

The Effect of Physical Exercise on Non-Motor Symptoms of Parkinson's Disease: An Article Review

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Abstract: *Parkinson's Disease (PD) is a progressive neurodegenerative disease that cause impairment of the motor system. Although PD is mostly known for its motor symptoms, there are several non-motor symptoms (NMS) that also shown in PD. The non-motor symptoms of PD can develop in the early stage of the disease and often become prominent in the later stage of PD. Oral medication often used to treat PD, but these oral medications can also generate non-motor symptoms for PD in long-term use. Therefore, physicians and researchers these days have turn their interest into the potential of non-pharmacological treatment for PD, such as exercise. Physical exercise is one of therapy method which is less side effect and effective to be done for PD patients. There are many different types of exercise activity, including stretching, walking, Tai Chi, aerobic exercise, dancing, resistance training and multimodal exercise activity that show benefits on non-motor symptoms in PD. Including physical exercise into the treatment plan for PD patients, besides the conventional pharmacologic therapy, can be beneficial for patients' symptoms and their quality of life.*

Keywords: Physical exercise, Parkinson's disease, Non-motor symptoms

1. Introduction

Parkinson's Disease (PD) is a progressive neurodegenerative disease that cause impairment of the motor system. It is characterized by resting tremor, rigidity, bradykinesia or akinesia and postural disability. These are the cardinal symptoms of PD. The motoric disability caused by PD can eventually lead to disability and impairment of the quality of life. PD usually occurred in the older person, of age 60 or more but several recent studies reported PD affecting younger age[1]. A systematic review of PD incidence published in 2003 reported the incidence rate of 17 per 100,000 population per year with the onset of men was often slightly earlier than women[2]. Nine studies of the systematic review reported ratio in men was greater by 1.5 to 2.0 than in women[2].

Although PD is mostly known for its motor symptoms, there are several non-motor symptoms (NMS) that also shown in PD. The non-motor symptoms of PD can develop in the early stage of the disease and often become prominent in the later stage of PD. NMS of PD can be generally categorized into cognitive dysfunction, autonomic dysfunction, mood and sensory deficits. The degeneration of dopaminergic neurons in the substantia nigra along with the deficit of noradrenergic and cholinergic is believed to be the problem of this NMS, although the exact mechanism is still unknown. These non-motor symptoms of PD can adversely affect quality of life and can be even more disabling than the motor symptoms itself.

Oral medication often used to treat PD, but these oral medications can also generate non-motor symptoms for PD in long-term use. Therefore, physicians and researchers these days have turn their interest into the potential of non-pharmacological treatment for PD, such as deep brain stimulation and the less invasive one, exercise [3]. There are many different types of exercise activity, including

stretching, walking, *Tai Chi*, aerobic exercise, dancing, resistance training and multimodal exercise activity that show benefits on non-motor symptoms in PD [3]. There are also researches reported exercise can improve sleep quality, autonomic function and also improve cognitive decline[3] Based on that research, this article is aimed to briefly described the overview of the effects of exercise on non-motor symptoms of Parkinson's Disease.

2. Neuropsychiatric Symptoms

2.1 Depression, anxiety and apathy in PD

Neuropsychiatric disorder, where the patient experience anxiety, apathy, depression and lack of motivation are the most common NMS of PD[4]. Among those symptoms, the major predictor of PD prognosis is the severity of depression[4]. The signs of depression most observed in PD patients, are loss of interest, irritability, lack of energy, fatigue, sadness and indicisiveness [4].

