Journal of Mind and Medical Sciences

https://scholar.valpo.edu/jmms/
https://proscholar.org/jmms/
ISSN: 2392-7674

Recent advances in the role of rehabilitative therapies for Parkinson's disease: A literature review

Bazza Sohail*, Muhammad Affan Iqbal, Aisha Razzaq, Abdul Wasay Nafe, Robina Malik

Faculty of Rehabilitation and Allied Health Sciences, Riphah International University, Islamabad, Pakistan

ABSTRACT

Regardless of medical therapies and surgical interventions for Parkinson's disease, patients develop progressive disability. The role of therapies is to maximize functional ability and minimize secondary complications through movement rehabilitation within a context of education and support for the whole person. The overall aim is to optimize independence, safety and wellbeing, thereby enhancing quality of life. Trials have shown that physiotherapy has short-term benefits in Parkinson's disease. However, which physiotherapy intervention are most effective remains unclear. This article provides a guidance framework rather than a 'recipe' for treatment. This review shows that a wide range of rehabilitative therapy interventions to treat Parkinson's disease have been tested. There is a need for more specific trials with improved treatment strategies to underpin the most appropriate choice of therapy intervention and the outcomes measured. According to research in the literature, this review is of particular importance because it discusses many rehabilitation therapies for patients with Parkinson's disease in a single paper, for the first time. The aim of this review article is to evaluate the effectiveness of one therapy intervention compared with a second approach in patients with Parkinson's disease.

Category: Review

Received: November 12, 2022
Accepted: January 16, 2023
Published: April 25, 2023

Keywords:
Parkinson's disease, rehabilitative therapies, dopaminergic neurons, motor and non-motor symptoms

***Corresponding author:**
Bazza Sohail,
Faculty of Rehabilitation and Allied Health Sciences, Riphah International University, Islamabad, Pakistan, 44000
E-mail: bazzasohail@yahoo.com

Introduction

Parkinson's disease (PD) is an overwhelming disorder of the human nervous system and the second most frequent type of neurodegenerative disease [1]. Pathologically, PD is characterized by the presence of abnormal intra-neuronal aggregates of α -synuclein, termed Lewy bodies and Lewy neuritis [2]. It is a chronic and progressive neurodegenerative condition distinguished by a progressive reduction of dopaminergic (DA) neurons in the substantia nigra pars compacta (SNc) [3]. Mechanism involves as L-tyrosine is converted into tyrosine-derived dopamine, stored in synaptic vesicles and released from the axon terminals, which in turn derive from a nigrostriatal DA neuron. This process declines very slowly in people with Parkinson's. It affects about 7 million people worldwide [4]. About 1% of Americans older than 60 years and projected 4% of the oldest Americans are currently diagnosed with PD. This occurrence is expected to double by 2030 [5]. To date, age is the only proven risk factor for PD, the average age of early diagnosis is about 60 years old while a type of young onset PD can happen, and diagnosis also can take place later in life [6]. Some other risk factors such as gene polymorphism, tobacco use, alcohol and caffeine consumption, pesticides and history of head trauma, hypertension, and diabetes mellitus have been widely investigated, but the impact of most of these factors on the risk of developing PD remains uncertain [7]. The epidemiological studies have exposed the male sex as a prominent risk factor for developing PD at all ages and for all nationalities studied. Reports of male to female ratios for incidence rates differ from 1.37 to 3.7, with a large meta-analysis study suggesting that, in any specific time-frame, twice as many men than women suffer from PD [8-10].

The PD is a multi-systemic disorder that is characterized by a combination of motor and non-motor symptoms. Motor cardinal signs of PD such as bradykinesia with rigidity, tremor at rest, postural instability, difficulty in swallowing (dysphagia) & producing speech, as well as deterioration of muscle strength, cardiorespiratory fitness, performance of balance,

To cite this article: Sohail B, Iqbal MA, Razzaq A, Nafe AW, Malik R. Recent advances in the role of rehabilitative therapies for Parkinson's disease: A literature review. *J Mind Med Sci*. 2023;10(1):85-105. doi: 10.22543/2392-7674.1365

gait, and mobility tasks [4,11]. Non-motor symptoms associated with the disorder include sensory complaints, autonomic dysfunction, fatigue, apathy, sleep disturbances, constipation, cognitive decline (i.e., executive function) and depression which can often reduce patients' quality of life (QoL) even more significantly than motor aspects [12]. Dopamine, the main neurotransmitter in short supply in the brains of people with PD, is also one of three neurotransmitters involved in depression. The other two, serotonin and noradrenaline, are also affected by the brain changes in PD. The people with PD often are classified by Hoehn and Yahr (H&Y) stages (from 1 to 5), with stage 1 representing only minor symptoms and stage 5 indicating that the person is entirely disabled and usually is restricted to a bed [13]. Disability can occur at all stages of PD leading to decreased independence, inactivity, social isolation, and reduced QoL by performance of activities of daily living and various aspects of mobility such as gait, transfers, balance, and posture [14]. In the majority cases, there is unknown cause of the disorder (idiopathic). The appearance of symptoms differs among the people. Though there is a variety of appearance, specific subtypes with separate clinical features and with various suggestions for diagnosis have been recognized [15]. The exclusively, PD is distinguished into two forms: tremor predominant and postural instability & gait difficulty [16]. Research work indicated that when between 70 and 80 percent of normal levels of dopamine supply have been lost; the typical motor symptoms of Parkinson's appear [17]. There may often be observed that Parkinson's-related signs and symptoms had been developing over the past five, ten or even twenty years. The slow but continuing fall in dopamine production over the years accounts for the ongoing degenerative course of the condition.

The PD causes problems with activities of daily living that are only partially treated by medication and occasionally surgery. Later on, the medication loses its effectiveness and progressing motor complications and other side effects (motor fluctuations, confusion, memory problems, and psychiatric complications) impulsive functional dependence and impairs QoL [18]. Thus, there is a convincing need for alternative therapies to improve function and QoL in persons with PD. Rehabilitative therapies such as physical therapy (PT), occupational therapy (OT), speech therapy as well as complementary therapies such as music therapy, contribute to the PD treatment providing better QoL to the patients [19]. Recently, several newly developed non-pharmacological therapeutic strategies, including gene therapy, cell replacement therapy, light therapy, deep brain stimulation and repetitive transcranial magnetic stimulation, have also been suggested to give benefits to relieve parkinsonian symptoms. The main objective of this review is to fill the gap between the researches and provide updated and productive information about most recent research reported in the last few years and can fulfill the most reassuring plausibility for encourage treatment of PD. This review also enlightens different types of rehabilitative therapies which are grouped into four main therapy groups: physical therapy, occupational therapy, specific therapies for specific purpose and newly developed therapies. Literature research was carried out by collecting recent data from different reviews, reports, and original articles on general or specific rehabilitation therapies which applied on patients of PD.

Literature Search

The authors surveyed the primary literature (Table 1) on physical therapy, occupational therapy, specific therapies for specific symptoms (speech therapy, dysphagia therapy, music therapy and hormone therapy), and newly developed non-pharmacological therapeutic strategies (gene therapy, stem cell therapy, light therapy, deep brain stimulation, and repetitive transcranial magnetic stimulation). Databases utilized included Science Direct, Pubmed, and EBSCO, Google Scholar as well as a hand search through journals and bibliographies was included. The search terms were: "Parkinson Disease" or "Parkinson's Disease" or "Parkinsonism" or "Parkinsonian", and "repetitive transcranial magnetic stimulation" or "rTMS" or "repetitive TMS" or "theta burst stimulation" or "TBS".

Table 1. Literature data

Therapies	Number of Selected Studies
Physical therapy	34
Occupational therapy	10
Speech therapy	17
Dysphagia therapy	9
Music therapy	10
Hormone therapy	13
Gene therapy	17
Stem cell therapy	16
Light therapy	17
Deep brain stimulation	18
Repetitive transcranial magnetic stimulation	19

Discussions

Initially, a total of 350 articles were identified, of which 199 were selected for detailed review on various therapies. Trials have shown that physiotherapy has short-term benefits in PD. However, which therapy intervention are most effective remains unclear. This article provides a guidance framework rather than a 'recipe' for treatment. This review indicates that a wide range of rehabilitative therapy interventions to treat PD have been tested. There is

a need for more specific trials with improved treatment strategies to support the most appropriate choice of therapy intervention and the outcomes measured. According to literature search, this narrative review has distinguishing importance to discuss many rehabilitative therapies for PD patients in one paper first time.

Physical therapy

Physiotherapy covers a wide range of techniques and its aim to increase (or maximize) movement quality, functional independence and general fitness while preventing (or minimizing) secondary complications and optimizing safety. As such, physical therapy (PT) includes support for self-management and participation in movement related activities [20]. Most important treatment strategies used by physiotherapists are exercise (like yoga, pilates therapy), practice and compensatory strategy training (i.e., cueing, treadmill, dance, material arts, hydrotherapy and strategies for complex motor sequences) [20]. Following some important physical therapies are given in discussion from literature.

Exercise (Yoga) physical *therapy*

Yoga is a form of exercise that may offer an alternative therapy to patients with PD that can be adapted to meet the desires of various neurological populations [21]. Various studies suggested that yoga resulted in modest improvements in functional mobility, balance, and lower-limb strength in persons with PD [22]. This has implications for postural stability, gait, balance confidence, and functional declines related to inactivity [23]. An improved upper- and lower-body flexibility following yoga in PD patient is applicable to rigidity, shuffling gait, and flexed posture [24,25]. The existing data also showed positive outcomes for mood and sleep, demonstrating yoga's benefit for self-efficacy and social support [25,26]. Three studies [22-24] reported significant improvements in balance [Berg Balance Scale (BBS), Falls Efficacy Scale] and one subjective report of improved balance confidence that accompany yoga also contributed to a reduced fear of falling in PD [26]. There is not enough research to provide strong scientific evidence for the use of yoga in PD, but there is no evidence suggesting it is harmful. Physical therapists can incorporate yoga principles into developing a preventative exercise program for those with progressively deteriorating neurological diseases such as PD and may improve QoL through improved function, which is essential to the successful management of PD.

Pilates therapy

Pilates is also a type of exercise therapy that is aimed to improve flexibility and axial stability by strengthening the core musculature of the body. This therapy is based on the performance of coordinated movement sequences rather than on simple repetitive movements, as in other exercise programs [27]. The positive effects of pilates therapy on balance in elderly individuals has been reported [28,29]. This therapy has also been found to be beneficial for postural stability in elderly patients with idiopathic PD [30]. Pandya et al. [31] suggested that pilates intervention with conventional balance training is more effective (improved functional balance, confidence level and functional activities in patients with Idiopathic PD) than conventional balance training alone. Recently, Mollinedo-Cardalda et al. [32] reported that the group that completed the mat pilates program under randomized control trial (RCT) presented significant improvements in Body Mass Index ($F_{1,21} = 3.986$; $p = 0.038$), the 30 Second Chair Stand test ($F_{1,21} = 6.716$; $p = 0.014$), the Five Times Sit to Stand test ($F_{1,21} = 5.213$; $p = 0.032$), and the time required to complete the TUG dynamic balance test ($F_{1,21} = 5.035$; $p = 0.035$) [32]. The data showed mat pilates program performed by a sample population with PD led to improvements in dynamic balance, and also increased strength in the lower limbs, but such improvements were not permanent after the activity ceased.

