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OPINION
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On Disease Modifying and Neuroprotective Treatments for Parkinson's Disease: Physical Exercise

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INTRODUCTION

For decades, the concept of "disease-modifying" treatment has been used profusely in several neurodegenerative diseases including Parkinson's disease (PD). This concept has been employed sometimes as an accomplished goal, and many more as a wishful thinking objective. In addition, the related concept of neuroprotective therapy has been widely used and a quick search on Medline shows a steady increase in the number of papers on this issue over time.

As Morant et al. (1) pointed out there is a particular interest in conceptually distinguishing disease-modifying treatments from symptomatic-only treatments.

Perhaps it is time to ponder over these two related concepts: disease modifying and neuroprotective therapies, at least in relation to PD. First, it is important to have (more or less) clear definitions, and then, we can discuss whether we have or we may have (or not) disease modifying and neuroprotective therapy for PD.

To begin with, the definition of "disease-modifying" treatment varies both within and between neurodegenerative disorders, and terminology in current regulatory guidelines also lacks consistency (1). Cummings suggested that disease modification can be defined as treatments or interventions that affect the underlying pathophysiology and have beneficial outcome on the course of the disease (2). Since the pathophysiology of PD is only partially known, we can employ a more clinical approach for disease-modifying measures as "effective treatments that modify the course of PD and maintain or improve patient quality of life" (3).

Here it must be pointed out that, in theory, any disease-modifying treatment may have symptomatic effect as well, possibly masking the modifications produced in the disease. Recently, Vijiaratnam et al. (3) reviewed the crucial issue of why we have failed to demonstrate disease-modifying effect of treatments on PD. Several reason may partly explain this shortcoming, including the complex pathophysiology and heterogeneity of the disease (3), but from a clinical viewpoint, detecting real modification with any given treatment may take an extended period of time.

To date, no disease-modifying drugs has been found, although some promising candidates are still in the pipeline including exenatide and gene therapy (4).

And still, probably, a real disease-modifying treatment for PD already exists and has been used for decades: Physical exercise. As Eric Ahlskog already suggested a decade ago, "often overlooked (…) is the potential benefit of sustained vigorous exercise on PD progression" (5).

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In this short review, we collect and summarize, the most relevant data of physical exercise as a symptomatic and preventive measure, and its potential for disease modifying therapy for patients with PD.

PHYSICAL EXERCISE AS SYMPTOMATIC TREATMENT

Although the role of physical exercise as symptomatic treatment for PD was already suggested in classic texts (6), this non-pharmacological approach attracted renew interest in the 90s; Comella et al. (7) carried out a controlled trial testing physical exercise in a group of moderately advanced PD. They authors found statistically significant difference in the experimental group, but also observed that motor improvement was not sustained once normal activity was resumed (7). Many other clinical trials, reviews and meta-analyses have been published on this issue over the last decades (5, 8–14). One particularly noteworthy example is the randomized controlled trial by Corcos et al. (8) which showed that progressive resistance exercise demonstrated a statistically significant reduction in UPDRS-III scores (8). Schenkman et al. (13) in a recent randomized clinical trial, studied the effect of high-intensity endurance exercise on motor symptoms in *de novo* PD patients. They found statistical differences in Unified Parkinson's Disease Rating Scale (UPSRS) motor score in the high-intensity group compared with the usual care group. Another interesting study was carried out by van der Kolk et al. (14). In a double blind randomized controlled trial, the authors studied the effectiveness of home-based supervised aerobic exercise on PD; The off-state MDS-UPDRS motor score revealed a significant difference in favor of aerobic exercise.

In addition, physical exercise showed potential to increase the efficacy of antiparkinsonian medication (9, 11). Recently, in their excellent overview of physical exercise on PD; Mak et al. suggested that exercise training can modify long term motor symptoms in PD (11). Finally, da Silva et al. (10) carried out a systematic review of physical exercise on cognitive function of PD; they suggested that physical exercise promotes significant effects on global cognitive function, processing speed, sustained attention and mental flexibility in PD patients. Even when used only as symptomatic treatment, physical exercise should be widely considered as a fundamental antiparkinsonian measure (5, 8–14).

