



PMD Alliance
Parkinson & Movement Disorder Alliance

The Skeptic's Guide to Living ("Better") with PD

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When living with PD, we want to know what we can do to improve our quality of life

- ▶ The clinician who treats us for PD is one source of information but...
 - ▶ Clinicians don't always have the *time* to keep up with newest treatments and research, after their specialty training is finished
- ▶ It is **empowering** to be able to make sense of new information about managing PD symptoms **ourselves**.



When living with PD, we want to know what we can do to improve our quality of life

- ▶ OTHER Sources of information about what might help
 - ▶ Hearing/reading/seeing the experiences of others
 - ▶ Websites : text or videos or social media
 - ▶ From major PD organizations (e.g. Michael J. Fox Foundation, Parkinson's Foundation, MJFF)
 - ▶ From 'alternative' news (Mercola.com)
 - ▶ From online support groups (FB groups for *PwP, Healthunlocked)
 - ▶ From lay language summaries of new research (subscription emails or press releases)
 - ▶ From Research Abstracts or Full text research articles

**HOW DO WE MAKE SENSE OF
COMPETING OR CONTRADICTIONARY
CLAIMS FROM THESE SOURCES OF INFORMATION?**

*PwP=People with Parkinson's

When living with PD, we want to know what we can do to improve our quality of life

- ▶ Types of information about ...
 - ▶ New prescription medications
 - ▶ New nonprescription supplements (“nutriceuticals”)
 - ▶ Vitamins or nutritional supplements
 - ▶ Herbal formulations
 - ▶ Dietary programs or interventions (Paleo, Ketogenic, Mediterranean diet)
 - ▶ Exercise and related physical programs
 - ▶ Cardio (forced cadence exercise, high intensity exercise) strength training, dance, physical therapy, hatha yoga, boxing, tai chi, aqua therapy

Skeptic's Guide

- ▶ A skeptic requires that new claims be backed by evidence.