Hydro or Aquatic physical therapy (HPT)

The HPT can be defined as a practice of methodologies and concepts in a heated pool whose objective is the kinetic recovery of a physically incapacitated individual [33]. The liquid medium with the proper hygiene and temperature enables the physiologic and therapeutic benefits for the PD patients. HPT uses the physical properties such as resistance noted in Archimedes' and Pascal's Principle [34]. These hydro effects are versatile and can be advantageous for the use of therapeutic intervention of PD patients. The Halliwick concept, created by James McMillan in England, is based on scientific principles of hydrodynamics and body mechanics and encourages the independence of the person in water [35]. The method developed with recreational activities in 3-stages and 10-point teaches aquatic motor skills in a subtle way [36]. Zotz et al. [37] used the Halliwick Principles' 3-phase 10-point methods for acquisition of aquatic motor skills. They observed an improvement in their ability to float in prone and supine positions and longitudinal rotation in the bipedal position, so activation of motor control improved the motor skills of the participants [37].

At present, there is no treatment that is known to be very effective for postural instability in PD. HPT might be effective for PD patients, but this has not been demonstrated yet. There are few studies about the effects of HPT on balance of patients with this disease. Andrade and colleague [38] assessed the effects of aquatic exercises in 7 patients with PD through a treatment program consisting on adaptation to the aquatic environment, stretching and static & dynamic balance exercises. The results showed that the 12 session of treatment promoted balance improvement. Vivas and others [33] compared the effects of HPT with conventional PT exercises on postural

stability and transfer of patients with PD. The 11participants were randomly divided into two groups: 5 participants in the HPT group and 6 participants in the conventional PT group. The groups performed the protocol for 4 week, 2 sessions per week, with duration of 45 minutes each one. Both protocols, consisted on specific movements of the trunk, pelvis, lower limbs and upper limbs, divided into warm-ups, trunk mobility, postural stability, transfers and changes in body position. The protocol for HPT was associated with Halliwick method in water and the conventional PT was performed trough exercises performed on a therapeutic ball. The results displayed that both groups had statistically significant improvement in functional reach however only the HPT group obtained improvement in BBS and Unified Parkinson's Disease Rating Scale (UPDRS) [33]. Likewise, Pompeu et al. [39] selected 17 patients with PD on stages 1-4 of H & Y scale, patients performed 36 sessions of HPT, 40 minutes each one, during 3 months. There was substantial improvement on Time Up and Go (TUG), BBS and UPDRS after the treatment. Volpe et al. [40] compared HPT with traditional land-based PT and selected 34 patients with PD on stages 2.5-3.0 of H & Y scale. Patients performed 60 minutes of treatment, 5 days a week for 2 months. There was a better improvement in patients who underwent HPT than in patients treated with land-based therapy in the center of pressure sway area closed eyes, BBS, Activities-specific Balance Confidence Scale, Falls Efficacy Scale, PD Questionnaire-39 and falls diary [40].

Most recently, Pinto and colleague [41] identified a total of 19 studies including 8 RCT, 3 non-RCT, and 8 pre-post studies. This meta-analysis exhibited a moderate quality of evidence for positive effects of HPT combined or not with land-based therapy on balance (133 patients; MD=2.00 [95% CI, 0.56 to 3.43; I^2 0%, p=0.01]) and functional mobility (133 patients; MD=−1.08 [95% CI, −1.99 to −0.18; I^2 8%, p=0.02]) [41]. However, HPT combined or not with land-based therapy did not improve QoL (76 patients; MD=−6.35 [95% CI, −13.04 to 0.33; I^2 7%, p=0.06]) and motor status (140 patients; MD=−1.11 [95% CI, −3.27 to 1.04; I^2 0%, p=0.31) [41]. The risk of bias across the included RCT was low. The data revealed that HPT combined or not with other therapies, may improve balance and functional mobility of patients with PD when compared to land-based PT alone or usual care. The results of above studies indicated that HPT may be a possible treatment for balance dysfunction in PD patients with a moderate stage of disease, with the potential to improve postural stability, reducing falls rate in protected conditions. Further studies with a follow-up period are necessary in order to evaluate whether the balance improvement persists over time and which protocol of water exercises is more effective for balance training in PD.

Massage therapy

Many PD patients revolve to massage in an attempt to alleviate symptoms of pain and rigidity, although the effects of massage with respect to PD are not well studied. A search of the literature resulted in only seven studies that investigated the effect of various forms of therapeutic massage relating to PD patients. Among these studies, one study [42] investigated traditional Japanese massage (applied with firm pressure through the clothing), one study [43] examined neuromuscular therapy (described as direct compression of trigger points, gliding and lengthening strokes, and moderate compressions), and one study [44] explored the Alexander technique (involves instruction on proprioceptive awareness and focused concentration on muscle tone coupled with light instructive touch). The remainder studies inspected nonspecific generalized "massage" [45-48]. The above-mentioned Alexander technique (complementary therapy to treat PD) is a learned method that is believed to change movement habits in daily or specialized activities. Proponents of this technique believe that it helps patient to discover balance in the body and mind by releasing unnecessary muscular tension through a series of learned patterns and postures [44]. This technique is usually taught in individual or small group lessons in which the teacher uses many modes of communication including skilled hand contact, talking, visual aids, imitating, modeling, mirrors, and text. With this technique, it is possible for an individual with PD to cope with increased muscle tension and to improve his/her QoL [44].

Virtual physical therapy

Virtual reality (VR), a popular alternative treatment method in the field of neuro-rehabilitation during last decade, can also be integrated into treatment for PD patients. VR is a computerized simulation that allows users to interact with images and virtual objects that appear in the virtual environment in real-time through multiple sensory modalities [49]. VR offers augmented feedback about performance, enables individualized repetitive practice of motor function, and stimulates both motor and cognitive processes simultaneously. One of the new resources available for VR is Nintendo's Wii videogame and its derived products, such as Wii Fit. Its interactive games can help in the recovery of motor skills, working on one's coordination skills, strength, and reasoning, which enable it to interact lucidly and rehabilitate at the same time [50]. Loureiro and others [51] selected six volunteers at intermediate level (H & Y Stage, II-III) of PD, patients of both sexes (65±13 years old) participated in activities involving Wii Fit, for a total of 12 interventions, twice per week. Penguin Slide, Ski Slalom, Soccer Heading and Table Tilt were the Wii games selected as a form of virtual therapy. Statistically significant differences were found in the following tests: Borg's Scale (P=0.0464), Berg

Functional Balance Scale (p=0.0277), lateral functional reach to the right (p=0.0431*) and lateral functional reach to the left (p=0.0277) [51]. Currently, scientists [52] conducted a trial on 16 patients (6 females and 10 males) with PD, the Dizziness Handicap Inventory (DHI), BBS, Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) and the Sitting-Rising Test (SRT) were applied before rehabilitation (1st assessment), and after the 20th session of rehabilitation (2nd assessment), with the aim of observing the post-intervention changes [52]. Final scoring for the DHI and BBS was better after rehabilitation. The SRT showed a significant result after rehabilitation. The SF-36 showed a significant change in the functional capacity for the Tightrope Walk and Ski Slalom VR games ($p<0.05$), as well as in the mental health aspect of the Ski Slalom game ($p<0.05$). The DHI and BBS showed significant changes in the Ski Slalom game ($p<0.05$). There was evidence of clinical improvement in patients in the final assessment after virtual rehabilitation. Above both studies suggested that exercises with VR therapy can be a useful tool to improve the balance in PD patients. This therapy provides a suitable context for learning new motor strategies of movement and relearning motor functions that have become impaired. VR also provides a safe and motivational environment for practice, thus making this therapy a useful tool for intervention in patients with neurodegenerative conditions such as PD [53].

Occupational Therapy (OT)

According to the World Federation of Occupational Therapists, OT is a profession concerned with promoting health and wellbeing through occupation. The primary objective of OT is to enable people to participate in the activities of everyday life [54]. Occupational therapists achieve this outcome by enabling people to do things that will enhance their ability to participate or by modifying their environment to better support participation. The occupational therapist focuses on enabling performance and engagement in meaningful activities and roles at home and in the community [55,56]. These activities and roles can be classified in activities associated to the home environment like self-care and functional mobility; work, either paid or unpaid; and leisure activities, e.g., shopping, visiting a restaurant or a theater [57]. Depending on the needs of the caregivers, the role of occupational therapist extends to enabling caregivers to support and supervise the patient in daily activities while considering their own well-being [55,57]. Occupational therapists mainly use a mix of strategies including (1) application of compensatory strategies in daily activities (i.e., movement strategies, cognitive strategies and planning); (2) adaptation of tasks and daily routines; and (3) adaptations of the physical environment.

There is currently no comprehensive, standardized, OT assessment or measurement tool specific to PD. In daily clinical practice, occupational therapists use a wide range of standardized and in-house assessment formats, with no single uniform assessment currently being used by occupational therapists. Three well-established models employed to underpin OT practice are currently considered appropriate for occupational therapists to use with people living with Parkinson's, namely, Canadian Occupational Performance Measure [58], Assessment of Motor and Process Skills [59], and the Fatigue Impact Scale [60]. There is limited published information about the processes and techniques used by occupational therapists when treating people with PD.

Collaborative approach between physical and occupational therapy

Both PT and OT aim to improve functional independence and participation. A collaborative approach between PT and OT is successful when both disciplines focus on complementary, different aspects in both the assessment and interventions, while being aware of the instructions and strategies used by each other [57]. To achieve this, full awareness of each other's expertise and effective and timely communication are essential [61]. Shared information should at least consist of the diagnostic results, treatment goals and the treatment plan. Contradictive interventions should be avoided and, when appropriate, treatment by physiotherapist, occupational therapist and other professionals should be sequenced in time to reduce the burden for the patient. Even though, a multidisciplinary approach is automatically the best approach, when dealing with a complex patient population as well as evidence for the (cost-) effectiveness of multidisciplinary care in PD is contradictory [62,63]. Many different models of multidisciplinary and interdisciplinary care exist, and it is unclear which of those is most effective. Much more work remains needed in this area.

Specific therapies for specific symptoms

Speech therapy

Scientists estimate that 89% of patients with PD have speech and voice disorders including disorders of laryngeal, respiratory and articulatory function [64]. Despite the high incidence of speech and voice impairment, studies imply that only 3-4% of patients with PD receive speech treatment [65,66]. Perceptually, speech and voice in patients with PD are characterized by monopitch, reduced loudness, mono-loudness, breathy, reduced stress, imprecise articulation, hoarse voice quality, short rushes of speech, and hesitant and dysfluent speech [66]. Collectively, these speech symptoms are called hypokinetic dysarthria. The neural mechanisms underlying these voice and speech disorders are unclear [66]. Currently, a speech treatment approach called Lee Silverman Voice Treatment (LSVT® LOUD), has generated efficacy data for successfully treating voice and speech disorders in this population. In this regard,

Yorkston et al. [67] reviewed some studies for speech therapy related to PD, 14 studies of LSVT LOUD totaling approximately 90 people; 3 studies of biofeedback devices totaling 39 people; 5 studies with devices (e.g., delayed auditory feedback) totaling 16 people; and 3 miscellaneous studies of group treatment. Conclusions from the review reported that LSVT LOUD has the greatest number of outcome measures associated with any speech treatment examined. Furthermore, the authors summarized that for the most part outcomes were positive and can be interpreted with confidence [67]. These scientists recommended that future research in LSVT LOUD included large multisite effectiveness studies (clinical trials), additional documentation of long-term maintenance effects, alternative modes of administration (e.g., different dosages of intensity) and further study of treated patients with PD to better define predictors of success or failure with the treatment. Moreover, these researchers also recommended that future research for biofeedback, devices and group treatment approaches included having a larger number of people in studies, well-controlled replicable and reliable studies of well-defined populations and control or comparison group studies (RCTs).