PHYSICAL EXERCISE AS A DISEASE-MODIFYING TREATMENT

In addition to having confirmed symptomatic antiparkinsonian effect, physical exercise may attenuate and influence the natural history of PD (5, 15–19). An increasing evidence suggests that vigorous exercise may exert a disease-modifying effect on PD (5, 15). A very recent publication from Japan showed that the maintenance of high physical exercise was clearly associated with better clinical course of PD (16). To date, the published evidence is indirect and based mainly on observational cohort studies and/or meta-analyzes (16–18), but it is worth stressing the inverse dose-response association between the amount of physical exercise with evolution and mortality in PD (17, 18).

PHYSICAL EXERCISE AS A PREVENTIVE MEASURE

If any disease-modifying treatment exits, then it would most likely be useful also as a preventive measure for neurodegenerative diseases including PD. Epidemiologic evidence suggests that physical exercise may protect against PD (20–25). Habitual vigorous exercise in midlife reduced the risk of later-developing PD in several cohorts (20–25). Physical exercise also seems to confer protective effect on different neurodegenerative diseases such as PD, Alzheimers's disease, Huntington's disease and degenerative ataxias (26). According to this data, exercise training would be a practical and inexpensive guide to counsel patients at risk of PD, such as LRRK2 carriers and others.

EXERCISE: MECHANISMS OF ACTION

Physical exercise has been recommended since the times of Hippocrates and Galen as a general measure for health and disease prevention (27), but its mechanism has been completely unknown for centuries. At present, some of the potential mechanisms have been studied both in experimental animal models (28–30), and in patients with neurodegenerative diseases as well as controls (31–34).

Potential mechanisms include neuronal survival and plasticity, neurogenesis, epigenetic modifications, angiogenesis, autophagy, and the synthesis and release of neurotrophins (28–35).

Possibly, the most interesting and testable mechanism includes the release of Brain Derived Neurotrophic Factor (BDNF) (28–34), suffice is to recall that BDNF is a crucial neurotrophic factor with multiple roles on regulation of neurophysiological processes (35), including survival of striatal neurons (36). Physical exercise increases plasma BDNF levels in individuals with neurodegenerative disorders (34); and interestingly, BDNF receptor blockade prevents the beneficial effects of exercise in animal models (29).

CONCLUSION

If physical exercise is symptomatically effective, probably prevents neurodegenerative diseases, and has potential neuroprotective mechanisms, why is it not universally used?

This conundrum may be explained by several factors. There are barriers to exercise (37, 38), as Ellis et al. suggested, low outcome expectation from exercise, lack of time, and fear of falling appear to be important perceived barriers to exercise. In addition, optimal benefit requires active and sustained participation of patients and families (37, 38). Finally, as Alberts commented (12), frequently, exercise recommendations lack specificity in terms of frequency, intensity and duration.

In summary, although physical exercise is inexpensive, its use as a treatment requires a complete change of strategy. Exercise training would be considered the first antiparkinsonian measure, even before (or at least at the same time) than drug therapy is added (12, 38, 39). Changes are not easy to implement, although other medical specialties such as endocrinology have well-designed patient education programs for chronic diseases uch as diabetes. Certainly, a long-term prospective studies are needed to confirm the neuroprotective capacity of physical exercise on PD (40). Ongoing Clinical Trials, (Including SPARX3 and CYCLE-II) Have Potential to Further Develop Patient-Specific Exercise Recommendations (12). Confirming this effect of exercise training would revolutionize the way we treat patients with neurodegenerative diseases, and also would open new avenues of basic and clinical research.

Finally, physical exercise would be a practical and inexpensive approach for those patients at risk for PD (such as LRKK2 carriers).

AUTHOR CONTRIBUTIONS

PG conception and design, interpretation of data, drafting the submitted material, and critical review. RL and JM drafting the submitted material and critical review. All authors contributed to the article and approved the submitted version.

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