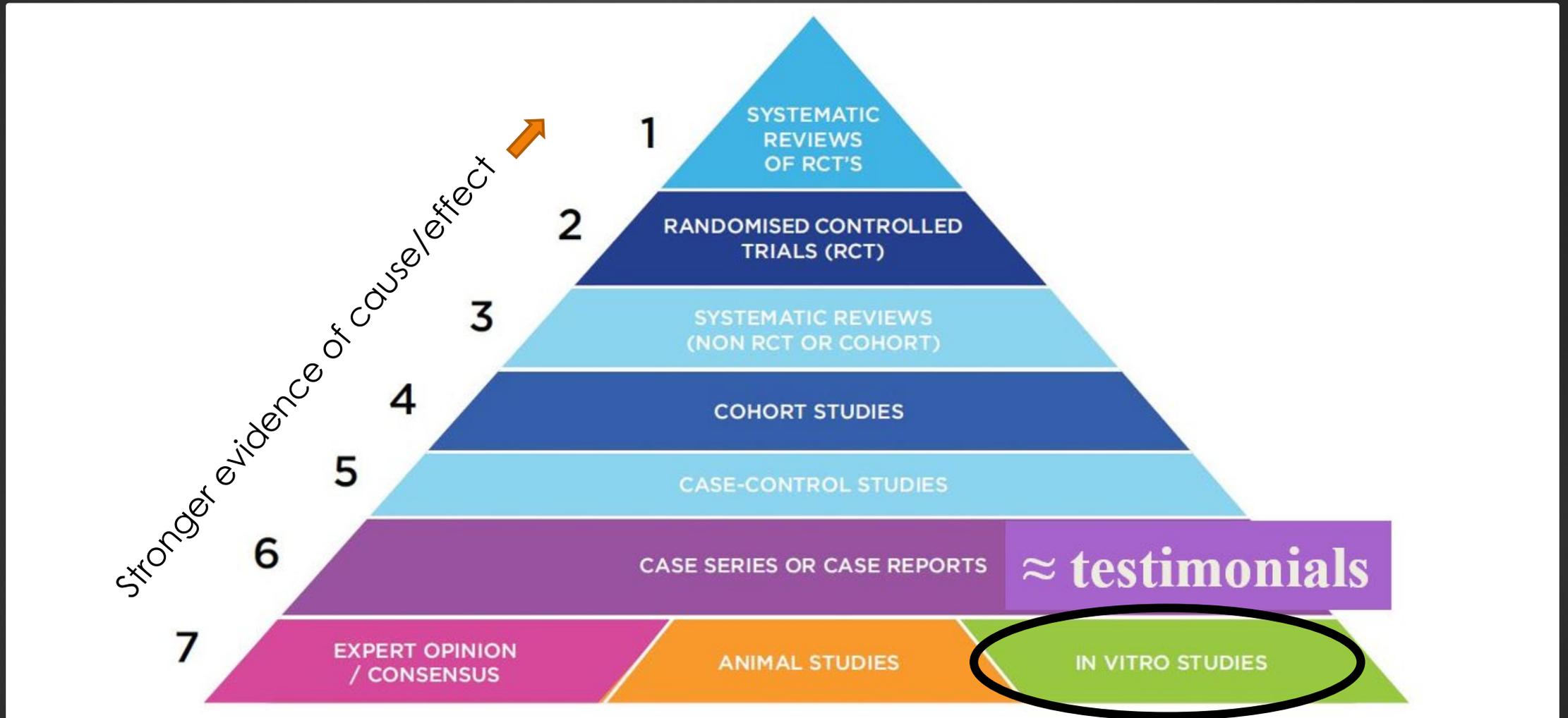


What counts is not what sounds plausible, not what we would like to believe, not what one or two witnesses claim, but only what is supported by hard evidence rigorously and skeptically examined. Extraordinary claims require extraordinary evidence.

(Carl Sagan)



