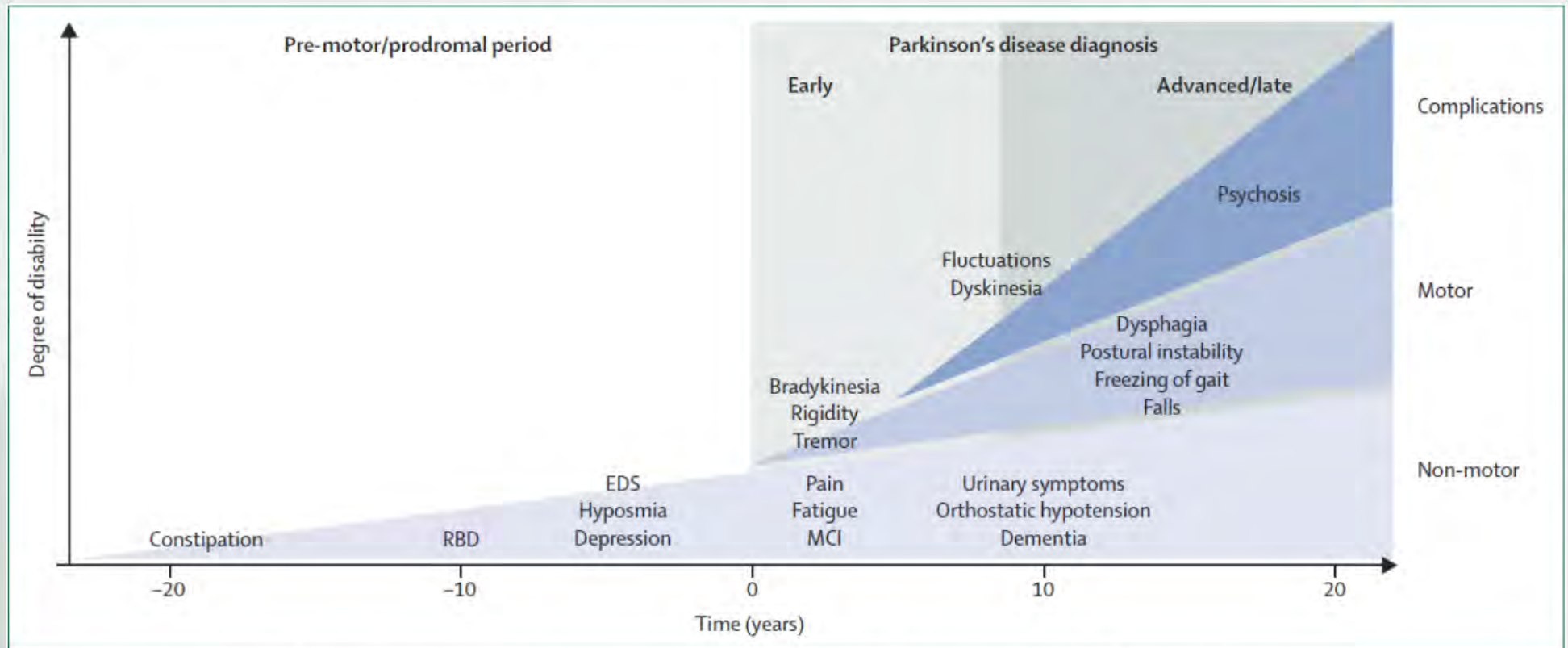
Cause of Parkinsonism	Texas 1995	Rochester 1967-1979
Parkinson disease	72.4%	85.5%
"Parkinson plus" syndromes	13.5%	
 PSP	5.7%	1.4%
MSA	5.0%	3.6%
CBD	2%	
Secondary parkinsonism	11.4%	
Vascular	5.1%	1.4%
Drug-induced	4.1%	7.2%
Other	2.2%	



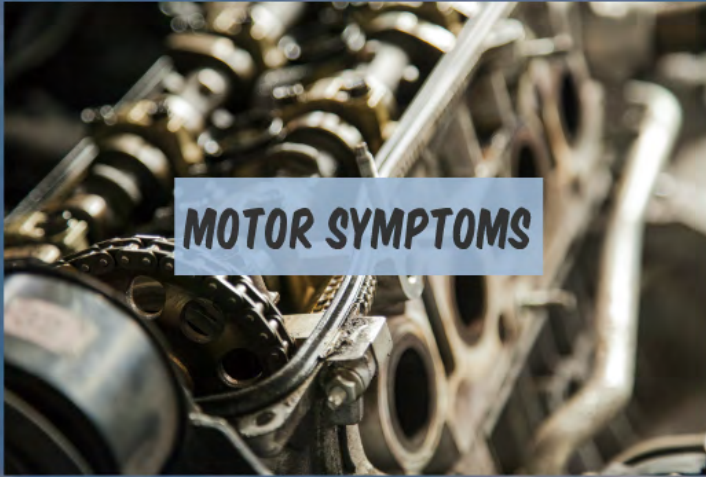
patterns of iron deposits might be visible on MRI



What will happen over time?