The large research based supporting training-increased vocal loudness through LSVT LOUD, it is useful to inspect this specific treatment protocol in more detail as it concerns to current and future speech treatment research [67-69]. The basics of LSVT LOUD are based upon the hypothesized features underlying voice disorders in patients with PD [70]. These features include; **firstly**, an overall amplitude scale down of the speech mechanism (reduced amplitude of neural drive to the muscles of the speech mechanism) that may result in a "soft voice that is monotone [71], **secondly**, problems in sensory perception of effort that prevents a person with PD from accurately monitoring his/her vocal output and results [72] and **thirdly**, the individual's difficulty in independently generating (internal cueing/scaling) the right amount of effort to produce adequate loudness [73].

Published pilot data from training loudness (LSVT LOUD) have documented that effects generalize beyond vocal loudness to improve swallowing, speech articulation, communicative gestures, facial expression and neural functioning [74-76]. Some scientists [77] assessed the impact of LSVT® on vocal loudness (sound pressure level/ SPL) in a group of dysarthric individuals with PD and found that individuals treated with LSVT increased voice SPL from baseline to post-treatment by an average of 8 dB and from baseline to 6 months follow-up by an average of 6 dB. These changes were statistically significant and perceptibly audible. Differences in SPL between the treated and untreated patients at post-treatment and follow-up were statistically significant for all voice and speech tasks [77]. Recently, scientists [78] conducted a trial on 15 (12 male and 3 female) patients, who had significant voice and speech disorders due to PD. The relationship between disease severity (according to UPDRS-III and H&Y), demographic features and voice parameters [mean F0 volume (Hz) and intensity (dB)] were investigated. The LSVT is a specific method which was developed for these disorders. The results showed that there was a statistically significant improvement between the pre-therapy and the post-therapy mean Hz and dB levels ($p=0.006$ and $p<0.001$ respectively) [78]. There was no correlation was detected between the age, age onset, disease duration, UPDRS, H&Y Scale and the pre-therapy and post-therapy mean Hz or dB levels of the patients ($p>0.05$) [78].

Advancement in computer and web-based technology offer potentially powerful solutions to the problems of delivering an intensive efficacious dosage of treatment, treatment accessibility and long-term maintenance in rehabilitation. For example, a computer training application for upper limb motor deficits following stroke has been developed for delivery of constraint induced therapy, a program which requires intensive motor training (e.g., 6 h/day for 2 weeks). This computerized system (called AutoCITE) was documented to result in comparable outcomes to live delivery of the therapy [79]. Computer technology has also been developed for delivery of an intensive speech treatment (LSVT LOUD). Some scientists [80] reported on the use of a personal digital assistant as an assistive device for delivering LSVT LOUD to people with PD. The LSVT LOUD companion is specially programmed to collect data and provide feedback as it guides people through the treatment exercises, enabling them to participate in therapy sessions at home [80]. The neuro-physiological mechanisms underlying speech and voice disorders in PD are still poorly understood at this time, particularly in regard to deficits in sensory processing.

Dysphagia therapy

Dysphagia is a general symptom in PD and may happen at any stage of disease. It is anticipated that up to 80% of patients with early-stage PD experience oropharyngeal dysphagia and as high as 95% may be occur at advanced stage [81]. The main symptoms of dysphagia in PD are: difficulties in bolus formation; posterior loss of bolus; multiple swallows; decreased swallowing reflex; decreased epiglottis rotation angle during swallowing; delayed oral transit; poor bolus ejection; residual food in the oral cavity; alterations in vocal fold closure; reduced pharyngeal and esophageal motility; pharyngeal stasis; esophageal sphincter dysfunction; gastroesophageal reflux; laryngeal penetration; pulmonary aspiration; oropharyngeal bradykinesia and reduced anterior hyoid bone movement [81]. Moreover, studies indicate that pneumonia is the major cause of death in patients with PD, representing the significance of speech-language pathologist (SLP)-based intervention for dysphagia to delay the onset of this symptom [82].

Keeping in view this perspective, some studies [83-85] evaluated the efficacy and efficiency of therapeutic interventions made by SLP for symptoms of dysphagia in PD, as explained above. These studies have demonstrated the benefits of several treatment strategies in decreasing symptoms of dysphagia and improving swallow safety in patients with PD, including expiratory muscle strength training, food consistency modification and thermal-tactile stimulation. According to literature [86-89] patients with PD scored lower in the SWAL-QoL survey, suggesting poor QoL. Moreover, patients with more advanced disease scored lower on the questionnaire. Thus, dysphagia has been linked with QoL, depression and anxiety. Likewise, Ayres and colleague also reported that patients displayed improvement in swallowing-related QoL after a SLP therapy program [81]. The earlier in the course of PD, greater the improvement noted after therapy. However, in this field too large well-designed trials are required.

Music therapy

Music can generate significant effects on movement-related symptoms and psychological ones in PD treatment. Concerning the first aspect, rhythm has a crucial role in rehabilitation, enhancing connections between the motor and auditory systems [90]. There are two main branches of music therapy (MT) i.e., active and passive [91]. In short, active MT is based on the improvisation of music by the therapist and patients, who play an active part by using instruments and voice. The use of instruments is structured to involve all the sensory organs; the rhythmic and melodic components of music may be used as specific stimuli to get certain motor and emotional responses, thus combining movement and stimulation of different sensory pathways i.e., auditory and tactile (multiple sensory stimulation), with a well-established emotional quality [91]. Passive MT is conducted with the patient at rest with the ambition of producing a state of mental relaxation. The therapist plays calming music and invites the patient to visualize peaceful images.

The use of music in neuro-rehabilitation is grounded in neuro-physiological theories, and research on the influence of music on cognitive processes and motor learning principles [92]. Studies showed that playing and listening to music may modulate emotions, behaviors, movements, communication, and cognitive factors, modifying the activity of the brain areas involved in the perception and regulation of these aspects [93,94]. The therapeutic approach established 20 years ago in the US called Neurologic Music Therapy (NMT) is known as an effective approach in neuro-rehabilitation [90]. NMT concepts distinguish 3 sensorimotor techniques, with motor skills improvement as an overall goal. The first one, Rhythmic Auditory Stimulation (RAS), is a technique that aims to develop and maintain a physiological rhythmic motor activity (gait) through rhythmic auditory cues. This technique has been proven effective for gait rehabilitation in PD [95,96]. The second technique is Patterned Sensory Enhancement (PSE). The objective of this technique is to facilitate movements associated with the activities of daily life, not necessarily rhythmical in nature. PSE uses complex music elements: pitch, dynamics, harmony, meter, and rhythm to enhance and organize movement patterns in time and space, and to favorably affect the activity, muscle coordination, strength, balance, postural control and range of motion [97]. The last technique, Therapeutic Instrumental Music Performance (TIMP), employs musical instruments as a task orientation training to simulate and facilitate functional movements. The technique most commonly uses percussion instruments, playing them in a traditional or non-traditional way to improve range of motion, limb coordination, postural control, dexterity, body perception, and sensation [98]. In order to optimize the music therapy process, NMT uses the Transformational Design Model (TDM) to translate theoretical knowledge into clinical practice. It promotes effective assessment, design and implementation of therapeutic music interventions [90,99]. Currently, Bukowska et al. [100] applied the combination of all three NMT sensorimotor techniques in improving spatio-temporal gait parameters, and postural stability in the course of PD. The subjects from the experimental group attended MT sessions 4 times a week for 4 weeks. The TIMP, PSE and RAS were used in every 45 min session for practicing daily life activities, balance, pre-gait, and gait pattern. Percussion instruments, the metronome and rhythmic music were the basis for each session. The results showed that the combination of the three NMT sensorimotor techniques can be used to improve gait and other rhythmical activities in PD rehabilitation [100]. The results demonstrated significant improvement in the majority of the spatiotemporal gait parameters in the experimental group as compared to the control group. In the stability tests with eyes closed, substantial differences were revealed, indicating improvement of proprioception (the sense of body position and movement).

During the last decade, an increasing number of controlled studies have assessed the potential rehabilitative effects of music-based interventions, such as music listening, singing, or playing an instrument, in several neurological diseases. Although the number of studies and extent of available evidence is greatest in stroke and dementia, there is also evidence for the effects of music-based interventions on supporting cognition, motor function, or emotional wellbeing in people with PD. Music-based interventions can affect divergent functions such as motor performance, speech, or cognition in these patient groups. However, the psychological effects and neurobiological mechanisms underlying the effects of music interventions are likely to share common neural

systems for reward, arousal, affect regulation, learning, and activity-driven plasticity. Although further controlled studies are needed to establish the efficacy of music in neurological recovery, music-based interventions are emerging as promising rehabilitation strategies.

Hormone therapy

Studies imply that estrogens may defend the nigrostriatal DA pathway exaggerated in PD [101,102]. Animal studies indicate that estrogens influence the synthesis, release and metabolism of dopamine and can modulate dopamine receptor expression and function [101,103]. Some clinical studies [104,105] recommend that PD symptoms may be aggravated after menopause and delayed or alleviated with hormone replacement therapy (HRT), but others [106,107] have failed to observe positive estrogenic effects. The contradictory findings suggest that several variables, including age, estrogen dose and formulation, and timing and length of dosing period, may determine whether benefits are seen and the nature of these benefits. Further investigation is therefore needed for the relationship between estrogens and the nigrostriatal DA system.

Several studies have investigated the role of HRT in the improvement of motor symptoms in postmenopausal women with PD [108-111]. A study [108] showed that 17β-estradiol has a slight or anti-parkinsonian effect without consistently altering dyskinesias in their double-blind, placebo-controlled, two-arm crossover study of high-dose transdermal 17β-estradiol in 8 postmenopausal women with mild-to-moderate PD. Tsang and colleague [110] observed a statistically significant improvement of motor function in those women receiving low-dose estrogen (0.625 mg/day), with a mean 3.5-point improvement on the motor UPDRS score. However, a placebo-controlled, randomized, double-blind trial involving 12 post-menopausal female PD patients under the age of 80 years revealed estradiol had no significant DA effect, whereas progesterone appeared to have an anti-DA effect [109]. In 2011, multicenter randomized, double-blind, placebo-controlled pilot trial from the Parkinson Study Group POETRY Investigators indicated a non-significant trend of symptomatic and functional improvement in those receiving HRT [111]. Likewise, Wang and others [1] found that results of meta-analysis do not support a protective role of HRT in female PD development. However, the significantly increased risk of PD in cohort studies remains to be clarified. Concerning the small number of participants included in each original study, it is conceivable that the inconsistent results were due to the small sample size.

Moreover, a double-masked, placebo-controlled, parallel-group, single-center trial in 30 male PD patients investigated the effect of testosterone therapy [112]. This study showed that there was no significant improvement of the motor and non-motor symptoms in the testosterone therapy group compared to placebo group. The authors were also aware of the possibility that the observed null effect may have resulted from various limitations, including the small sample size, a strong placebo effect with intramuscular therapy, and the short follow-up period [112]. Therefore, whether sex hormones play a role in the improvement of PD symptoms also remains for future study and more well-designed studies are warranted to clarify this issue.

Newly developed non-pharmacological therapeutic strategies

Gene therapy

Gene therapy (GT) is the use of genetic material to treat genetic diseases. This may involve adding a wild type copy of the gene (gene addition) or altering a gene with mutation to the wild type gene (gene editing). The treatment may take place outside or inside of the body. To get the gene into the genome inside the cells, modified viruses or other vectors are used [113]. This is a new approach to treating medical conditions, in essence using genes as drugs. It works by introducing normal genes into the cells of people with certain disorders to overcome the effects of defective genes, which may cause or have a part to play in the development of the condition. Although in most cases Parkinson's is not thought to be genetically inherited, it is hoped that GT could still be used to prevent the death of nerve cells and promote the regeneration of cells in the early stages of the condition. The advantage of GT is that a gene can deliver as an agent to the specific brain region to alter function and treat PD [114], while avoiding the off-target effects [115]. Although GT is mainly at experimental stage at present, the promising future makes a lot of researchers seeing it as a new class of drugs for PD. Basically, delivery method of GT can divide into two types i.e., viral and non-viral mediates ways [116].