Depression in PD usually seen through decreased activity in orbitofrontal and limbic cortices, whereas apathy and abulia can be explained through loss of dopaminergic neurons beyond the substantia nigra into the ventral tegmental and orbitofrontal areas[4]. There is also deficiencies of several neurotransmitter including norepinephrine (NE), serotonin (5-HT) and dopamine (DA), which is compounded by the decrease of 5-HT-1A binding throughout the limbic, frontal and temporal cortices[4]. Several studies have confirmed that depression in PD is not merely a reaction of PD but it is a part of PD, which may be caused by degeneration of DA neurons in the ventral mesencephalon[4]. PD-related depression can be treated with second generation non-ergot DA agonists such as pramipexole and ropinirole[4]. These drugs is highly selective for D3 than for D2 and D4 DA receptors. Thus, through D3 stimulation, pramipexole simultaneously excites the direct striatopallidal pathway and

inhibits the indirect striatopallidal pathway through the stimulation of D2[5].

The prevalence of anxiety in PD patients is about 25-40% and usually manifested as generalized anxiety disorder, panic attack, or various phobias[4]. The comparison between anxious and non-anxious PD patients showed that DA deficits alone do not drive these, thus the prevailing hypotheses for the cause of anxiety are possible deficits in serotonergic, dopaminergic and adrenergic systems[4]. Benzodiazepines, buspirone and SSRIs can help reduce anxiety, however, to control PD motor symptoms would be the better options, as above agents. Especially benzodiazepines, are associated with adverse side effects[4].

Apathy in PD often accompanied by depression and anxiety, but now it is classified as a distinctive symptom independent of depression or anxiety[4]. The estimated prevalence of apathy symptoms in PD is about 17-42%, treated or untreated[4]. As per definition, apathy is a lack of goal-oriented behavior accompanied by diminished/blunted emotion, initiative and/or loss of interest[6]. Dopaminergic neuron deficiency may cause the disruptions to the frontal subcortical circuit, which will implicate the roles of limbic loop and anterior cingulate cortex[4]. Currently, there are no approved drugs for the treatment of apathy and also very little literature available. Most dopaminergic drugs have not been shown to be useful, however pramipexole and ropinirole may help to treat apathy in PD by enhancing DA-3 receptor activity[4].

2.2 Effect of exercise on neuropsychiatric symptoms in PD

Physical exercise has shown to be effective to decrease depression through an increase in the release of β -endorphins, in brain-derived neurotrophic factors or brain neurotransmitter, such as serotonin, noradrenaline and dopamine[7]. Also, exercise can lead to improvement in self-evaluation self-esteem and a sense of achievement[7]. Research evidence showed improved quality of life and reduced depression in older people with exercise[8]. This result is then supported by *Bridleet al.* who reviewed nine RCTs and described the 3-12 months exercise treatment had an effect on the severity of depressive symptoms in older people overall [9]. However, in PD patients, the exercise needs to be at least 12 weeks to decrease the depressive symptoms[9]. Aerobic exercise 3 times per week for 50 minutes can decrease depressive symptoms, however it is more beneficial to combine aerobic with qigong[7]. Also, aerobic and stretch-balances are viable intervention for PD patients and can have a protective effect against depressive symptoms worsening [7]. On the other hand, Tai-chi have no effect on depressive symptoms but can improve quality of life by improving physical function [7].

3. Sleep Disturbance

3.1 Sleep disturbance in PD

Sleep disturbance is one of the most common NMS in PD patients. There are many sleep disorders that can cause sleep disturbance in PD, including night time insomnia, excessive

day time sleepiness (EDS), sleep fragmentation and REM behavioral disorder (RBD)[10]. RBD may be an indicator for early clinical development of PD as 40-65% patients with RBD develop into PD[4]. RBD may also be a preclinical feature of α -synucleinopathy, occurring about 47% of PD patient and 80% in Lewy Body dementia patients[4]. RBD is characterized by a muscle tone retention during REM sleep with excessive motor activity during dream state, shown as episodes of yelling, kicking and punching[4]. The speculation of the mechanism of RBD is the neurodegeneration of the extranigral brainstem and the olfactory bulb, with α -synucleinopathy as a major cause[4].