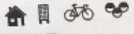


*Remember: no two patients are the same
(different symptoms, different rates)



When to start treatment?

When Parkinson's Disease begins...




Important targets:

- Maximize functional improvement
- Maximize quality of life

The "Shen of Shen" Model





Levodopa

• It is important to start treatment with the lowest dose possible

• When starting to start treatment, the lowest dose is 100mg



Levodopa: How to start

Timeline

Timeline

Timeline

Timeline

When to start treatment?

When Parkinson's Disease impairs...



Treatment targets:

- Minimize functional impairment
- Maintain quality of life



Levodopaphobia

- Levodopa is not toxic and does not cause disease to progress
- What matters is not how long it has been taken, it's how long someone has had Parkinson's



AMANTADINE

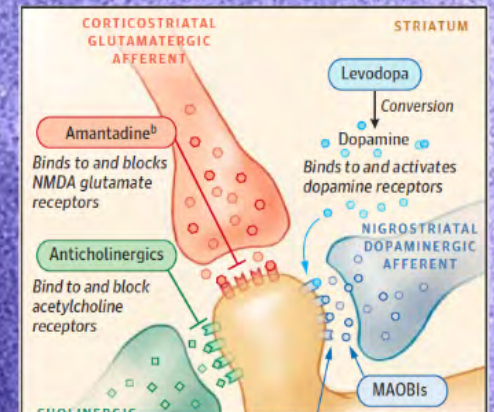
Dopamine
release

Glutamate

Dopamine
activity

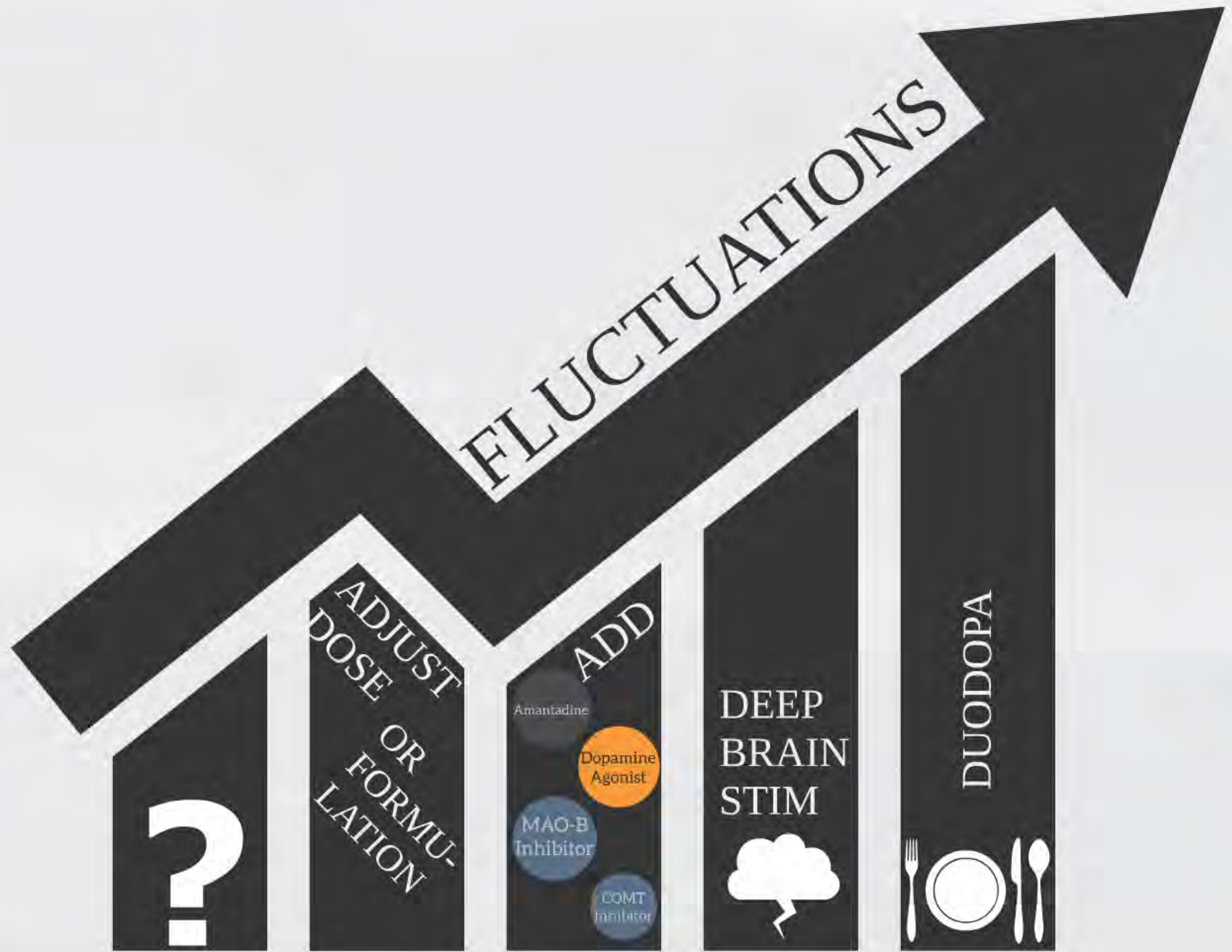
Some effect on
tremor, fatigue,
possibly on gait