Neurotrophic factors, such as glial cell-derived neurotrophic factor (GDNF), neurturin are secreted proteins that play regulatory roles in the development, survival and maintenance of the nervous system [117]. While the neurodegeneration progressing, the progresses in the constructor of viral vectors for gene transfer make GT a realistic form for PD treatment. *In vitro*, GDNF promoted the survival of cultured ventral midbrain DA neuron [118]. Some studies [119,120] supporting the positive effect of GDNF expression on nigrostriatal degeneration and related motor symptom in PD model animals. Some researchers use mifepristone and Adeno-associate virus (AAV)-5 vectors that expressing GDNF to establish an intermittent and reversible mode to control the expression of GDNF, in this system, mifepristone was used as a gene switch to induce a transient impact on expression [121]. Some researchers [122,123] used 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated rhesus monkeys and

aged monkeys with parkinsonian symptom as the model animals, both groups use AAV2-GDNF vector injected the putamen, the result turns out that AAV2-GDNF enhanced the locomotor activities and increased the DA terminals in the putamen. Although there is lot of benefits in the GDNF GT, significant weight loss induced by nigral GDNF expressing is disturbing. The GDNF therapy needs more understanding and further development at every level.

The gene of neurturin (NTN) is a member of the GDNF gene family. The NTN can rescue DA neurons damage [124]. Marks et al. [125] reported that 12 PD patients received an injection of AAV NTN and their symptomatic syndrome showed a significant improvement, although the DA terminal showed no significant increases in PET imagination. However, in an effort to validate the efficacy in the former trial, same researchers [126] launched a randomized, sham surgery controlled, double-blind clinical trials which include 58 PD patients. There is no substantial improvement observed in the NTN-treated patients until it comes to the 18 months. In 2008, 2010 and 2015, Ahmed and colleague [127-129] used the lentivirus-mediated over expression of GRK6 to desensization the DA receptors, this approach had got lot of benefits that is unattainable while directly targeting the signaling pathways, but a lot of problems still remain. The GT as discussed above is directly sent the complexes to the target area, how can we avoid the inflammation. In the GT of GDNF, weigh loss is a disturbing thing remained unsolved, and the development of some antibody against the GDNF was observed. With the advancing of the biology, there is hope to see more help from RNA interference that rescue gene deficit than is observed in diagnosis. However, applications of the RNA interference technique in clinical practice still have a long way to go.

Stem cell therapy

Cell therapy is the use of cells that are taken either from the patient themselves or a donor to treat diseases. Cells used for cell therapy are often stem cells; cells that can mature into different types of specialized cells [113]. Cells used for cell therapy may or may not be genetically altered. It is sometimes easier to remove cells from the body, treat them with gene therapy and then place them back than treating the cells inside the body. This is the case for gene therapy for blood disorders [113]. Gene and cell therapy therefore often go together.

Neural stem cells (NSCs) are multi-potent cells capable of differentiating into both neurons and glial cells of the nervous system. The current studies [130,131] have indicated that certain NSCs persist in the adult nervous system and are capable of regenerating new neurons. Compared with pluripotent stem cells, these multipotent NSCs display higher cellular survival rates and lower risk of teratoma formation [130]. In addition to the fetal isolation of NSCs, these cells can be obtained from areas of the adult brain including the sub-ventricular zone, the sub-granular zone, and the hippocampus [132]. Acquisition of NSCs from non-fetal sources avoids the ethical issues that are presented by embryonic stem cells. Because of the abilities of NSCs to self-renew and differentiate into many types of neurons, including those that are dysfunctional in neurodegenerative diseases, their potential use in the treatment of patients with PD holds promise [133].

As know, one of the major problems in PD is the inability of the substantia nigra to produce dopamine. Many studies on NSCs and their application in treating PD have focused on the damaged or dysfunctional DA neurons as targets for stem cell transplantation [130]. To attain a flourishing cell-based therapy in PD, some criteria for cell transplantation are generally suggested as the cells should possess the molecular, morphological and electro-physiological properties of DA neurons in substantia nigra, the therapy should enable 100,000 or more DA neurons to survive long-term in human putamen and the grafted cells should re-establish a dense terminal network throughout the striatum to functionally integrate into host neural circuitries [134]. Studies have been done using forebrain-derived human NSCs (FD-hNSCs) to determine the biochemical signals necessary for differentiation of hNSCs into DA neurons [135,136]. In an *in vitro* study [135], scientists cultured FD-hNSCs and treated them with combinations of bone morphogenetic protein-7, pramipexole, and various growth factors: acidic fibroblast factor, forskolin, and phorbol-12-myristate-13-acetate. Measurements of the levels of typical gene products produced by DA neurons were used to determine the level of successful differentiation. When compared with the control, FD-hNSCs treated with bone morphogenetic protein-7, pramipexole, and growth factors showed significantly increased gene expression of various products associated with DA neurons including tyrosine hydroxylase, an enzyme involved in the production of dopamine. The study also found that the levels of both basal and evoked dopamine released by the treated FD-hNSCs were increased compared with the control groups [135].

A study [137] used NSCs derived from embryonic stem cells to transplant into the patients (42 to 79 years of age). For up to 57 months after surgery, no tumor formation or immune rejection was found. In addition, there were no graft-induced or delivery-related adverse effects. As this particular study [137] appeared to show transplantation success, other studies have shown variable outcomes. Most studies have reported that patients experienced moderate improvement, while others have described less well tolerated transplantation procedures [130]. Reasons for this inconsistency comprise difficulties obtaining fetal sources and lack of adult sources of NSCs [130]. Research

regarding improved stem cell harvesting techniques and procedures that may decrease the cellular mortality rate, may cause produce more consistent studies outcome.

Induced pluripotent stem cells (iPSCs) are adult somatic cells that are converted into pluripotent cells via the introduction of specific transcription factors that are found in normal pluripotent stem cells [131]. Then cells can be differentiated into most somatic cell types and are self-renewable. In addition, iPSCs can easily be used to create a cell line that is matched to the adult without resorting to cloning that can cause abnormal karyotypes and teratomas [136]. Regarding to PD, iPSCs are useful in three ways such as, disease modeling, drug screening and cell replacement therapy [138]. During last decade, direct therapeutic treatment for PD through transplantation of iPSCs was not feasible. Transplantation faced many problems like low efficiency, use of viruses and tendency to cause teratomas [138]. Now, researchers have successfully used a xeno-free media alongside a feeder-free culture system and Cre-mediated excision of reprogramming factors to get transgene-free iPSCs at a greater efficiency (0.15- 0.3%) than before [139]. One study [140] found that human iPSCs transplanted into 6-hydroxydopamine–induced PD rats improved their functional defects of rotational asymmetry at 4, 8, 12 and 16 weeks after transplantation.

Therapeutic stem cell studies have often focused on the use of multipotent mesenchymal stem cells (MSCs) as opposed to embryonic stem cells, the use of which poses ethical concerns. The use of embryonic stem cells is controversial specifically because it involves the destruction of human embryos, which some people view as having the same moral status as an adult. Now-a-days, researchers began to explore the possibility of using adipose tissue stroma as an alternate source for stem cells because it can be easily isolated from humans using suction-assisted lipectomy [141]. After the discovery of adipose-derived stem cells (ADSCs), scientists sharpened their focus on the structure and function of human ADSCs (hADSCs) to better understand the prospect of using them in clinical research. One study conducted by Tomita et al. who sought to clarify hADSC characteristics and their capability in producing neurotrophic factors in vitro as differentiated Schwann cell-like cells [142]. Similar to the study done by Zuk and colleague [143] who, reported that an analysis of the full structural profile conducted of hADSCs collected from the abdomen, buttock, and thigh using procedures of flow cytometry, immunohistochemistry, and western blotting. According to another study [144], intravenous hADSCs improved motor and behavioral performances [144]. A study conducted by Zhou and others [145] who performed on hemiparkinsonian rhesus monkeys analyzed the value of gene therapy using a vector encoding the TH gene and a trophic factor enhancing neuron survival in conjunction with neuronal-primed ADSCs. Recent animal studies [136,144] have shown that PD improvement due to ADSCs can be equally or more successful in comparison with currently administered reference drugs. It may be concluded that stem cell techniques must continue to improve and be tested in living animals and humans before becoming the next major PD treatment option. Based on studies, it appears that iPSCs are the most promising upcoming stem cell technique not only because of therapeutic uses, but also the applications in disease modeling and drug testing. In spite of, more clinical trials must be conducted across all potential treatment types to find a truly effective solution.

Light therapy

Red and infrared light (λ= 600-1,070 nm) therapy, confounded here to the term ‘near infrared light (NIr), also known as photobiomodulation, has been reported to offer neuroprotection and to improve locomotor behavior in animal models of PD, from rodents to non-human primates [146-148]. Two studies [149,150] reported that neuroprotection by NIr after parkinsonian insult demonstrated that NIr treatment reduced cell death, increased ATP content and decreased levels of oxidative stress in rat striatal and cortical cells exposed to the parkinsonian toxins rotenone and MPP+ (1-methyl-4-phenylpyridium) *in vitro*.

Several clinical case reports have used a transcranial approach, with either a hand-held laser or light emitting device (LED) or a helmet lined with many LED strips covering the bulk of the head. There is a clinical report [151] indicating improved speech, cognition, freezing episodes and gait in 8 parkinsonian patients after 2 weeks application of photobiomodulation across the head from a laser device. Moreover, from a study [152] of 36 patients, photobiomodulation from an intranasal device resulted in improvements in the majority of parkinsonian signs (~90%) after treatment for 30 minutes per day for 10 days. There is also an incidental finding of a reduction in clinical signs in one patient after photobiomodulation with a 660 *nm* laser device for a dental problem; the device was directed at the back of the head and the photobiomodulation was applied for 2 to 3 minutes [153]. There are some encouraging observations from 3 patients with PD [154], using a photobiomodulation helmet, lined with LED strips of various wavelengths across the red to near infrared light range (i.e., 670 nm, 810 nm, 850 nm, 940 nm).

The mechanism that underlies the observed beneficial outcomes of the transcranial photobiomodulation in the patients is not known, however there are three possibilities. Firstly, by direct stimulation, where photobiomodulation is applied directly on the distressed neurons themselves, activating mitochondrial function that then increases both ATP energy and the expression of stimulatory and/or

protective genes [147,148,154]. Secondly, by indirect stimulation, where photobiomodulation triggers recruitment of a "middle man" such as, cells of the immune and/ or stem cell systems [147,148]. These activated cells may swarm to the region of distressed neurons and helps them survive and function, by potentially increasing the expression of anti-inflammatory cytokines while decreasing the pro-inflammatory ones [147,148]. Thirdly, rather than acting on the distressed neurons through either a direct or indirect stimulation as described above, photobiomodulation may act on other brain regions, for example motor cortex, that then stimulate the neural networks that underpin the behavioral improvements [155].

There are several key advantages for the use of light therapy over current treatments for PD. First and prime, light therapy has the potential to be neuroprotective. There are some substances (e.g., coenzyme Q10 and melatonin) [156] or methods (like, deep brain stimulation at high frequency) [157] that have been shown to be neuroprotective in experimental animals, and light therapy definitely fits into this category. These show potential for a neuroprotective function in humans. Second, light therapy is safe, and there are no reported side effects. Previous studies [158-160] using external (such as, WARP-LED) or internal (like, optical fiber device) methods to deliver light therapy at power intensities ranging from ~1–700 mW/cm^2 have reported no adverse effect on brain tissue structure and function (810 nm, laser and 670 nm, LED). Third, treatment with light therapy is simple. For effective neuroprotection of the SNc, the patient would require a minimally invasive surgical stereotactic procedure for the insertion of a light-optical device within the brain. This device would be linked to a battery source and pacemaker device (as with patients receiving deep brain stimulation), applying the light to the SNc when required [161]. The procedural risks would be comparable to those of single electrode deep brain stimulation.