EDS a persistent sleepiness after sufficient night time sleep, is observed in almost 50% of PD patients, with increase of 6% every year[4,11]. EDS may eventually result in reduction of self-consciousness, self-esteem, social isolation and loss of independence[11]. The sleepiness in EDS can be disabling and reach to the level of sudden-onset sleep disorder as demonstrated by a polysomnographic studies that showed transition between wakefulness and stage 2 sleep can be as little as 2 seconds[11]. Improving night time sleep can help with EDS and also CNS stimulants such as Modafinil and Ritalin can help improve the wakefulness in patients[11].

Another very common sleep disturbance in PD is restless leg syndrome (RLS). It affects a significant number of PD patients and characterized by discomfort in the lower extremities leading the patient into walking or moving[12]. The symptoms of RLS include burning or itching sensation which worsen with dormancy and improve with movement, hence the urge to move the affected limb to alleviate the symptoms[12]. During sleep, the patient will have a repetitive, myoclonic jerky limb movement which will affect the quality of sleep[12]. Although the exact pathophysiology of RLS is uncertain, various dopaminergic system thought to be involved[4]. DA agonists, such as ropinirole and pramipexole, can be effective to control RLS symptoms, but there is a side effect of augmented symptoms which accounted for up to 40% of RLS patients using DA agonists for longer duration[4].

3.2 Effect of exercise on sleep disturbance in PD

Another common non-motor symptoms in PD is sleep disturbance, which affect up to about 98% PD patients[3]. In healthy adults, exercise interventions improve sleep as described in meta-analyses that chronic exercise training increases sleep efficiency and total sleep time, increase slow wave sleep and reduces latency to sleep onset[13]. Also, acute exercise reduces REM sleep and delays REM latency as well as increases total sleep time and slow wave sleep[13]. In PD patients, exercise has shown promise in improving sleep as well. There are some RCTs evaluating sleep as an outcome after exercise intervention in PD. A study from Nascimento *et al.* evaluated 42 PD patients, which divided into exercise groups of 23 patients and 19 patients in control group assessed by Mini-Sleep Questionnaire before and after a 6 month, multimodal exercise, including aerobic, balance and resistance training[14]. The result of this study found significant improvement in sleep quality in the exercise group[14].

Another RCT from Silva-Batista *et al.* in 22 patients divided into resistance training group and no-exercise control group for 12 weeks with 2 sessions per week, demonstrated improvements in sleep quality and better sleep quality scores, with Pittsburgh Sleep Quality Index (PSQI), compared to the control group[15].

4. Cognitive Decline and Dementia

4.1 Cognitive decline and dementia in PD

Mild cognitive decline can be observed in the earlier stage of PD, with the progression interfering daily functioning, for about 20% of the prevalence[10]. The cognitive decline, manifested as language deficit, long-term memory, executive functioning and visuospatial functioning[10]. Dopaminergic dysfunction in the caudate is thought to be contributed to cognitive dysfunction, despite reduced dopaminergic function has been observed in PD patients with or without cognitive dysfunction[10].

The cognitive decline can develop into mild cognitive impairment (MCI). MCI characterized as the onset and growth of cognitive impairment not associated with normal aging and interference of daily activities[16]. The lack of neuropathological data available contributed to the unclear of underlying mechanism of MCI associated with PD. Structural and functional MRI of MCI patients with PD showed selective loss of grey matter. Dementia occurs in about 40% of all PD patients, which is six-times higher than the prevalence of dementia without PD population[4]. The mechanism of this is the disruption of synaptic plasticity changes dependent on DA-acetylcholine[10]. The manifestation of dementia associated with PD are memory impairment, frontal executive dysfunction such as planning and organizing difficulties, cognitive slowing, concentration difficulties, decrease of attentiveness, personality changes and visuospatial problem[4,10]. There is various risk factor for dementia in PD patients, which are age above 70. Unified Parkinson's Disease Rating Scale (UPDRS) motor score >25, development of agitation, disorientation, mania or psychosis, depression, facial masking at presentation, cardiovascular abnormalities, psychological stress, low education and socioeconomic status, and predominant bradykinesia with postural disturbance[10,17].