Extended release
form in phase III
(ALLAY)



Where are those capsules?





TREMOR

NOT ALL PARKINSONIAN TREMOR RESPONDS TO LEVODOPA
OTHER OPTIONS

- ANTICHOLINERGICS
- AMANTADINE
- MIRTAZAPINE
- CLOZAPINE

HIGH INTENSITY FOCUSED ULTRASOUND

- WORKS
- IS HARD TO ACCESS
- IS COMING (?)

FALLS

31% have a fall within 12 months of diagnosis

Cochrane review: Physiotherapy, exercise

- 33 trials, 1518 participants
- Improved
 - gait
 - functional mobility
 - UPDRS scores

Evidence for

- Tai Chi
- Tango
- Cycling
- Yoga
- ...

Rivastigmine for gait stability in patients with Parkinson's disease (ReSPonD): a randomised, double-blind, placebo-controlled, phase 2 trial

Dr Emily J Henderson, MRCP¹, Prof Stephen R Lord, DSc, Matthew A Brodie, PhD, Daisy M Gaunt, MSc, Prof Andrew D Lawrence, PhD, Prof Jacqueline C T Close, MD, A L Whone, FRCP¹, Prof Y Ben-Shlomo, FFPH¹

† Joint senior authors

Published Online: 12 January 2016

Findings

Between Oct 4, 2012 and March 28, 2013, we enrolled 130 patients and randomly assigned 65 to the rivastigmine group and 65 to the placebo group. At week 32, compared with patients assigned to placebo (59 assessed), those assigned to rivastigmine (55 assessed) had improved step time variability for normal walking (ratio of geometric means 0.72, 95% CI 0.58–0.88; $p=0.002$) and the simple dual task (0.79; 0.62–0.99; $p=0.045$). Improvements in step time variability for the complex dual task did not differ between groups (0.81, 0.60–1.09; $p=0.17$). Gastrointestinal side-effects were more common in the rivastigmine group than in the placebo group ($p<0.0001$); 20 (31%) patients in the rivastigmine group versus three (5%) in the placebo group had nausea and 15 (17%) versus three (5%) had vomiting.

Interpretation

Rivastigmine can improve gait stability and might reduce the frequency of falls. A phase 3 study is needed to confirm these findings and show cost-effectiveness of rivastigmine treatment.

Cannabis



- There is currently no good quality evidence to show it helps patients with Parkinson's
- Some patients find it helpful for sleep, anxiety, nausea, appetite, pain
- Be alert for potential side effects (blood pressure, falls, confusion)



Can there be side effects?

- depends on the person
- depends on the illness
- depends on the product

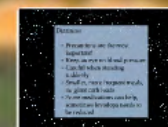
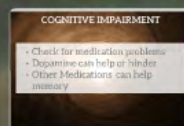
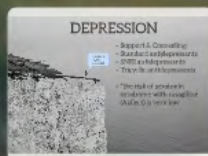


How do you know what you're getting?