A disadvantage of light therapy is that it may not be effective in treating the non-motor symptoms of the PD. Reports of animal models indicate that DA neurons in regions outside of the SNc are less likely to be protected by light treatment after parkinsonian insult [162]. However, these symptoms are minor compared to the prominent motor signs of the disease. There is true prospective for the development of light therapy as a treatment option for PD patients–one that slows the ongoing neuronal death and progression of the disease.

Deep brain stimulation

About 9,000 patients with PD undergo deep brain stimulation (DBS) implantation annually worldwide [163]. During 2013, the EARLY-STIM trial provided Class I evidence for the use of DBS earlier in PD [164]. This finding led to the 2016 FDA approval of DBS in patients with at least 4 years of disease duration and 4 months of motor complications as an adjunct therapy for patients not adequately controlled with medications. Meta-analysis of 6 RCTs of DBS demonstrates significant improvements in activities of daily living, motor disability, mental health, behavioral problems, medication use, mood, and QoL [165]. In contrast of above studies, Daniels and colleague [166] reported that 43% of patients showed no improvement at 6 months, and Soulas et al. [167] found 37% of subjects showed no improvement or a decline in QoL. For composite indices and individual domains of global disease specific (e.g., PD Questionnaire-39), and generic QoL measures, there are cumulative improvements in activities of daily living, motor signs, mobility, stigma and bodily discomfort, but no improvement or decline in social support, emotional wellbeing, cognition and communication [167,168]. On an average, DBS is used after 11 to 13 years of PD. Use of DBS has the potential to improve QoL if used as soon as motor fluctuations occur [169]. Latest UK NICE guidelines (2017) recommend DBS be considered for people with advanced Parkinson's whose symptoms are not adequately controlled by the best medical therapy [170].

The DBS of the subthalamic nucleus (STN) and globus pallidus interna (GPi) is considered an essential therapy in the management paradigm of PD [171]. The option of the DBS target between STN and GPi is determined by the accumulation of motor and non-motor symptoms which are key determinants to QoL. In terms of motor effectiveness, a few variables were compared in a recent meta-analysis of the outcomes between the two targets after 36 months follow-up [172]. Improvements in motor symptoms during the "on-medication" period, was not different between STN and GPi DBS, however, reduction of the impact of motor symptoms during the "off-period" and the total daily medication dosage were more significant for STN DBS. The GPi DBS procedure showed a trend towards stronger dyskinesia reduction. Follett et al. reported results from a randomized, blinded, controlled, prospective study of 299 patients comparing STN vs GPi DBS outcomes [173]. Similar improvement in motor function (on UPDRS-III) was noted after GPi and STN DBS. The same Veteran Affairs (VA) Cooperative Study follow-up at 36 months again showed similar and stable motor improvements in both groups [174]. Interestingly, Southwell et al. [175] observed that after publication of the VA Cooperative Study, there was a sixfold increase in GPi- vs STN-target choice for patients with higher age, depression, and cognitive problems (perhaps reflecting higher neuropsychiatric adverse-event rates in the VA Cooperative Study STN DBS group). These authors concluded that these among other factors (such as brittle dyskinesia, having difficulties with follow-up) favor GPi,

whereas in persons with higher preoperative levodopa-equivalent dose, the STN target is to be favored [175]. It should be noted that although neuropsychiatric adverse-event rates might be higher after STN than GPi DBS (and some thus favor GPi over STN DBS in patients deemed at risk of neuropsychiatric adverse events), adverse-event reporting may not be highly reliable [176]. Furthermore, the largest and highest-quality randomized trials reported minimal differences in cognitive and psychiatric outcomes, and differences in effect size were small [177]. Odekerken and others [178] randomized 128 patients to GPi or STN DBS, found no differences by surgical target on primary outcomes either (weighted Academic Medical Center Linear Disability Scale [ALDS] or composite score for cognitive, mood, and behavioral effects) 1 year after surgery, but they did find differences in secondary outcomes. Specifically, larger improvements were observed after STN than GPi DBS in the off-medication state (UPDRS-III, 20.3% vs 11.4% improvement; ALDS, 20.3% vs 11.8% improvement) [178]. A meta-analysis of 563 patients in six trials conducted by Liu and others [179], who found that GPi and STN improved motor function (UPDRS-III medication off and on states) and activities of daily living (in the on state) similarly 1 year after surgery. However, STN DBS allowed greater medication reduction, whereas GPi DBS was associated with greater improvement in depressive symptoms (by Beck Depression Inventory). Only one case series has documented significant medication reduction with GPi DBS [180]. There is a need for further qualitative research to understand the nature of this transition to inform how best patients can be supported by healthcare professionals before, during and after DBS. Studies that examine the outcomes of DBS require longer term follow-up.

Repetitive transcranial magnetic stimulation

During last few years, repetitive transcranial magnetic stimulation (rTMS) has been closely examined as a possible treatment for PD [181]. As a noninvasive procedure, rTMS does not require surgery or anesthesia. It delivers repeated magnetic pulses to a specific brain area within a short time through a stimulation coil placed over the scalp. The repeated magnetic pulses not only alter excitability at the site of stimulation but also influence brain regions anatomically connected to the stimulation site [182].

High frequency rTMS (>1.0 Hz) can enhance the cortical excitability whereas low frequency (≤1.0 Hz) rTMS can decrease the cortical excitability [183]. Theta burst stimulation (TBS) is another form of rTMS protocol with a high frequency and low intensity stimulation. Intermittent TBS enhances cortical excitability, whereas continuous TBS decreases cortical excitability [184]. Recent studies [185,186] displayed the therapeutic effects of rTMS on motor dysfunction of PD patients as evaluated with the motor section of the UPDRS-III and the optimal parameters of rTMS on the functional motor improvement of PD. Likewise, randomized, double-blind, sham-controlled, multicenter studies on rTMS for PD have been conducted 3 times (in 2003, 2008, and 2013) in Japan [187]. These studies revealed that 5-Hz rTMS over the supplementary motor area (SMA) is the most effective modality for improving motor symptoms. Several functional imaging studies showed reduced SMA excitability in patients with PD, probably secondary to basal ganglia dysfunction. Therefore, 5-Hz rTMS is assumed to normalize SMA excitability and amend basal ganglia function secondarily. However, recently Khedr et al. reported that both 20 Hz and 1 Hz rTMS improved motor function in PD, but 20 Hz rTMS is more effective [188]. In addition, several powerful rTMS have been developed in recent times, including quadripulse stimulation (QPS), which most potently induces neural plasticity. QPS is also expected to be a potential therapeutic tool to treat patients with PD [187]. Currently, Hai-Jiao and colleague [189] compared to sham-rTMS, rTMS over dorsolateral prefrontal cortex (DLPFC) improved depression, but there was no significant difference in depression improvement between rTMS and selective serotonin reuptake inhibitor (SSRI) treatment. In contrast, rTMS over DLPFC did not improve motor function compared to sham-rTMS or SSRI, and the studies that included neurocognitive measures showed no significant difference between rTMS and sham-rTMS. This meta-analysis indicated that rTMS over DLPFC can improve depression similar to SSRI treatment, however no effect on the motor function and cognition of PD patients with depression [189].

Many studies used rTMS protocols varying in stimulation parameters such as: (a)- Stimulation sites of primary motor cortex [190,191], supplementary motor area [191,192], dorsal lateral prefrontal cortex [191,193], the dorsal pre-motor [194]. (b)- Low frequency-rTMS [from 0.2 Hz to 1.0 Hz; [190,195], or high frequency-rTMS ([5.0 Hz, 25.0 Hz, 50.0 Hz) [191,196,197]. (c)- The rTMS sessions (one session [190,192], 3-6 sessions [191,198], 8 sessions [199], and 10 sessions [190,193]).

Conclusions

This review highlights the variety of physiotherapy intervention being tested for the treatment of PD. All kinds of rehabilitation therapies for PD have potential to maximize functional ability and minimize secondary complications by focusing on improving balance, posture, gait, upper limb function, physical capacity, and cognition, as well as minimizing falls, in order to optimize individuals' independence, safety, and well-being, thereby enhancing QoL. Evidence has shown that physiotherapy has short-term benefits in PD, however which approach of physiotherapy is most effective remains unclear.

Regarding newly developed therapies, gene therapy has yet to deliver the true cure for PD, there is increasing data supporting that this treatment modality could become an important avenue for future PD treatment. Stem cell techniques must continue to improve and be tested in living animals and humans before becoming the next major PD treatment option. The iPSCs are the most promising upcoming stem cell technique not only because of therapeutic uses, but also the applications in disease modeling and drug testing. NIr therapy (because of its lack of side effects and neuroprotective potential) is agreeable to use in conjunction with other treatments. For example, patients may have NIr therapy with a reduced dosage of drugs as a first line treatment; the potential neuroprotective effect of NIr could prolong the efficacy of the drug therapy. Further, in PD patients selected for DBS, they may also have an NIr optical fiber implanted surgically at the same time, thereby potentially offering neuroprotection of the remaining DA cells. The use of DBS has the potential to improve QoL if applied as soon as motor fluctuations occur. DBS must consider for people with advanced Parkinson's whose symptoms are not adequately controlled by best medical therapy. The studies suggested that rTMS improves motor symptoms for patients with PD. Combinations of rTMS site and frequencies as well as the number of rTMS pulses are key modulators of rTMS effects. In spite of above advantages of various kinds of therapies, much research is still needed to determine which of these therapies best alleviates the motor and non-motor symptoms, needed dose and intensity of these therapies, and long-term retention effects.

Compliance with ethical standards

Any aspect of the work covered in this manuscript has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

Conflict of interest disclosure

There are no known conflicts of interest in the publication of this article. The manuscript was read and approved by all authors.