4.2 Effect of exercise on cognitive decline and dementia in PD

Cognitive decline has been recognized as a significant predictor of quality of life in PD[3]. Medication used to treat cognitive impairment in PD, unfortunately, can have side effect of other symptoms and are not effective at slowing or stopping the cognitive decline[3]. Therefore, it is important to evaluate non-pharmacological therapies to improve cognitive function in PD. A recent meta-analysis of the effect of exercise on cognition in adults over age 50 showed significant improvements in multiple cognitive domains due to all modes of exercise reviewed, such as aerobic, tai chi, yoga and resistance training[18]. In this meta-analysis, described that this effect can be achieved by exercise with 54-60 minutes duration per session with best effects for moderated to high intensity exercise[18]. On the structural

level, physical exercise can increase hippocampal volume, which will be the neuroprotective effect for the brain[18]. In PD, many clinical trials investigating different exercise types, frequencies and duration also reported promises for exercise-induced cognitive function improvement. These exercises are aerobic, tango, resistance training and combined resistance and aerobic exercise[3].

5. Dysautonomia

5.1 Dysautonomia in PD

The dysfunction of nuclei mediating autonomic functions, such as the dorsal vagal nucleus, nucleus ambiguus and other medullary centers are believed to be the pathophysiology of autonomic dysfunction in PD[10]. The impaired autonomic nervous system associated with this damage including sympathetic ganglia, cardiac sympathetic efferent sans mesenteric plexus of the gastrointestinal tract[10]. Urinary incontinence (UI) in PD patients due to spastic bladder, where the bladder become overactive and contract, are difficult to stop and can further exacerbated in later stage of PD[10]. However, UI in PD is not the most common, as hyperhidrosis is three times more common in PD patients[10]. Hyperhidrosis in PD patients only occur in the trunk, head and face and not correlated with disease severity, rather with other symptoms such as dyskinesia[10]. Besides those symptoms mentioned above, drooling has been classified as top five of the most disturbing symptoms of PD[10]. Up to 35-75% PD patients endure drooling in their daily life and feel extremely embarrassed by it[4]. The cause of drooling in PD patients is not the excessive production of saliva, rather than the difficulty of swallowing. This can result in reduced activity of the epiglottis leading bolus entrance into the trachea[10]. Dysphagia can be found in about 86% of PD patients which increases the chance of bronchopneumonia, a leading cause of death in PD patients[4,10]. Sexual dysfunction (SD) play a major role in the deterioration of quality of life of PD patients and also affect their partner. Male PD patients suffer erectile dysfunction (ED) and ejaculation problems, while females experience loss of lubrication and involuntary urination[4].

Of all various manifestation of autonomic dysfunction in PD patients, light-headedness due to postural hypotension is the most frequent[4]. The autonomic nervous system, which compensate the decreased blood pressure by pumping the heart faster is damaged. Often, the use of dopaminergic agonists can result in postural hypotension[4]. Orthostatic hypotension in PD patients is dangerous as it can lead to falls and serious disability[4,10].

Gastrointestinal (GI) problem in PD is one of the major problems affecting PD patients' quality of life. These GI problems, include constipation, dysphagia, poor dental care due to dysphagia, heartburn, nausea due to gastric hypermotility and poor nutrition[4]. The damage of dorsal motor nucleus of the vagus nerve in PD patients, resulting in deficits of GI function along with irregularities of the enteric nervous system, as most of parasympathetic signal derived from the dorsal motor nucleus of the vagus nerve, which function is to accelerate GI function[19]. α -synuclein shown

to be involved in the GI dysfunction of PD. Many studies shown accumulation of α -synuclein containing Lewy bodies in the enteric nervous system and autonomic ganglia[19]. 50% of all PD patients experiencing reduce stool frequency and about 57-67% experienced difficulty of bowel movements[19]. Dysphagia often occur in later stage of PD and occur for about 80% of all PD patients[19]. The severity of dysphagia depends on the duration of PD and actually this dysfunction has little effect on the nutritional status of patients[19]. Softening food and thickening liquids may help to manage dysphagia as it helps patients to chew thoroughly before eating and swallowing[19].