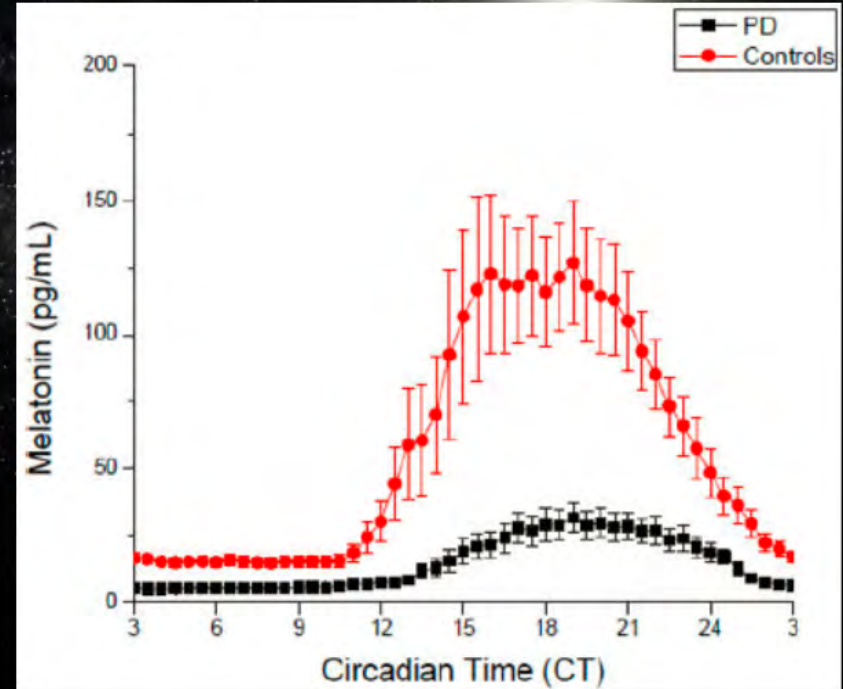
How will you decide if it works?

NONMOTOR SYMPTOMS




SLEEP

Restless legs
Insomnia
Nighttime mobility
Frequent urination
Somnolence
Fatigue
Dream behavior



Videvonic A et al. Circadian melatonin rhythm and excessive daytime sleepiness in Parkinson's disease. JAMA Neurol. 2014 April ; 71(4): 463-469.

DEPRESSION



Anxiety is highly comorbid!

- Support & Counseling
- Standard antidepressants
- SNRI antidepressants
- Tricyclic antidepressants
- *the risk of serotonin syndrome with rasagiline (Azilect) is very low

COGNITIVE IMPAIRMENT

- Check for medication problems
- Dopamine can help or hinder
- Other Medications can help memory