Types of evidence: The strength of evidence pyramid

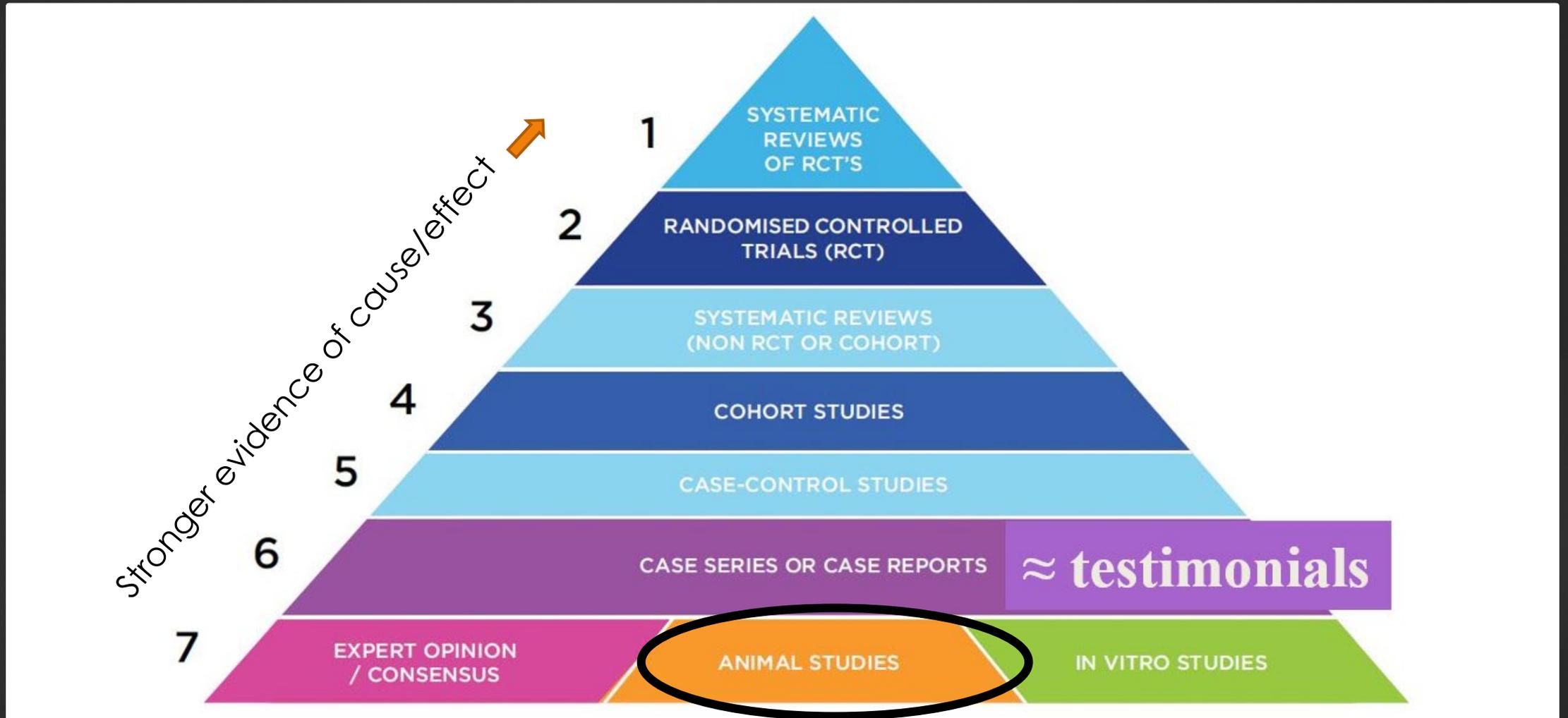


Types of Evidence: In vitro studies



- ▶ *In vitro* studies use cells derived from animals or cell lines.
- ▶ They look at possible causes of PD and try to ‘attack’ these possible causes
- ▶ These model systems are relatively cheap and simple to procure and can sometimes be used for drug discovery in certain disorders
- ▶ They don’t capture the inherent complexity of organ systems, especially the most complex (human brain).
- ▶ Findings don’t replicate in PwP.

Types of evidence: The strength of evidence pyramid



Animal studies



- ▶ The problem is that animals other than humans (and maybe occasionally our closest primate relatives) don't get PD. These studies use artificially induced animal models of PD.

- ▶ We and, to a lesser extent, our primate relatives have dopaminergic neurons that produce neuromelanin, which makes them appear dark.



primate relatives have **neuromelanin** (what makes them appear dark).

- ▶ These neuromelanin-producing neurons are particularly susceptible to any attack on the substantia nigra.

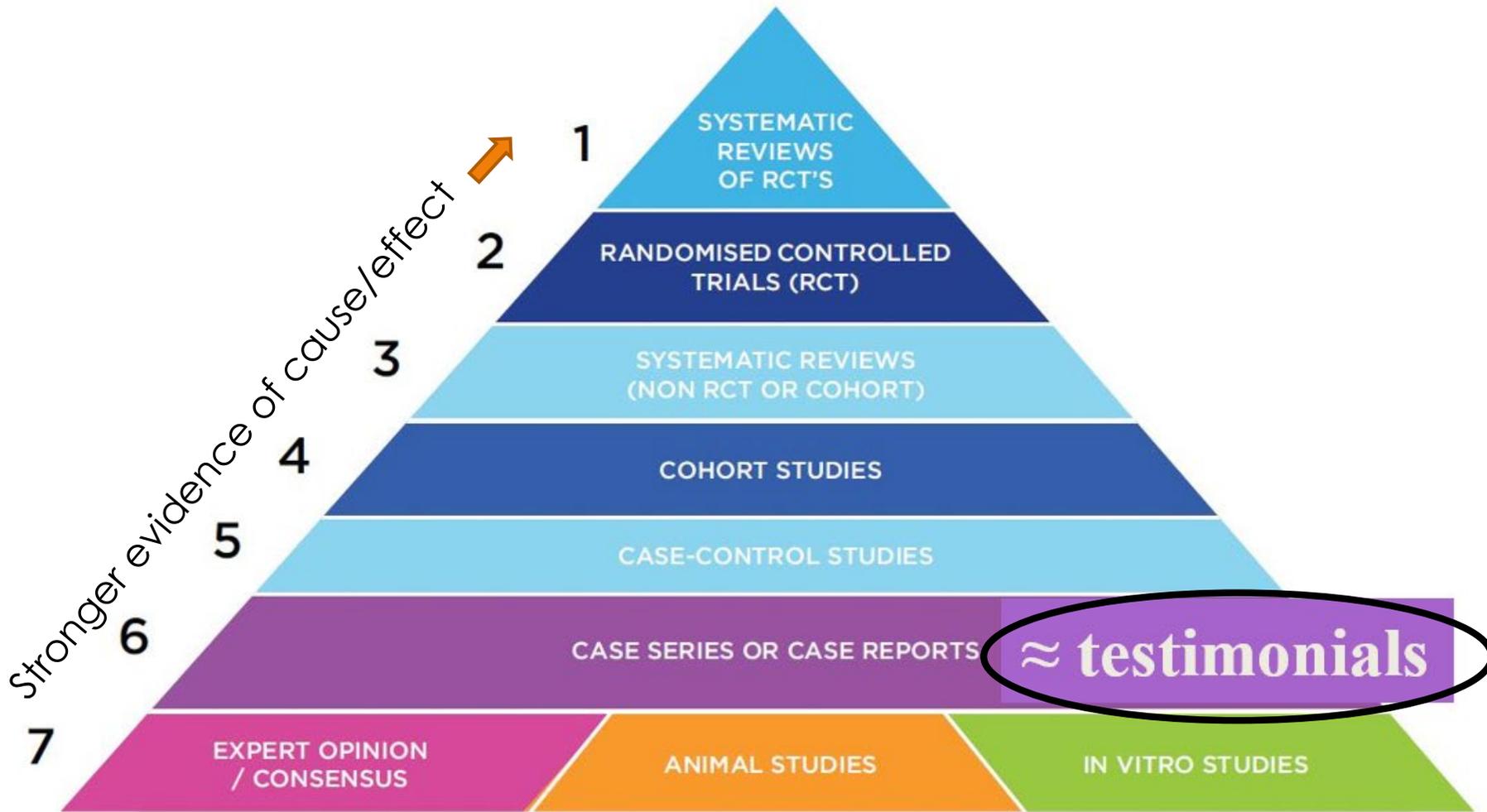
are particularly susceptible to any attack on the substantia nigra.