5.2 Effect of exercise on dysautonomia in PD

As mentioned before, dysautonomia may include dysregulation of cardiovascular, urinary, gastrointestinal, thermoregulatory and pupillary systems[3] Also, dysautonomia can occur at any stage of PD, with urinary, gastrointestinal and orthostatic symptoms notable in early and even premotor stages and increasing overtime[3] Pharmacological therapy for orthostatic hypotension (OH) known to have limited efficacy and can produce serious side effects, including exacerbation of ventricular hypertrophy and supine hypertension[3] Therefore, exploring more in safe and effective non-pharmacological therapy is important. Exercise has potential to enhance dysautonomia healthy adult[3]. However, there is only one randomized controlled trial addressing the effects of exercise on cardiovascular dysautonomia symptoms in PD patients. This study included 30 PD patients and were assigned to either resistance training group or control group for 12 weeks[20]. The result showed improvement on cardiac sympathetic modulation, as measured by heart rate variability and blood pressure response[20]. There is no change in parasympathetic modulation.

Bladder dysfunction in PD, including increased urinary urgency, frequency and nocturia is one of the most commonly reported symptoms of dysautonomia in PD [3]. Affecting up to 93% PD patients, these symptoms can affect quality of life by inhibiting social activity and cause sleep disturbance [3]. However, there is still no study investigating the influence of exercise on bladder dysfunction in PD, but bladder training exercise have been proven effective to improve bladder dysfunction in PD[21].

In healthy adults, exercise can improve constipation[3]. But, the question is whether it will have the same effect on PD patients. A randomized controlled pilot study, evaluated the effects off meditation movement exercise, called *Qigong*, on constipation as a secondary outcome and found persistent benefit of the exercise over time in PD patients[22].

6. Pain and Sensory Disturbance

6.1 Pain and sensory disturbance in PD

Any form of pain, experienced by all PD patients for approximately 40% and present several years before or after the diagnosis of PD. Pain perception in PD affected by lateral pain pathway and spinoreticulothalamic pathway. Lateral pain pathway is a fast system projecting to the

thalamus and primary sensory cortex, while spinoreticulothalamic pathway is a slow system promotes autonomic, affective and cognitive pain[23]. DA has been observed to increase pain threshold, however dopaminergic involvement to pain in PD has not always proven to be consistent[23]. Recent studies has also linked pain in PD to involvement of glutamatergic, serotonergic and noradrenergic neurotransmitter system[23]. Detection and management of pain in PD can sometimes be difficult as PD-related pain have to be distinguished from other pain before treatment. Classifying pain in PD into categories has proven to be beneficial for symptoms management, such as musculoskeletal pain, radicular nerve pain, central pain, dystonia and akathisia[23]. Various treatments are available depending on the origin of the pain. Musculoskeletal pain can be treated with NSAIDs, exercise programs and physical therapy. Central pain is harder to diagnose and manage, especially there is no effect of dopaminergic treatment, although opiates, analgesics and atypical neuroleptics may help[23]. Pain secondary to dystonia has been treated with deep brain stimulation (DBS) and dopaminergic medication modulation, also focal dystonia can be alleviated with botulinum toxin. Dopaminergic treatment can be beneficial to treat pain resulting from akathisia[23]. Interestingly, traditional PD treatment with L-Dopa can help to increase pain threshold by decreasing abnormal recruitment of neurons in the insula, cingulate and prefrontal cortex, as described by PET imaging[23].