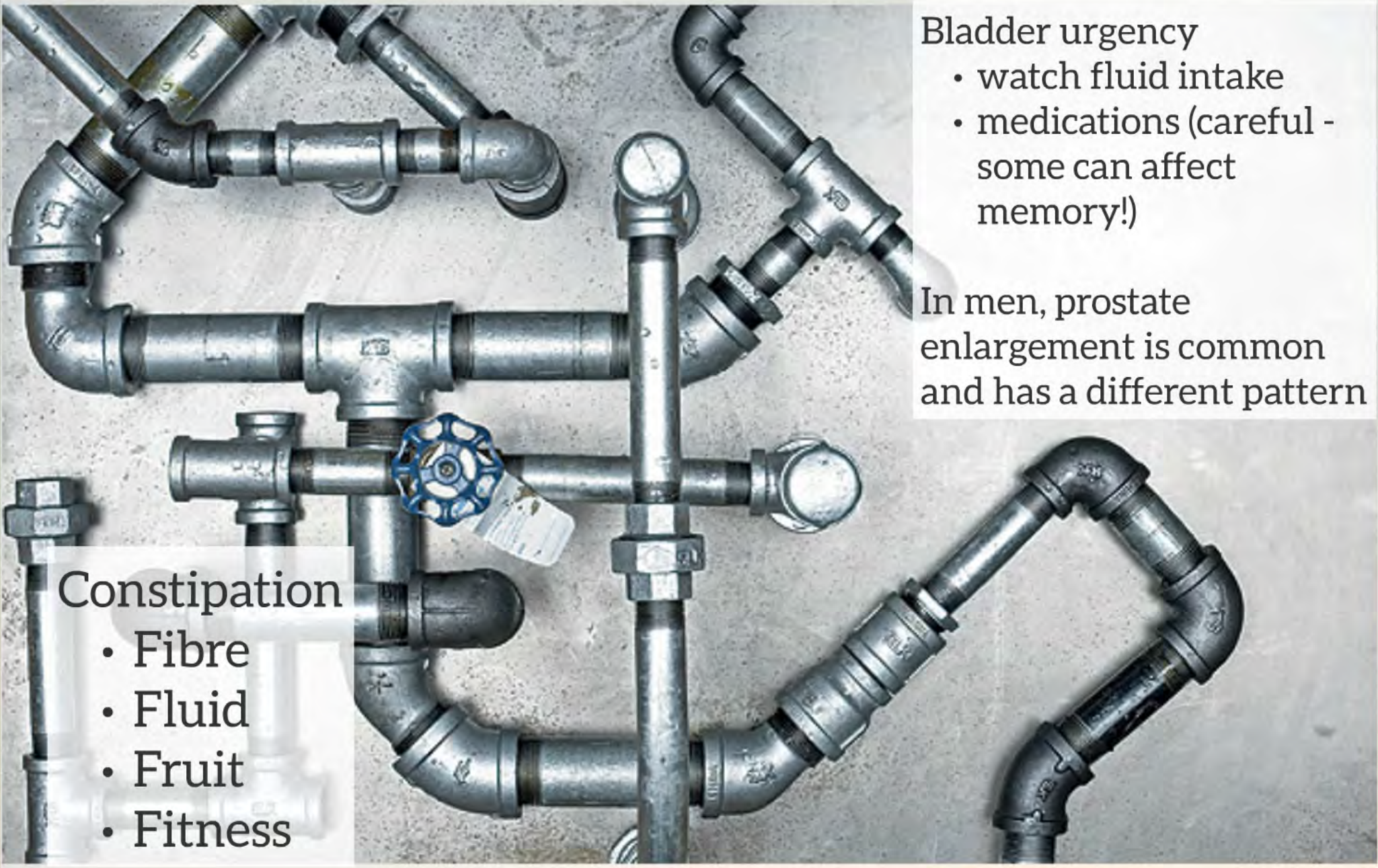
Hallucinations or delusions
sense of presence...

- 8-40%



Most medications for
hallucinations can harm
patients with Parkinson's

Any treatments that work in
the brain should be run by a
neurologist



Bladder urgency

- watch fluid intake
- medications (careful - some can affect memory!)

In men, prostate enlargement is common and has a different pattern

Constipation

- Fibre
- Fluid
- Fruit
- Fitness

Dizziness

- Precautions are the most important!
- Keep an eye on blood pressure
- Careful when standing suddenly
- Smaller, more frequent meals, no giant carb loads
- Some medications can help, sometimes levodopa needs to be reduced

[illegible]

Major Unmet Needs

- Neuroprotective / restorative treatments **THAT WORK**
- Biomarkers: earlier diagnosis and tracking effectiveness
- Starting **EARLY**
- Getting **everyone EXERCISING** safely

Neutrophilic cells - Practice parameter 2006

- Low-dose gabapentin is a safe adjunctive PD
- The treatment has been shown to be antidepressant
- No evidence for vitamin or folic acid addition to improve function
- Exercise may be helpful to improve function



© study-education, 2002 and 2003 study-
education, 2003: copyright due to history

© 2005 Blackwell Publishing Ltd *Journal of Internal Medicine* 258: 101–108

[illegible]

tested in RPP machine model
 two levels observed among 10 patients
 STUPP study numbers and RPP patients, but
 not in RPP model

- Deficiency and insufficiency associated with PD
- Commonly deficient in Canadian population

1. **Introduction**
 2. **Background**
 3. **Methodology**
 4. **Results**
 5. **Conclusion**
 6. **References**

[illegible]

RESEARCH DESIGN: STUDIES OF BEHAVIOR: QUALITATIVE RESEARCH

— *Book 1001: "The World" and "The World"*
 1001. *THE WORLD* (1001) (1001) (1001) (1001)
 1001. *THE WORLD* (1001) (1001) (1001) (1001)
 1001. *THE WORLD* (1001) (1001) (1001) (1001)
 1001. *THE WORLD* (1001) (1001) (1001) (1001)



...with a *châli* of a *châli*...

It is important to note that the results of this study are based on a cross-sectional design, which means that the data were collected at a single point in time. This limits the ability to establish causality between the variables studied. Future research should consider longitudinal designs to better understand the temporal relationships between the variables.