- ▶ Neuromelanin is absent in humans and gradually increases throughout a person's lifetime.

Cynomolgus Macaques

Classic PD symptoms: bradykinesia, tremor, and postural instability;
Responsive to L-dopa and apomorphine treatment.

Types of evidence: The strength of evidence pyramid



Personal testimonials:

- ▶ “I have been trying to preach to Pd sufferers for the past eight years. My **book** is my own personal account of what I have been able to do to reverse my Pd symptoms. I stress that I have not been cured of my Pd, but have managed to reduce its effects to the level that I am able to live a normal life, no worse than anybody else who has not got Pd.” ---- John D. Pepper
- ▶ “I recovered from Parkinson’s Disease and have been free of it for 6 years. I based my recovery on my learning from Dr. Norman Doidge’s book “The Brain that Changes Itself.”
--Chris from Australia

Problems with personal testimonial #1

► **Placebo** effects are caused by the **expectation** of an effect based on prior experience

► Expectations can be compared to the effects of levodopa (neuroimaging)

► Optimizing personal testimonial confounds in

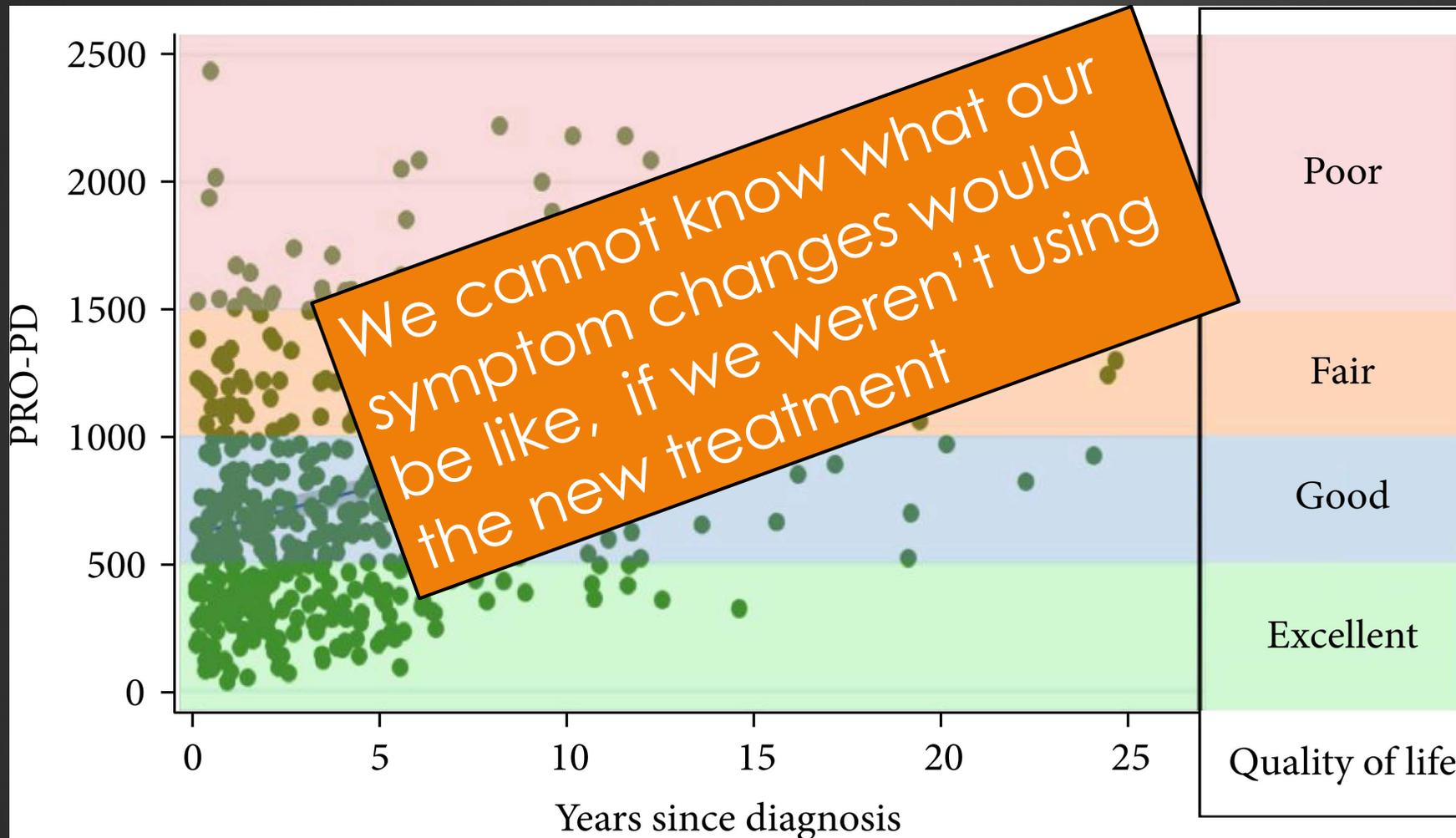
Hard science tells us that placebos can reduce symptoms such as pain and muscle rigidity in Parkinson's disease, yet the progression of the disease is not affected; for example, in Parkinson's disease, neurons keep degenerating even though some symptoms can be reduced for a short time.
--- Benedetti, 2019 (the "father" of the biology of the placebo response.)