6.2 Effect of exercise on pain in PD

Pain in PD is associated with depression, lack of sleep and decrease in overall quality of life. Pain is a very disturbing and distressing symptoms, yet it is often receiving less attention. The pain in PD can be multifactorial, which include the impairment as well as co-existing musculoskeletal and/or neuropathic pain conditions[24]. Although, pain in PD can be controlled by the use of dopaminergic agents, the study emphasizing physical exercise can affect pain greatly by contributing to neuroplasticity and neuro-restoration, by increasing synaptic strength and angiogenesis, brain neurotrophic factors, as well as stimulating neurogenesis and improving central processing of pain[24]. This study also described that exercise can activate dopaminergic neurons that have an anti-nociceptor role, which will suppress nociceptive signaling in dorsal root ganglion and modulating pain in rostral-ventral medulla[24].

7. Conclusion

Non-motor symptoms ins Parkinson's disease is a disturbing and distressing symptom as it significantly affects quality of life of PD patients. This leads to lack of good sleep quality and eventually depression. Physical exercise is one of therapy method which is less side effect and effective to be done for PD patients. Including physical exercise into the treatment plan for PD patients, besides the conventional pharmacologic therapy, can be beneficial for patients' symptoms and their quality of life.

References

- [1] Post B, Van Den Heuvel L, Van Prooije T, Van Ruissen X, Van De Warrenburg B, Nonnekes J. Young Onset Parkinson's Disease: A Modern and Tailored Approach. 2020;
- [2] Twelves D, Perkins KSM, Counsell C. Systematic review of incidence studies of Parkinson's disease. *Mov Disord*. 2003;18(1):19–31.
- [3] Amara AW, Memon AA. Effects of Exercise on Non-Motor Symptoms in Parkinson's Disease. 2019;40(1):8–15.
- [4] Rana AQ, Ahmed US, Chaudry ZM, Vasani S, Qayyum A, Ahmed US, et al. Expert Review of Neurotherapeutics symptoms Parkinson's disease: a review of non-motor symptoms. 2017;7175(September).
- [5] Constantinescu R. Update on the use of pramipexole in the treatment of Parkinson's disease [Internet]. Vol. 4, *Neuropsychiatric Disease and Treatment*. DOVE Medical Press Ltd.; 2008 [cited 2020 Dec 5]. p. 337–52. Available from: <https://pubmed.ncbi.nlm.nih.gov/11384893/>
- [6] Starkstein SE, Petracca G, Chemerinski E, Kremer J. Syndromic validity of apathy in Alzheimer's disease. *Am J Psychiatry* [Internet]. 2001 [cited 2020 Dec 5];158(6):872–7. Available from: <https://pubmed.ncbi.nlm.nih.gov/11384893/>
- [7] Wu P-L, Lee M, Huang T-T. Effectiveness of physical activity on patients with depression and Parkinson's disease: A systematic review. 2017 [cited 2020 Dec 12]; Available from: <https://doi.org/10.1371/journal.pone.0181515>
- [8] Park SH, Han KS, Kang CB. Effects of exercise programs on depressive symptoms, quality of life, and self-esteem in older people: A systematic review of randomized controlled trials. *Appl Nurs Res* [Internet]. 2014;27(4):219–26. Available from: <http://dx.doi.org/10.1016/j.apnr.2014.01.004>
- [9] Bridle C, Spanjers K, Patel S, Atherton NM, Lamb SE. Effect of exercise on depression severity in older people: Systematic review and meta-analysis of randomised controlled trials [Internet]. Vol. 201, *British Journal of Psychiatry*. Cambridge University Press; 2012 [cited 2020 Dec 12]. p. 180–5. Available from: <https://www.cambridge.org/core>.