References

1. Wang P, Li J, Qiu S, Wen H, Du J. Hormone replacement therapy and Parkinson's disease risk in women: a meta-analysis of 14 observational studies. *Neuropsychiatr Dis Treat*. 2014;11:59-66. Published 2014 Dec 31. doi:10.2147/NDT.S69918
2. Spillantini MG, Schmidt ML, Lee VM, Trojanowski JQ, Jakes R, Goedert M. Alpha-synuclein in Lewy bodies. *Nature*. 1997;388(6645):839-840. doi:10.1038/42166
3. Fahn S, Sulzer D. Neurodegeneration and neuroprotection in Parkinson disease. *NeuroRx*. 2004;1(1):139-154. doi:10.1602/neurorx.1.1.139
4. Uhrbrand A, Stenager E, Pedersen MS, Dalgas U. Parkinson's disease and intensive exercise therapy--a systematic review and meta-analysis of randomized controlled trials. *J Neurol Sci*. 2015;353(1-2):9-19. doi:10.1016/j.jns.2015.04.004
5. Dorsey ER, Constantinescu R, Thompson JP, et al. Projected number of people with Parkinson disease in the most populous nations, 2005 through 2030. *Neurology*. 2007;68(5):384-386. doi:10.1212/01.wnl.0000247740.47667.03
6. Hely MA, Morris JG, Traficante R, Reid WG, O'Sullivan DJ, Williamson PM. The sydney multicentre study of Parkinson's disease: progression and mortality at 10 years. *J Neurol Neurosurg Psychiatry*. 1999;67(3):300-307. doi:10.1136/jnnp.67.3.300
7. Noyce AJ, Bestwick JP, Silveira-Moriyama L, et al. Meta-analysis of early nonmotor features and risk factors for Parkinson disease. *Ann Neurol*. 2012;72(6): 893-901. doi:10.1002/ana.23687
8. Shulman LM, Bhat V. Gender disparities in Parkinson's disease. *Expert Rev Neurother*. 2006;6(3):407-416. doi:10.1586/14737175.6.3.407
9. Taylor KS, Cook JA, Counsell CE. Heterogeneity in male to female risk for Parkinson's disease. *J Neurol Neurosurg Psychiatry*. 2007;78(8):905-906. doi: 10.1136/jnnp.2006.104695
10. Elbaz A, Bower JH, Maraganore DM, et al. Risk tables for parkinsonism and Parkinson's disease. *J Clin Epidemiol*. 2002;55(1):25-31. doi:10.1016/s0895-4356(01)00425-5
11. Müller B, Assmus J, Herlofson K, Larsen JP, Tysnes OB. Importance of motor vs. non-motor symptoms for health-related quality of life in early Parkinson's disease. *Parkinsonism Relat Disord*. 2013;19(11): 1027-1032. doi:10.1016/j.parkreldis.2013.07.010
12. Hurt CS, Rixon L, Chaudhuri KR, Moss-Morris R, Samuel M, Brown RG. Barriers to reporting non-motor symptoms to health-care providers in people with Parkinson's. *Parkinsonism Relat Disord*. 2019;64:220-225. doi:10.1016/j.parkreldis.2019.04.014
13. Templeton JM, Poellabauer C, Schneider S. Classification of Parkinson's disease and its stages using machine learning. *Sci Rep*. 2022;12(1):14036. Published 2022 Aug 18. doi:10.1038/s41598-022-18015-z
14. Tomlinson CL, Herd CP, Clarke CE, et al. Physiotherapy for Parkinson's disease: a comparison of techniques. *Cochrane Database Syst Rev*. 2014; 2014(6):CD002815. Published 2014 Jun 17. doi:10.1002/14651858.CD002815.pub2
15. Samii A, Nutt JG, Ransom BR. Parkinson's disease. *Lancet*. 2004;363(9423):1783-1793. doi: 10.1016/S0140-6736(04)16305-8
16. Thenganatt MA, Jankovic J. Parkinson disease subtypes. *JAMA Neurol*. 2014;71(4):499-504. doi: 10.1001/jamaneurol.2013.6233

17. Pike AF, Szabò I, Veerhuis R, Bubacco L. The potential convergence of NLRP3 inflammasome, potassium, and dopamine mechanisms in Parkinson's disease. *NPJ Parkinsons Dis*. 2022;8(1):32. Published 2022 Mar 24. doi:10.1038/s41531-022-00293-z
18. Lee TK, Yankee EL. A review on Parkinson's disease treatment. *Neuroimmunol Neuroinflammation*. 2021 Dec 21;8:222-244. doi:10.20517/2347-8659.2020.58
19. Osborne JA, Botkin R, Colon-Semenza C, et al. Physical Therapist Management of Parkinson Disease: A Clinical Practice Guideline From the American Physical Therapy Association. *Phys Ther*. 2022; 102(4):pzab302. doi:10.1093/ptj/pzab302
20. Radder DLM, Lígia Silva de Lima A, Domingos J, et al. Physiotherapy in Parkinson's Disease: A Meta-Analysis of Present Treatment Modalities. *Neurorehabil Neural Repair*. 2020;34(10):871-880. doi:10.1177/1545968320952799
21. Mishra SK, Singh P, Bunch SJ, Zhang R. The therapeutic value of yoga in neurological disorders. *Ann Indian Acad Neurol*. 2012;15(4):247-254. doi:10.4103/0972-2327.104328
22. Lee L. The effect of yoga exercises on balance, lower-extremity function and gait in people with Parkinson's disease. *Archiv Phys Med Rehabil*. 2006 Nov 01; 87(11):E19.
23. Hall E, Verheyden G, Ashburn A. Effect of a yoga programme on an individual with Parkinson's disease: a single-subject design. *Disabil Rehabil*. 2011;33(15-16):1483-1489. doi:10.3109/09638288.2010.529233
24. Colgrove YS, Sharma N, Kluding P, Potter D, Imming K, VandeHoef J, Stanhope J, Hoffman K, White K. Effect of yoga on motor function in people with Parkinson's disease: a randomized, controlled pilot study. *J Yoga Phys Ther*. 2012; 2(2): 1000112. doi:10.4172/2157-7595.1000112
25. Moriello G, Denio C, Abraham M, DeFrancesco D, Townsley J. Incorporating yoga into an intense physical therapy program in someone with Parkinson's disease: a case report. *J Bodyw Mov Ther*. 2013;17(4):408-417. doi:10.1016/j.jbmt.2013.01.005
26. Taylor M. Yoga therapeutics in neurological physical therapy: application to a patient with Parkinson's disease. *Neurol Report*. 2001; 25(2):55-62.
27. Kloubec JA. Pilates for improvement of muscle endurance, flexibility, balance, and posture. *J Strength Cond Res.* 2010;24(3):661-667. doi:10.1519/JSC.0b013e3181c277a6
28. Newell D, Shead V, Sloane L. Changes in gait and balance parameters in elderly subjects attending an 8-week supervised Pilates programme. *J Bodyw Mov Ther.* 2012;16(4):549-554. doi:10.1016/j.jbmt.2012.02.002
29. Bird ML, Hill KD, Fell JW. A randomized controlled study investigating static and dynamic balance in older adults after training with Pilates. *Arch Phys Med Rehabil*. 2012;93(1):43-49. doi:10.1016/j.apmr.2011.08.005
30. Johnson L, Putrino D, James I, Rodrigues J, Stell R, Thickbroom G, Mastaglia FL. The effects of a supervised pilates training program on balance in parkinson's disease. *Adv Parkinson's Dis*. 2013;2(2): 58-61. doi:10.4236/apd.2013.22011
31. Pandya S, Nagendran T, Shah A, Chandrabharu V. Effect of pilates training program on balance in participants with idiopathic Parkinson's disease- an interventional study. *Int J Health Sci Res*. 2017 May; 7(5):186-196. https://www.ijhsr.org/IJHSR_Vol.7_Issue.6_June2017/28.pdf
32. Mollinedo-Cardalda I, Cancela-Carral JM, Vila-Suárez MH. Effect of a Mat Pilates Program with TheraBand on Dynamic Balance in Patients with Parkinson's Disease: Feasibility Study and Randomized Controlled Trial. *Rejuvenation Res*. 2018;21(5):423-430. doi: 10.1089/rej.2017.2007
33. Vivas J, Arias P, Cudeiro J. Aquatic therapy versus conventional land-based therapy for Parkinson's disease: an open-label pilot study. *Arch Phys Med Rehabil*. 2011;92(8):1202-1210. doi:10.1016/j.apmr.2011.03.017
34. Carroll LM, Morris ME, O'Connor WT, Clifford AM. Is Aquatic Therapy Optimally Prescribed for Parkinson's Disease? A Systematic Review and Meta-Analysis. *J Parkinsons Dis*. 2020;10(1):59-76. doi: 10.3233/JPD-191784
35. Dai S, Yuan H, Wang J, Yang Y, Wen S. Effects of aquatic exercise on the improvement of lower-extremity motor function and quality of life in patients with Parkinson's disease: A meta-analysis. *Front Physiol*. 2023;14:1066718. Published 2023 Feb 3. doi:10.3389/fphys.2023.1066718
36. Jessop RT, Horowicz C, Dibble LE. Motor learning and Parkinson disease: Refinement of movement velocity and endpoint excursion in a limits of stability balance task. *Neurorehabil Neural Repair*. 2006;20(4):459-467. doi:10.1177/1545968306287107
37. Zotz TGG, Souza EA, Israel VL, Loureiro APC. Aquatic physical therapy for Parkinson's disease. *Adv Parkinson's Dis*. 2013 Nov; 2(4):102-107. doi: 10.4236/apd.2013.24019
38. Siega J, Iucksch DD, Israel VL. Multicomponent Aquatic Training (MAT) Program for People with Parkinson's Disease: A Protocol for a Controlled Study. *Int J Environ Res Public Health*. 2022;19(3):1727. Published 2022 Feb 2. doi:10.3390/ijerph19031727
39. Pompeu JE, Gimenes RO, Pereira RP, Rocha SL, Santos MA. Effects of aquatic physical therapy on balance and gait of patients with Parkinson's disease. *J Health Sci Inst*. 2013;31(2):201-204.
40. Volpe D, Giantin MG, Maestri R, Frazzitta G. Comparing the effects of hydrotherapy and land-based therapy on balance in patients with Parkinson's disease: a randomized

controlled pilot study. *Clin Rehabil*. 2014; 28(12):1210-1217. doi:10.1177/0269215514536060

41. Pinto C, Salazar AP, Marchese RR, Stein C, Pagnussat AS. The Effects of Hydrotherapy on Balance, Functional Mobility, Motor Status, and Quality of Life in Patients with Parkinson Disease: A Systematic Review and Meta-analysis. *PM R*. 2019;11(3):278-291. doi:10.1016/j.pmrj.2018.09.031
42. Donoyama N, Ohkoshi N. Effects of traditional Japanese massage therapy on various symptoms in patients with Parkinson's disease: a case-series study. *J Altern Complement Med*. 2012;18(3):294-299. doi: 10.1089/acm.2011.0148
43. Craig LH, Svircev A, Haber M, Juncos JL. Controlled pilot study of the effects of neuromuscular therapy in patients with Parkinson's disease. *Mov Disord*. 2006; 21(12):2127-2133. doi:10.1002/mds.21132
44. Stallibrass C, Sissons P, Chalmers C. Randomized controlled trial of the Alexander technique for idiopathic Parkinson's disease. *Clin Rehabil*. 2002; 16(7):695-708. doi:10.1191/0269215502cr544oa
45. Hernandez-Reif M, Field T, Largie S, Cullen C, Beutler J, Sanders C, Weiner W, Rodriguez-Bateman D, Zelaya L, Schanber S, Kuhn C. Parkinson's disease symptoms are differentially affected by massage therapy vs. progressive muscle relaxation: a pilot study. *J Bodywork Mov Ther*. 2002;6(3):177-182. doi: 10.1054/jbmt.2002.0282
46. Paterson C, Allen JA, Browning M, Barlow G, Ewings P. A pilot study of therapeutic massage for people with Parkinson's disease: the added value of user involvement. *Complement Ther Clin Pract*. 2005; 11(3):161-171. doi:10.1016/j.ctcp.2004.12.008
47. Törnhage CJ, Skogar Ö, Borg A, et al. Short- and long-term effects of tactile massage on salivary cortisol concentrations in Parkinson's disease: a randomised controlled pilot study. *BMC Complement Altern Med*. 2013;13:357. doi:10.1186/1472-6882-13-357
48. Casciaro Y. Massage Therapy Treatment and Outcomes for a Patient with Parkinson's Disease: a Case Report. *Int J Ther Massage Bodywork*. 2016;9(1): 11-18. doi:10.3822/ijtmb.v9i1.287
49. Bisson E, Contant B, Sveistrup H, Lajoie Y. Functional balance and dual-task reaction times in older adults are improved by virtual reality and biofeedback training. *Cyberpsychol Behav*. 2007;10(1):16-23. doi: 10.1089/cpb.2006.9997
50. Sevcenko K, Lindgren I. The effects of virtual reality training in stroke and Parkinson's disease rehabilitation: a systematic review and a perspective on usability. *Eur Rev Aging Phys Act*. 2022;19(1):4. Published 2022 Jan 25. doi:10.1186/s11556-022-00283-3
51. Loureiro APC, Ribas CG, Zotz TGG, Chen R, Ribas F. Feasibility of virtual therapy in rehabilitation of Parkinson's disease patients: pilot study. *Fisioter Mov Curitiba*. 2012 July;25(3):659-66.
52. Severiano MIR, Zeigelboim BS, Teive HAG, Santos GJB, Fonseca VR. Effect of virtual reality in Parkinson's disease: a prospective observational study. *Arq Neuropsiquiatr*. 2018;76(2):78-84. doi: 10.1590/0004-282X20170195
53. Taylor MJ, McCormick D, Shawis T, Impson R, Griffin M. Activity-promoting gaming systems in exercise and rehabilitation. *J Rehabil Res Dev*. 2011;48(10):1171-1186. doi:10.1682/jrrd.2010.09.0171
54. Omar Ahmad S, Longhurst J, Stiles D, Downard L, Martin S. A meta-analysis of exercise intervention and the effect on Parkinson's Disease symptoms. *Neurosci Lett*. 2023;801:137162. doi:10.1016/j.neulet.2023.137162
55. Nijkrake MJ, Keus SH, Quist-Anholts GW, et al. Evaluation of a Patient-Specific Index as an outcome measure for physiotherapy in Parkinson's disease. *Eur J Phys Rehabil Med*. 2009;45(4):507-512.
56. Jansa J, Aragon A. Living with Parkinson's and the Emerging Role of Occupational Therapy. *Parkinsons Dis*. 2015;2015:196303. doi:10.1155/2015/196303
57. Radder DLM, Sturkenboom IH, van Nimwegen M, et al. Physical therapy and occupational therapy in Parkinson's disease. *Int J Neurosci*. 2017;127(10):930-943. doi: 10.1080/00207454.2016.1275617
58. Kobayashi E, Himuro N, Mitani Y, Tsunashima T, Nomura K, Chiba S. Feasibility and informativeness of the Canadian occupational performance measure for identifying priorities in patients with Parkinson's disease. *Physiother Theory Pract*. 2023;39(3):607-614. doi:10.1080/09593985.2021.2023926
59. Hinkle JT, Pontone GM. Psychomotor processing and functional decline in Parkinson's disease predicted by the Purdue Pegboard test. *Int J Geriatr Psychiatry*. 2021;36(6):909-916. doi:10.1002/gps.5492
60. Whitehead L. The measurement of fatigue in chronic illness: a systematic review of unidimensional and multidimensional fatigue measures. *J Pain Symptom Manage*. 2009;37(1):107-128.
61. van der Eijk M, Faber MJ, Al Shamma S, Munneke M, Bloem BR. Moving towards patient-centered healthcare for patients with Parkinson's disease. *Parkinsonism Relat Disord*. 2011;17(5):360-364. doi: 10.1016/j.parkreldis.2011.02.012
62. van der Marck MA, Bloem BR, Borm GF, Overeem S, Munneke M, Guttman M. Effectiveness of multidisciplinary care for Parkinson's disease: a randomized, controlled trial. *Mov Disord*. 2013;28(5): 605-611. doi:10.1002/mds.25194
63. Monticone M, Ambrosini E, Laurini A, Rocca B, Foti C. In-patient multidisciplinary rehabilitation for Parkinson's