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line of functional

cial to PwP, but it testimonial.

Problems with personal testimonial #2



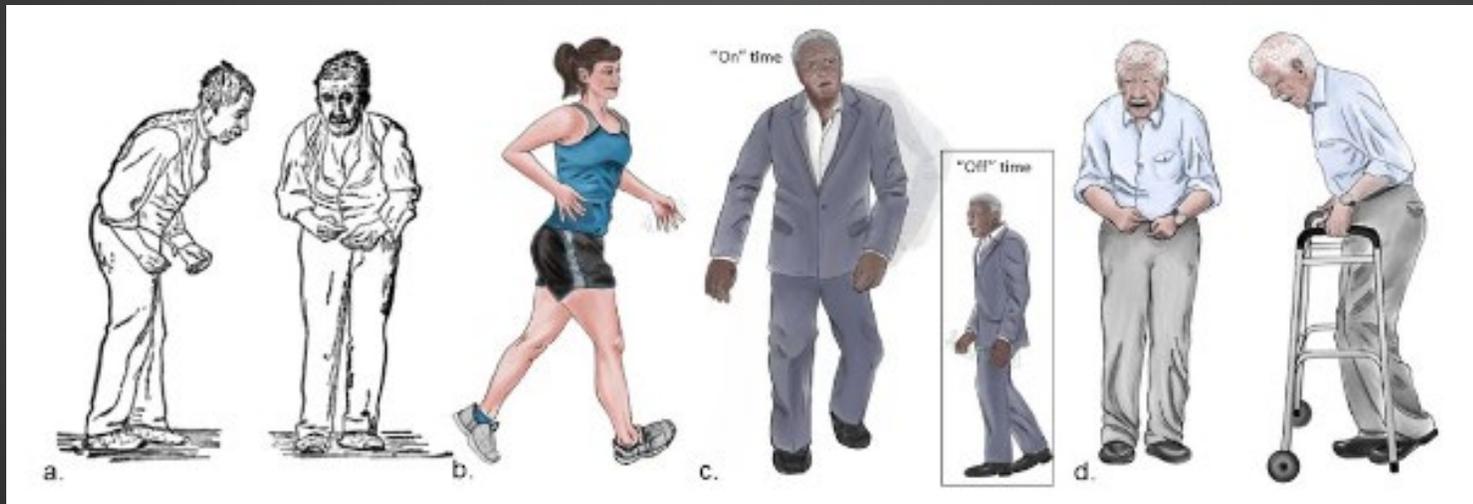
The PRO-PD score is the sum of 33 motor, mood, and other nonmotor symptoms common in PD. Higher scores represent either more symptoms or greater symptom severity of a few symptoms.