1999, 2000, 2001, 2002, 2003, 2004, 2005, 2006, 2007, 2008, 2009, 2010, 2011, 2012, 2013, 2014, 2015, 2016, 2017, 2018, 2019, 2020, 2021, 2022, 2023, 2024, 2025, 2026, 2027, 2028, 2029, 2030, 2031, 2032, 2033, 2034, 2035, 2036, 2037, 2038, 2039, 2040, 2041, 2042, 2043, 2044, 2045, 2046, 2047, 2048, 2049, 2050, 2051, 2052, 2053, 2054, 2055, 2056, 2057, 2058, 2059, 2060, 2061, 2062, 2063, 2064, 2065, 2066, 2067, 2068, 2069, 2070, 2071, 2072, 2073, 2074, 2075, 2076, 2077, 2078, 2079, 2080, 2081, 2082, 2083, 2084, 2085, 2086, 2087, 2088, 2089, 2090, 2091, 2092, 2093, 2094, 2095, 2096, 2097, 2098, 2099, 2100, 2101, 2102, 2103, 2104, 2105, 2106, 2107, 2108, 2109, 2110, 2111, 2112, 2113, 2114, 2115, 2116, 2117, 2118, 2119, 2120, 2121, 2122, 2123, 2124, 2125, 2126, 2127, 2128, 2129, 2130, 2131, 2132, 2133, 2134, 2135, 2136, 2137, 2138, 2139, 2140, 2141, 2142, 2143, 2144, 2145, 2146, 2147, 2148, 2149, 2150, 2151, 2152, 2153, 2154, 2155, 2156, 2157, 2158, 2159, 2160, 2161, 2162, 2163, 2164, 2165, 2166, 2167, 2168, 2169, 2170, 2171, 2172, 2173, 2174, 2175, 2176, 2177, 2178, 2179, 2180, 2181, 2182, 2183, 2184, 2185, 2186, 2187, 2188, 2189, 2190, 2191, 2192, 2193, 2194, 2195, 2196, 2197, 2198, 2199, 2200, 2201, 2202, 2203, 2204, 2205, 2206, 2207, 2208, 2209, 2210, 2211, 2212, 2213, 2214, 2215, 2216, 2217, 2218, 2219, 2220, 2221, 2222, 2223, 2224, 2225, 2226, 2227, 2228, 2229, 2230, 2231, 2232, 2233, 2234, 2235, 2236, 2237, 2238, 2239, 2240, 2241, 2242, 2243, 2244, 2245, 2246, 2247, 2248, 2249, 2250, 2251, 2252, 2253, 2254, 2255, 2256, 2257, 2258, 2259, 2260, 2261, 2262, 2263, 2264, 2265, 2266, 2267, 2268, 2269, 2270, 2271, 2272, 2273, 2274, 2275, 2276, 2277, 2278, 2279, 2280, 2281, 2282, 2283, 2284, 2285, 2286, 2287, 2288, 2289, 2290, 2291, 2292, 2293, 2294, 2295, 2296, 2297, 2298, 2299, 2300, 2301, 2302, 2303, 2304, 2305, 2306, 2307, 2308, 2309, 2310, 2311, 2312, 2313, 2314, 2315, 2316, 2317, 2318, 2319, 2320, 2321, 2322, 2323, 2324, 2325, 2326, 2327, 2328, 2329, 2330, 2331, 2332, 2333, 2334, 2335, 2336, 2337, 2338, 2339, 2340, 2341, 2342, 2343, 2344, 2345, 2346, 2347, 2348, 2349, 2350, 2351, 2352, 2353, 2354, 2355, 2356, 2357, 2358, 2359, 2360, 2361, 2362, 2363, 2364, 2365, 2366, 2367, 2368, 2369, 2370, 2371, 2372, 2373, 2374, 2375, 2376, 2377, 2378, 2379, 2380, 2381, 2382, 2383, 2384, 2385, 2386, 2387, 2388, 2389, 2390, 2391, 2392, 2393, 2394, 2395, 2396, 2397, 2398, 2399, 2400, 2401, 2402, 2403, 2404, 2405, 2406, 2407, 2408, 2409, 2410, 2411, 2412, 2413, 2414, 2415, 2416, 2417, 2418, 2419, 2420, 2421, 2422, 2423, 2424, 2425, 2426, 2427, 2428, 2429, 2430, 2431, 2432, 2433, 2434, 2435, 2436, 2437, 2438, 2439, 2440, 2441, 2442, 2443, 2444, 2445, 2446, 2447, 2448, 2449, 2450, 2451, 2452, 2453, 2454, 2455, 2456, 2457, 2458, 2459, 2460, 2461, 2462, 2463, 2464, 2465, 2466, 2467, 2468, 2469, 2470, 2471, 2472, 2473, 2474, 2475, 2476, 2477, 2478, 2479, 2480, 2481, 2482, 2483, 2484, 2485, 2486, 2487, 2488, 2489, 2490, 2491, 2492, 2493, 2494, 2495, 2496, 2497, 2498, 2499, 2500, 2501, 2502, 2503, 2504, 2505, 2506, 2507, 2508, 2509, 2510, 2511, 2512, 2513, 2514, 2515, 2516, 2517, 2518, 2519, 2520, 2521, 2522, 2523, 2524, 2525, 2526, 2527, 2528, 2529, 2530, 2531, 2532, 2533, 2534, 2535, 2536, 2537, 2538, 2539, 2540, 2541, 2542, 2543, 2544, 2545, 2546, 2547, 2548, 2549, 2550, 2551, 2552, 2553, 2554, 2555, 2556, 2557, 2558, 2559, 2560, 2561, 2562, 2563, 2564, 2565, 2566, 2567, 2568, 2569, 2570, 2571, 2572, 2573, 2574, 2575, 2576, 2577, 2578, 2579, 2580, 2581, 2582, 2583, 2584, 2585, 2586, 2587, 2588, 2589, 2590, 2591, 2592, 2593, 2594, 2595, 2596, 2597, 2598, 2599, 2600, 2601, 2602, 2603, 2604, 2605, 2606, 2607, 2608, 2609, 2610, 2611, 2612, 2613, 2614, 2615, 2616, 2617, 2618, 2619, 2620, 2621, 2622, 2623, 2624, 2625, 2626, 2627, 2628, 2629, 2630, 2631, 2632, 2633, 2634, 2635, 2636, 2637, 2638, 2639, 2640, 2641, 2642, 2643, 2644, 2645, 2646, 2647, 2648, 2649, 2650, 2651, 2652, 2653, 2654, 2655, 2656, 2657, 2658, 2659, 2660, 2661, 2662, 2663, 2664, 2665, 2666, 2667, 2668, 2669, 2670, 2671, 2672, 2673, 2674, 2675, 2676, 2677, 2678, 2679, 2680, 26