disease: A randomized controlled trial. *Mov Disord*. 2015;30(8):1050-1058. doi:10.1002/mds.26256

64. Hartelius L, Svensson P. Speech and swallowing symptoms associated with Parkinson's disease and multiple sclerosis: a survey. *Folia Phoniatr Logop*. 1994;46(1):9-17. doi:10.1159/000266286
65. Ho AK, Iansek R, Marigliani C, Bradshaw JL, Gates S. Speech impairment in a large sample of patients with Parkinson's disease. *Behav Neurol*. 1999;11(3):131-137.
66. Ramig LO, Fox C, Sapir S. Speech treatment for Parkinson's disease. *Expert Rev Neurother*. 2008;8(2): 297-309. doi:10.1586/14737175.8.2.297
67. Helm-Estabrooks N, Duffy Yorkston KM, Spencer KA, Joseph R. Behavioral management of respiratory/ phonatory dysfunction from dysarthria: a systematic review of the evidence. *J Med Speech-Lang Pathol*. 2003 June;11(2), pp. xiii+
68. Pinto S, Ozsancak C, Tripoliti E, Thobois S, Limousin-Dowsey P, Auzou P. Treatments for dysarthria in Parkinson's disease. *Lancet Neurol*. 2004;3(9):547-556. doi:10.1016/S1474-4422(04)00854-3
69. Trail M, Fox C, Ramig LO, Sapir S, Howard J, Lai EC. Speech treatment for Parkinson's disease. *NeuroRehabilitation*. 2005;20(3):205-221.
70. Fox CM, Morrison CE, Ramig LO, Sapir S. Current perspectives on the Lee Silverman Voice Treatment (LSVT) for people with idiopathic Parkinson's disease. *Am J of Speech-Lang Pathol*. 2002 May 1;11:111-123. doi:10.1044/1058-0360(2002/012)
71. Albin RL, Young AB, Penney JB. The functional anatomy of basal ganglia disorders. *Trends Neurosci*. 1989;12(10):366-375. doi:10.1016/0166-2236(89)90074-x
72. Berardelli A, Dick JP, Rothwell JC, Day BL, Marsden CD. Scaling of the size of the first agonist EMG burst during rapid wrist movements in patients with Parkinson's disease. *J Neurol Neurosurg Psychiatry*. 1986;49(11):1273-1279. doi:10.1136/jnnp.49.11.1273
73. Demirci M, Grill S, McShane L, Hallett M. A mismatch between kinesthetic and visual perception in Parkinson's disease. *Ann Neurol*. 1997;41(6):781-788. doi:10.1002/ana.410410614
74. El Sharkawi A, Ramig L, Logemann JA, Pauloski BR et al. Swallowing and voice effects of Lee Silverman Voice Treatment (LSVT): a pilot study. *J Neurol Neurosurg Psychiatry*. 2002;72(1):31-36. doi: 10.1136/jnnp.72.1.31
75. Liotti M, Ramig LO, Vogel D, et al. Hypophonia in Parkinson's disease: neural correlates of voice treatment revealed by PET. *Neurology*. 2003;60(3): 432-440. doi:10.1212/wnl.60.3.432
76. Sapir S, Spielman JL, Ramig LO, Story BH, Fox C. Effects of intensive voice treatment (the Lee Silverman Voice Treatment [LSVT]) on vowel articulation in dysarthric individuals with idiopathic Parkinson disease: acoustic and perceptual findings. *J Speech Lang Hear Res*. 2007;50(4):899-912. doi:10.1044/1092-4388(2007/064)
77. Ramig LO, Sapir S, Fox C, Countryman S. Changes in vocal loudness following intensive voice treatment (LSVT) in individuals with Parkinson's disease: a comparison with untreated patients and normal age-matched controls. *Mov Disord*. 2001;16(1):79-83. doi:10.1002/1531-8257(200101)16:1<79::aid-mds1013>3.0.co;2-h
78. Gundogdu AA, Akidil AO, Kotan D. Resolving speech disorders in Parkinson disease: our clinical experience with voice therapy. *Biomed Res*. 2017;28(7):3313-17.
79. Taub E, Lum PS, Hardin P, Mark VW, Uswatte G. AutoCITE: automated delivery of CI therapy with reduced effort by therapists. *Stroke*. 2005;36(6):1301-1304. doi:10.1161/01.STR.0000166043.27545.e8
80. Sadagopan N, Huber JE. Effects of loudness cues on respiration in individuals with Parkinson's disease. *Mov Disord*. 2007;22(5):651-659. doi:10.1002/mds.21375
81. Ayres A, Jotz GP, Rieder CR, Schuh AF, Olchik MR. The Impact of Dysphagia Therapy on Quality of Life in Patients with Parkinson's Disease as Measured by the Swallowing Quality of Life Questionnaire (SWALQOL). *Int Arch Otorhinolaryngol*. 2016;20(3): 202-206. doi:10.1055/s-0036-1582450
82. Pinter B, Diem-Zangerl A, Wenning GK, et al. Mortality in Parkinson's disease: a 38-year follow-up study [published correction appears in Mov Disord. 2017 Jan;32(1):178]. *Mov Disord*. 2015;30(2):266-269. doi:10.1002/mds.26060
83. Pitts T, Bolser D, Rosenbek J, Troche M, Okun MS, Sapienza C. Impact of expiratory muscle strength training on voluntary cough and swallow function in Parkinson disease. *Chest*. 2009;135(5):1301-1308. doi:10.1378/chest.08-1389
84. Regan J, Walshe M, Tobin WO. Immediate effects of thermal-tactile stimulation on timing of swallow in idiopathic Parkinson's disease. *Dysphagia*. 2010;25(3): 207-215. doi:10.1007/s00455-009-9244-x
85. Smith SK, Roddam H, Sheldrick H. Rehabilitation or compensation: time for a fresh perspective on speech and language therapy for dysphagia and Parkinson's disease? *Int J Lang Commun Disord*. 2012 Jul-Aug; 47(4):351-364. doi: 10.1111/j.1460-6984.2011.00093.x
86. Leow LP, Huckabee ML, Anderson T, Beckert L. The impact of dysphagia on quality of life in ageing and Parkinson's disease as measured by the swallowing quality of life (SWAL-QOL) questionnaire. *Dysphagia*. 2010;25(3):216-220. doi:10.1007/s00455-009-9245-9
87. Heijnen BJ, Speyer R, Baijens LW, Bogaardt HC. Neuromuscular electrical stimulation versus traditional

therapy in patients with Parkinson's disease and oropharyngeal dysphagia: effects on quality of life. *Dysphagia*. 2012;27(3):336-345. doi:10.1007/s00455-011-9371-z