Problems with personal testimonial #3

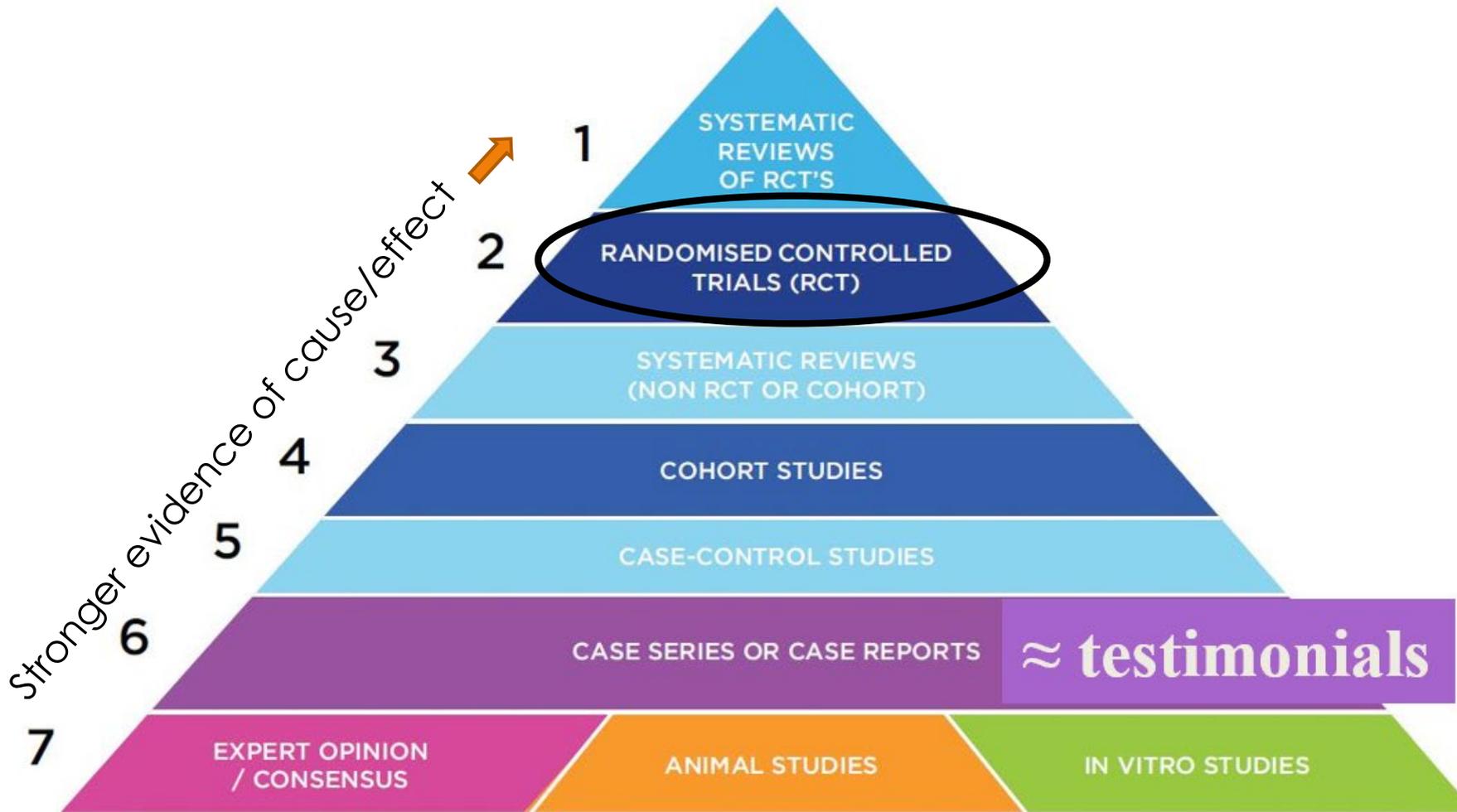


Problems with personal testimonial #4

- ▶ For those who say they were 'cured' of PD by a particular treatment program, we have to ask: Were they **correctly diagnosed** with the progressive neurodegenerative condition of Parkinson's Disease (PD)?



Types of evidence: The strength of evidence pyramid



Randomized control trial

- ▶ If done well, the randomized control trial allows for the *strongest* evidence about whether a treatment is likely to improve symptoms/quality of life for PwP.
- ▶ PwP are randomly assigned (“flip of coin”) to two or more potentially helpful treatments
 - ▶ Random assignment is to make the groups equivalent on symptoms and other characteristics at the start of the study.
 - ▶ If differences between groups are found by the end of the trial, we infer that the end-of-treatment differences between groups were due to the groups getting different treatments.

Randomized control trial: critique

- ▶ They take SO LONG and can be SO EXPENSIVE.
- ▶ ~~Only rich pharmaceutical companies will fund clinical trials.~~
- ▶ They *don't* tell you how every PwP will feel at the end of treatment, even PwP who have similar characteristics to those enrolled in the study.
 - ▶ They describe the likely outcome for the “average person” enrolled in the trial who received different treatments.
 - ▶ Is there an average PwP?
- ▶ Difficult to understand the **probabilistic** thinking underlying biostatistical testing in clinical trials

Probabilistic thinking.....