Antioxidants

- Sirtuin 3
- Exonatide
- Insulin / IGF
- Deacetylase

- Phenylbutyrate
- Simvastatin
- Anti-tumor antibody

- Sildenafil
- Tadalafil
- Nitroglycerine
- Isradefylline (A)

- GDNF

- Neuritis

Dr. Thomas J. Patterson, Jr.
Department of Psychology
University of Minnesota
150 East River Street
St. Paul, MN 55101
U.S.A.
Tel: 612/625-4300
Fax: 612/625-4300
E-mail: tpattson@tc.umn.edu



Search for the appropriate word in the glossary.

A study conducted at the University of Connecticut's Farmington campus involving 16 adult patients with Parkinson's disease with dementia who were given 100 mg of L-Dopa against a background of low-dose levodopa therapy for 12 weeks found that L-Dopa was effective in improving cognition, motor skills and quality of life in 12 patients but ineffective in 4.

Major Unmet Needs

- Neuroprotective / restorative treatments
THAT WORK
- Biomarkers: **earlier diagnosis** and
tracking effectiveness
- Starting **EARLY**
- Getting **everyone EXERCISING** safely

Neuroprotection - Practice parameter 2006

- Levodopa does not accelerate PD
- No treatment has been shown to be neuroprotective
- No evidence for vitamin or food additives to improve function
- Exercise may be helpful to improve function



n - Practice parameter 2006

celerate PD

shown to be

in or food
function

ful to improve



- QE2 study (80 patients, 2002) and QE3 study (600 patients, 2012): stopped due to futility



- NET-PD study (2013) stopped due to futility



- May not get to CNS adequately
- IV open label 9 patients 1996: 2-4 month benefit
- 20 person double blind (2009): safe, tolerated, possible benefit
- intranasal study underway



- Worked in MPTP mouse model
- Lower levels observed among PD patients
- DATATOP study randomized 800 patients for 1 year - no benefit



- Deficiency and insufficiency associated with PD
- Commonly deficient in Canadian population

DNA variants in *CACNA1C* modify Parkinson disease risk only when vitamin D level is deficient
(2020)