- [10] Hou JGG, Lai EC. Non-motor symptoms of Parkinson's disease. Vol. 1, *International Journal of Gerontology*. Elsevier (Singapore) Pte Ltd; 2007. p. 53–64.
- [11] Lökk J. Neuropsychiatric Disease and Treatment Daytime sleepiness in elderly Parkinson's disease patients and treatment with the psychostimulant modafinil: A preliminary study [Internet]. 2010 [cited 2020 Dec 4]. Available from: www.dovepress.com
- [12] Lin GG, Scott JG. Circadian and Sleep Disorders in Parkinson's Disease Aleksandar. NIH Public Access. 2012;100(2):130–4.
- [13] Kredlow MA, Capozzoli MC, Hearon BA, Calkins AW, Otto MW. The effects of physical activity on sleep: a meta-analytic review. *J Behav Med*. 2015;38(3):427–49.
- [14] Nascimento CMC, Ayan C, Cancela JM, Gobbi LTB, Gobbi S, Stella F. Effect of a multimodal exercise program on sleep disturbances and instrumental activities of daily living performance on Parkinson's and Alzheimer's disease patients. *Geriatr Gerontol Int*. 2014;14(2):259–66.
- [15] Silva-Batista C, De Brito LC, Corcos DM, Roschel H, De Mello MT, Piemonte MEP, et al. Resistance training improves sleep quality in subjects with moderate Parkinson's disease. *J Strength Cond Res*. 2017;31(8):2270–7.
- [16] Yarnall AJ, Breen DP, Duncan GW, Khoo TK, Coleman SY, Firbank MJ, et al. Characterizing mild cognitive impairment in incident Parkinson disease The ICICLE-PD Study [Internet]. 2014 [cited 2020 Dec 3]. Available from: www.neurology.org
- [17] Robottom BJ, Weiner WJ. Chapter 12 Dementia In Parkinson's Disease [Internet]. 1st ed. Vol. 84, *International Review of Neurobiology*. Elsevier Inc.; 2009. 229–244 p. Available from: [http://dx.doi.org/10.1016/S0074-7742\(09\)00412-7](http://dx.doi.org/10.1016/S0074-7742(09)00412-7)
- [18] Northey JM, Cherbuin N, Pumpa KL, Smee DJ, Rattray B. Exercise interventions for cognitive function in adults older than 50: A systematic review with meta-analysis [Internet]. Vol. 52, *British Journal of Sports Medicine*. BMJ Publishing Group; 2018 [cited 2020 Dec 10]. p. 154–60. Available from: <https://pubmed.ncbi.nlm.nih.gov/28438770/>
- [19] Lubomski M, Davis RL, Sue CM. Gastrointestinal dysfunction in Parkinson's disease. *J Neurol*. 2020;267(5):1377–88.
- [20] Kanegusuku H, Silva-Batista C, Peçanha T, Nieuwboer A, Silva ND, Costa LA, et al. Effects of Progressive Resistance Training on Cardiovascular Autonomic Regulation in Patients With Parkinson Disease: A Randomized Controlled Trial. *Arch Phys Med Rehabil* [Internet]. 2017;98(11):2134–41. Available from: <http://dx.doi.org/10.1016/j.apmr.2017.06.009>
- [21] Vaughan CP, Juncos JL, Burgio KL, Goode PS, Wolf RA, Johnson TM. Behavioral therapy to treat urinary incontinence in Parkinson disease. *Neurology*. 2011;76(19):1631–4.
- [22] Schmitz-Hübsch T, Pyfer D, Kielwein K, Fimmers R, Klockgether T, Wüllner U. Qigong exercise for the symptoms of Parkinson's disease: A randomized, controlled pilot study. *Mov Disord*. 2006;21(4):543–8.
- [23] Ford B. Pain in Parkinson's disease. *Mov Disord*. 2010;25(SUPPL. 1):98–103.
- [24] Fayyaz M, Jaffery SS, Anwar F, Zil-E-Ali A, Anjum I. The Effect of Physical Activity in Parkinson's Disease: A Mini-Review. *Cureus*. 2018;10(7).

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