- ▶ Unlike physics or chemistry proofs, humans (with or without PD) respond differently to different treatments.
- ▶ Clinical trials use inferential statistics to determine the probability that the pattern of difference between the active/new versus control treatment(s) could have occurred *if the reality is that there IS no difference*.
- ▶ If a treatment effect is found to be statistically significant ($p < .05$ or less), we are willing to say that we are comfortable for now in **rejecting** the idea that the treatment **doesn't work** and **accepting** the idea that the new treatment **works** better than the control treatment *for the average person in the group under study, NOT for each and every person who could have qualified for the trial.*
 - ▶ Said differently, the **probability** of an improved symptom outcome increases for those receiving a treatment found to be “statistically significant.”

Example: mannitol

- ▶ Low calorie sweetener that is sometimes used to lower increased pressure around the brain
- ▶ *In vitro* study found that mannitol interfered with formation of abnormal protein aggregates (Lewy bodies) which are found in the brains of PwP.
- ▶ An early fruit fly (*animal*) model of PD found that fruit flies fed mannitol recovered from their motor problems.
- ▶ A second (*animal*) mouse model of PD found that mice injected with mannitol improved motor function
- ▶ Really powerful *personal testimonials* of symptom remission in PwP.
 - ▶ Case report published in an academic journal by a PwP:
 - ▶ “I am 66 years old and had all the symptoms of Parkinson’s...I started taking mannitol orally...After 30 days, I could stand and walk regularly. I had given the compound to others who have had similar results...I have two patents pending on the compound.”

–D. McCammon (2014)



Example: mannitol (cont.)

THE JERUSALEM POST

Israeli man finds creative way to raise awareness on unprofitable drugs

When Dan Vesely was diagnosed with Parkinson's, he had to do his own research, which involved manipulating the system that leaves many without an option.



- He read the animal studies. Frustrated with “undone science” with no potential profit for pharmaceutical companies, Vesely created a crowdsourcing platform, [Clinicrowd](#), where patients could report their own experience with mannitol.
- In 2018, CliniCrowd reported. “more than 1,500 Parkinson's patients from 42 countries” had tried mannitol using the CliniCrowd platform.
- **But** only 78 used it >6 months. 56% of the 78 reported improvement. What about everyone else?

- In late 2018, Hadassah Medical Center in Jerusalem funded a small **clinical trial**. Although 60 PwP were to have been randomly assigned to receive mannitol or dextrose (placebo).
- Unfortunately, only 27 were actually randomly assigned and only 22 completed the 5-visit study.
- No surprise with such a small study: **NO SIGNIFICANT DIFFERENCES** in outcome between the two groups. No further studies on mannitol planned.

Facebook Group devoted to “translating” PD research literature: **Parkinson’s Research Interest Group**



- ▶ 3,200 members; I am one of the original administrators.
- ▶ Not a support group.
- ▶ All posts are screened first by an administrator.
- ▶ You are welcome to apply for membership!
- ▶ <https://www.facebook.com/groups/482344755486600>

Skepticism=Pessimism?

- ▶ NO, not at all.
- ▶ PD was only recognized as a distinct clinical entity a little over 200 years ago by James Parkinson.
- ▶ Levodopa wasn't available until mid-1960s.
 - ▶ Now we are looking at better ways to absorb levodopa.
- ▶ The foundation work for Deep Brain Stimulation wasn't done until the late 1980s.
- ▶ The importance of exercise for symptom improvement (disease modification still unclear) was first modeled in animals and now is clear for people with PD.
- ▶ Therapeutic approaches on the horizon..
 - ▶ Cell replacement therapy (stem cell therapy), infusion or gene therapy of dopamine neurotrophic growth factors

Notice I haven't yet used the word "cure" yet?

- ▶ Slow progression? Great goal.
- ▶ So far, we can assume that, since the biggest risk factor for PD is aging, **lifestyle factors associated with healthy aging probably have the best chance of slowing progression:**
- ▶ **Exercise!**
- ▶ Mediterranean diet
- ▶ Solid sleep, practicing good sleep hygiene.