Abstract
Background: Vitamin D deficiency has been associated with Parkinson's disease (PD) risk. We investigated whether genetic variants in *CACNA1C*, which encodes the L-type calcium channel α_1D , modify PD risk in the context of vitamin D deficiency. Methods: Two thousand six hundred and thirty-four PD patients and 2,635 controls from the International Parkinson's Disease Genomics Consortium (IPDGC) were genotyped for 10 *CACNA1C* variants. Vitamin D levels were measured in a subset of 1,000 PD patients and 1,000 controls. Results: The *CACNA1C* variant rs1044396 (G>A) was associated with PD risk in individuals with vitamin D deficiency (OR = 1.2, 95% CI = 1.05-1.38). This association was not observed in individuals with sufficient vitamin D levels. Conclusion: Our results suggest that vitamin D deficiency is a modifier of PD risk, and that genetic variants in *CACNA1C* modify this risk. Further studies are needed to clarify the underlying mechanisms.

Keywords: Parkinson's disease, vitamin D, *CACNA1C*, genetics, Parkinson's disease, vitamin D deficiency, L-type calcium channel, α_1D .



- QE2 study (80 patients, 2002) and QE3 study (600 patients, 2012): stopped due to futility



- NET-PD study (2013) stopped due to futility



- May not get to CNS adequately
- IV open label 9 patients 1996: 2-4 month benefit
- 20 person double blind (2009): safe, tolerated, possible benefit
- intranasal study underway



- Worked in MPTP mouse model
- Lower levels observed among PD patients
- DATATOP study randomized 800 patients for 1 year - no benefit



- Deficiency and insufficiency associated with PD
- Commonly deficient in Canadian population

DNA variants in *CACNA1C* modify Parkinson disease risk only when vitamin D level is deficient

[OPEN](#)

Liyong Wang, PhD
Lizmarie Maldonado, MSPH
Gary W. Beecham, PhD
Eden R. Martin, PhD
Marian L. Furr, MD
James C. Ritchie, PhD
Jonathan L. Haines, PhD
Cyrus P. Zabetian, MS, MD
Haydeh Payami, PhD
Margaret A. Pericak-Vance, PhD
Jeffery M. Vance, MD, PhD
William K. Scott, PhD

Correspondence to:
Dr. Scott:
bscott@med.miami.edu or
Dr. Wang:
lwang10@med.miami.edu

ABSTRACT

Objective: To evaluate the association between the genetic variants in *CACNA1C*, which encodes the α_1 subunit of the L-type voltage-sensitive calcium channel (LVSCC) and Parkinson disease (PD) while accounting for interactions with vitamin D concentration.

Methods: Two independent case-control data sets (478 cases and 431 controls; 482 cases and 412 controls) were used. Joint effects of single nucleotide polymorphisms (SNPs) and SNP-vitamin D interaction were analyzed by comparing models containing vitamin D deficiency, SNP genotypes, SNP-vitamin D interaction, and covariates to a restricted model with only vitamin D deficiency and covariates. Meta-analysis was used to combine the joint effects in the 2 data sets. Analysis was stratified by vitamin D deficiency to demonstrate the pattern of SNP-vitamin D interaction.

Results: Vitamin D deficiency was associated with PD in both data sets (odds ratio [OR] = 1.9–2.7, $p < 0.009$). SNP rs34621387 demonstrated a significant joint effect (meta-analysis, $p = 7.5 \times 10^{-5}$; Bonferroni corrected, $p = 0.02$). The G allele at rs34621387 is associated with PD in vitamin D-deficient individuals in both data sets (OR = 2.0–2.1, confidence interval = 1.3–3.5, $p = 0.002$) but is not associated with PD in vitamin D-sufficient individuals ($p > 0.8$ in both data sets).

Conclusions: Previous studies suggest that vitamin D deficiency is associated with PD and sustained opening of LVSCC contributes to the selective vulnerability of dopaminergic neurons in PD. Our data demonstrate that the association between genetic variations in *CACNA1C* and PD depends on vitamin D deficiency, providing one potential mechanism underlying the association between vitamin D deficiency and PD. *Neurol Genet* 2016;2:e72; doi: 10.1212/NXG.000000000000072

Antioxidants

- Sirtuin 3
- Exenatide
- Inosine / uric acid
- Deferiprone*

Protein accumulation

- Phenylbutyrate
- Sirolimus
- Affitope (antibody)

Multiple mechanisms

- Safinamide
- Isradipine (Ca++)
- Nicotine patch
- Istradefylline (A2A)

Regenerative

- GDNF
- Neurturin