Another critical lifestyle factor we can modify:

▶ **SOCIAL ISOLATION AND LONELINESS**

- ▶ **In a nationally representative population sample of 15,000 people in the US (NHANES III, 1988-1994)--**
Compared with participants who were not socially isolated, **those who were most isolated had 33% increased risk of death from all causes** during a 20 year follow-up period.
 - ▶ **As deadly as increased mortality risk from smoking, not exercising, or being “morbidly” obese.**

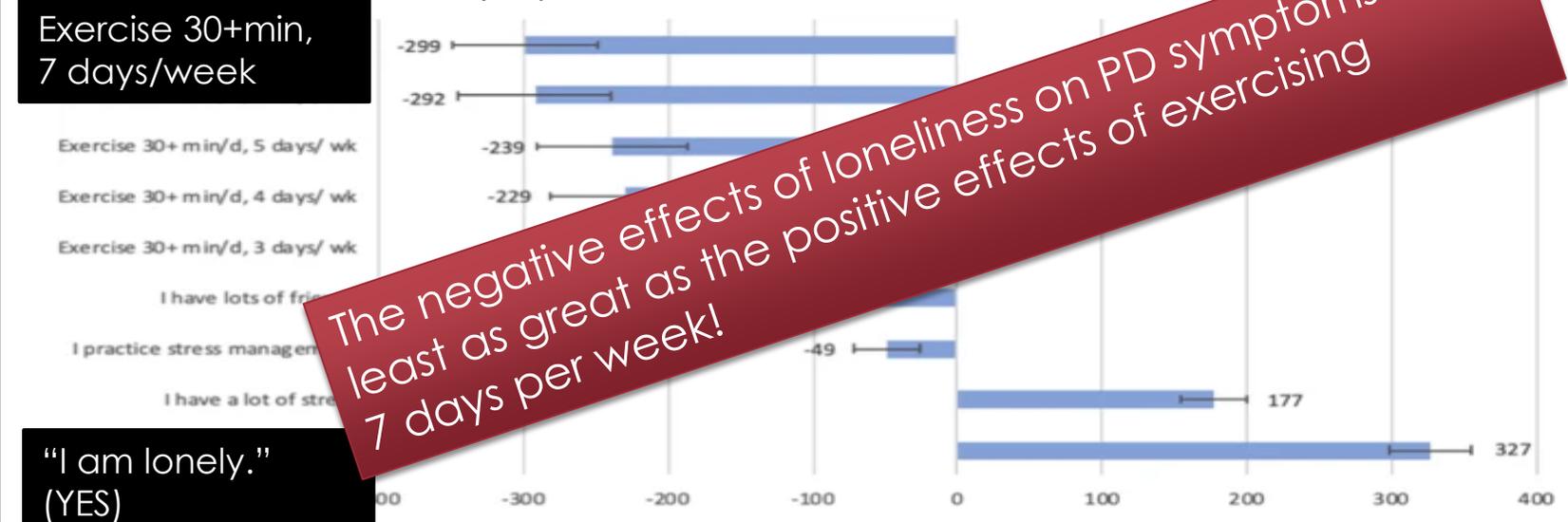
Another critical lifestyle factor we can modify:

▶ AVOID SOCIAL ISOLATION AND LONELINESS

▶ What are the consequences for PD symptoms specifically?

Subramanian,
Farahnik, &
Mischley, 2020

Fig. 4: Modifiable lifestyle variables and impact on patient-reported outcomes (PRO-PD) score. Better symptoms



The negative effects of loneliness on PD symptoms is at least as great as the positive effects of exercising 7 days per week!

Error bars indicate one standard deviation. Regression analysis adjusted for age, gender, income, and years since diagnosis.

Another critical lifestyle factor we can modify:

▶ **AVOID SOCIAL ISOLATION AND LONELINESS**

▶ **What are the consequences for PD symptoms specifically?**

▶ In early 2021, subscribers to the PMD Alliance News and Info list were asked to complete an online survey about how the pandemic affected social support outside the household (Hermanowicz et al., 2022)

▶ Among the 10% completing the survey, reports of decreased outside support during the pandemic were associated with:

▶ Higher symptoms of depression and anxiety

▶ Reports of increases in several nonmotor and motor symptoms

Bottom line:

- ▶ **Lifestyle factors associated with healthy aging probably have the best chance of slowing progression:**
- ▶ Don't forget how critical social connections are, especially in the latter days of the pandemic.
 - ▶ If you have a phone or a computer for virtual meetings or still drive...
 - ▶ **FIND THE SUPPORT THAT DIMINISHES YOUR LONELINESS.**
 - ▶ **SUPPORT GROUPS, PD-centered exercise or dance or singing groups.**
- ▶ Say **YES** to **CONNECT** whenever you can. It will make your life richer.
- ▶ Keep an OPEN and HOPEFUL but SKEPTICAL mind.
- ▶ Don't wait for "motivation" (to expand your social support network, to exercise, etc.) :
- ▶ **LIVE YOUR BEST LIFE NOW!**

EXPECT NOTHING

APPRECIATE
everything

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