88. Argolo N, Sampaio M, Pinho P, Melo A, Nóbrega AC. Swallowing disorders in Parkinson's disease: impact of lingual pumping. *Int J Lang Commun Disord*. 2015; 50(5):659-664. doi:10.1111/1460-6984.12158
89. Rinaldi D, Imbalzano G, Galli S, et al. The impact of dysphagia in Parkinson's disease patients treated with levodopa/carbidopa intestinal gel. *Parkinsonism Relat Disord*. 2023;109:105368.
90. Hsu P, Ready EA, Grahn JA. The effects of Parkinson's disease, music training, and dance training on beat perception and production abilities. *PLoS One*. 2022; 17(3):e0264587. doi:10.1371/journal.pone.0264587
91. Pacchetti C, Mancini F, Aglieri R, Fundarò C, Martignoni E, Nappi G. Active music therapy in Parkinson's disease: an integrative method for motor and emotional rehabilitation. *Psychosom Med*. 2000;62(3):386-393. doi:10.1097/00006842-200005000-00012
92. Kitago T, Krakauer JW. Motor learning principles for neurorehabilitation. *Handb Clin Neurol*. 2013;110:93-103. doi:10.1016/B978-0-444-52901-5.00008-3
93. Hillecke T, Nickel A, Bolay HV. Scientific perspectives on music therapy. *Ann N Y Acad Sci*. 2005;1060:271-282. doi:10.1196/annals.1360.020
94. Koelsch S. A neuroscientific perspective on music therapy. *Ann N Y Acad Sci*. 2009;1169:374-384. doi:10.1111/j.1749-6632.2009.04592.x
95. Thaut MH, McIntosh GC, Rice RR, Miller RA, Rathbun J, Brault JM. Rhythmic auditory stimulation in gait training for Parkinson's disease patients. *Mov Disord*. 1996;11(2):193-200. doi:10.1002/mds.870110213
96. Forte R, Tocci N, De Vito G. The Impact of Exercise Intervention with Rhythmic Auditory Stimulation to Improve Gait and Mobility in Parkinson Disease: An Umbrella Review. *Brain Sci*. 2021;11(6):685. doi: 10.3390/brainsci11060685
97. Naro A, Pignolo L, Bruschetta D, Calabrò RS. Data on a novel approach examining the role of the cerebellum in gait performance improvement in patients with Parkinson disease receiving neurologic music therapy. *Data Brief*. 2023;47:109013. Published 2023 Feb 27. doi:10.1016/j.dib.2023.109013
98. Wu Z, Kong L, Zhang Q. Research Progress of Music Therapy on Gait Intervention in Patients with Parkinson's Disease. *Int J Environ Res Public Health*. 2022;19(15):9568. Published 2022 Aug 4. doi:10.3390/ijerph19159568
99. Lee H, Ko B. Effects of Music-Based Interventions on Motor and Non-Motor Symptoms in Patients with Parkinson's Disease: A Systematic Review and Meta-Analysis. *Int J Environ Res Public Health*. 2023; 20(2):1046. doi:10.3390/ijerph20021046
100. Bukowska AA, Krężałek P, Mirek E, Bujas P, Marchewka A. Neurologic Music Therapy Training for Mobility and Stability Rehabilitation with Parkinson's Disease - A Pilot Study. *Front Hum Neurosci*. 2016; 9:710. doi:10.3389/fnhum.2015.00710
101. Shulman LM. Is there a connection between estrogen and Parkinson's disease?. *Parkinsonism Relat Disord*. 2002;8(5):289-295. doi:10.1016/s1353-8020(02)00014-7
102. Smith KM, Dahodwala N. Sex differences in Parkinson's disease and other movement disorders. *Exp Neurol*. 2014 Sep; 259: 44-56. doi: 10.1016/j.expneurol.2014.03.010
103. Jacobs E, D'Esposito M. Estrogen shapes dopamine-dependent cognitive processes: implications for women's health. *J Neurosci*. 2011;31(14):5286-5293. doi:10.1523/JNEUROSCI.6394-10.2011
104. Benedetti MD, Maraganore DM, Bower JH, et al. Hysterectomy, menopause, and estrogen use preceding Parkinson's disease: an exploratory case-control study. *Mov Disord*. 2001;16(5):830-837. doi:10.1002/mds.1170
105. Currie LJ, Harrison MB, Trugman JM, Bennett JP, Wooten GF. Postmenopausal estrogen use affects risk for Parkinson disease. *Arch Neurol*. 2004;61(6):886-888. doi:10.1001/archneur.61.6.886
106. Simon KC, Chen H, Gao X, Schwarzschild MA, Ascherio A. Reproductive factors, exogenous estrogen use, and risk of Parkinson's disease. Mov Disord. 2009 July; 24:1359-1365. doi: 10.1002/mds.22619.
107. Rugbjerg K, Christensen J, Tjønneland A, Olsen JH. Exposure to estrogen and women's risk for Parkinson's disease: a prospective cohort study in Denmark. *Parkinsonism Relat Disord*. 2013;19(4):457-460. doi:10.1016/j.parkreldis.2013.01.008
108. Blanchet PJ, Fang J, Hyland K, Arnold LA, Mouradian MM, Chase TN. Short-term effects of high-dose 17beta-estradiol in postmenopausal PD patients: a crossover study. *Neurology*. 1999;53(1):91-95. doi: 10.1212/wnl.53.1.91
109. Strijks E, Kremer JA, Horstink MW. Effects of female sex steroids on Parkinson's disease in postmenopausal women. *Clin Neuropharmacol*. 1999;22(2):93-97. doi:10.1097/00002826-199903000-00005
110. Tsang KL, Ho SL, Lo SK. Estrogen improves motor disability in parkinsonian postmenopausal women with motor fluctuations. *Neurology*. 2000;54(12):2292-98. doi:10.1212/wnl.54.12.2292
111. Parkinson Study Group POETRY Investigators. A randomized pilot trial of estrogen replacement therapy in post-menopausal women with Parkinson's disease. *Parkinsonism Relat Disord*. 2011;17(10):757-760. doi:10.1016/j.parkreldis.2011.07.007

112. Okun MS, Fernandez HH, Rodriguez RL, et al. Testosterone therapy in men with Parkinson disease: results of the TEST-PD Study. *Arch Neurol*. 2006;63(5):729-735. doi:10.1001/archneur.63.5.729
113. Rafi MA. Gene and stem cell therapy: Alone or in Combination? *Bioimpacts*. 2011;1(4):213-218. doi: 10.5681/bi.2011.030
114. Stayte S, Vissel B. Advances in non-dopaminergic treatments for Parkinson's disease. *Front Neurosci*. 2014;8:113. Published 2014 May 22. doi:10.3389/fnins.2014.00113
115. Allen PJ, Feigin A. Gene-based therapies in Parkinson's disease. *Neurotherapeutics*. 2014;11(1):60-67. doi: 10.1007/s13311-013-0233-2
116. Lewis TB, Glasgow JN, Harms AS, Standaert DG, Curiel DT. Fiber-modified adenovirus for central nervous system Parkinson's disease gene therapy. *Viruses*. 2014;6(8):3293-3310. Published 2014 Aug 21. doi:10.3390/v6083293
117. Hegarty SV, O'Keeffe GW, Sullivan AM. Neurotrophic factors: from neurodevelopmental regulators to novel therapies for Parkinson's disease. *Neural Regen Res*. 2014;9(19):1708-1711. doi:10.4103/1673-5374.143410
118. Eggert K, Schlegel J, Oertel W, Würz C, Krieg JC, Vedder H. Glial cell line-derived neurotrophic factor protects dopaminergic neurons from 6-hydroxydopamine toxicity in vitro. *Neurosci Lett*. 1999;269(3):178-182. doi:10.1016/s0304-3940(99)00443-7
119. Eslamboli A, Cummings RM, Ridley RM, et al. Recombinant adeno-associated viral vector (rAAV) delivery of GDNF provides protection against 6-OHDA lesion in the common marmoset monkey (Callithrix jacchus). *Exp Neurol*. 2003;184(1):536-548. doi:10.1016/j.expneurol.2003.08.007
120. Eslamboli A, Georgievska B, Ridley RM, et al. Continuous low-level glial cell line-derived neurotrophic factor delivery using recombinant adeno-associated viral vectors provides neuroprotection and induces behavioral recovery in a primate model of Parkinson's disease. *J Neurosci*. 2005;25(4):769-777. doi:10.1523/JNEUROSCI.4421-04.2005
121. Kirik D, Cederfjäll E, Halliday G, Petersén Å. Gene therapy for Parkinson's disease: Disease modification by GDNF family of ligands. *Neurobiol Dis*. 2017;97(Pt B):179-188. doi:10.1016/j.nbd.2016.09.008
122. Eberling JL, Kells AP, Pivirotto P, et al. Functional effects of AAV2-GDNF on the dopaminergic nigrostriatal pathway in parkinsonian rhesus monkeys. *Hum Gene Ther*. 2009;20(5):511-518. doi: 10.1089/hum.2008.201
123. Johnston LC, Eberling J, Pivirotto P, et al. Clinically relevant effects of convection-enhanced delivery of AAV2-GDNF on the dopaminergic nigrostriatal pathway in aged rhesus monkeys. *Hum Gene Ther*. 2009;20(5):497-510. doi:10.1089/hum.2008.137
124. Biju KC, Santacruz RA, Chen C, et al. Bone marrow-derived microglia-based neurturin delivery protects against dopaminergic neurodegeneration in a mouse model of Parkinson's disease. *Neurosci Lett*. 2013; 535:24-29. doi:10.1016/j.neulet.2012.12.034
125. Marks WJ Jr, Ostrem JL, Verhagen L, et al. Safety and tolerability of intraputaminal delivery of CERE-120 (adeno-associated virus serotype 2-neurturin) to patients with idiopathic Parkinson's disease: an open-label, phase I trial. *Lancet Neurol*. 2008;7(5):400-408. doi:10.1016/S1474-4422(08)70065-6
126. Marks WJ Jr, Bartus RT, Siffert J, et al. Gene delivery of AAV2-neurturin for Parkinson's disease: a double-blind, randomised, controlled trial. *Lancet Neurol*. 2010;9(12):1164-1172. doi:10.1016/S1474-4422(10)70254-4
127. Ahmed MR, Bychkov E, Gurevich VV, Benovic JL, Gurevich EV. Altered expression and subcellular distribution of GRK subtypes in the dopamine-depleted rat basal ganglia is not normalized by l-DOPA treatment. *J Neurochem*. 2008;104(6):1622-1636. doi:10.1111/j.1471-4159.2007.05104.x
128. Ahmed MR, Berthet A, Bychkov E, et al. Lentiviral overexpression of GRK6 alleviates L-dopa-induced dyskinesia in experimental Parkinson's disease. *Sci Transl Med*. 2010;2(28):28ra28. doi:10.1126/scitranslmed.3000664
129. Ahmed MR, Bychkov E, Kook S, Zurkovsky L, Dalby KN, Gurevich EV. Overexpression of GRK6 rescues L-DOPA-induced signaling abnormalities in the dopamine-depleted striatum of hemiparkinsonian rats. *Exp Neurol*. 2015;266:42-54. doi:10.1016/j.expneurol.2015.02.008
130. Pardal R, López-Barneo J. Neural stem cells and transplantation studies in Parkinson's disease. *Adv Exp Med Biol*. 2012;741:206-216. doi:10.1007/978-1-4614-2098-9_14
131. Gandhi V, Burle S, Kosalge S. Stem cell therapy for Parkinson’s disease: A Review. *PharmaTutor*. 2018; 6(6):1-8. doi:10.29161/PT.v6.i6.2018.1
132. Wang S, Okun MS, Suslov O, et al. Neurogenic potential of progenitor cells isolated from postmortem human Parkinsonian brains. *Brain Res*. 2012;1464:61-72. doi:10.1016/j.brainres.2012.04.039
133. Choi DH, Kim JH, Kim SM, Kang K, Han DW, Lee J. Therapeutic Potential of Induced Neural Stem Cells for Parkinson's Disease. *Int J Mol Sci*. 2017;18(1):224. Published 2017 Jan 22. doi:10.3390/ijms18010224
134. Lindvall O, Kokaia Z. Stem cells for the treatment of neurological disorders. *Nature*. 2006;441(7097):1094-1096. doi:10.1038/nature04960
135. Yang H, Wang J, Wang F, et al. Dopaminergic Neuronal Differentiation from the Forebrain-Derived

Human Neural Stem Cells Induced in Cultures by Using a Combination of BMP-7 and Pramipexole with Growth Factors. *Front Neural Circuits*. 2016;10:29. Published 2016 Apr 20. doi:10.3389/fncir.2016.00029

136. Hwang S, Gill S, Pathak S, Subramanian S. A Comparison of stem cell therapies for parkinson disease. *Georgetown Med Rev*. 2018 March 30;2(1). doi:10.52504/001c.3420
137. Lige L, Zengmin T. Transplantation of Neural Precursor Cells in the Treatment of Parkinson Disease: An Efficacy and Safety Analysis. *Turk Neurosurg*. 2016;26(3):378-383. doi:10.5137/1019-5149.JTN.10747-14.4
138. Li W, Chen S, Li JY. Human induced pluripotent stem cells in Parkinson's disease: A novel cell source of cell therapy and disease modeling. *Prog Neurobiol*. 2015; 134:161-177. doi:10.1016/j.pneurobio.2015.09.009
139. Pei Y, Peng J, Behl M, et al. Comparative neurotoxicity screening in human iPSC-derived neural stem cells, neurons and astrocytes. *Brain Res*. 2016;1638(Pt A):57-73. doi:10.1016/j.brainres.2015.07.048
140. Han F, Wang W, Chen B, et al. Human induced pluripotent stem cell-derived neurons improve motor asymmetry in a 6-hydroxydopamine-induced rat model of Parkinson's disease. *Cytotherapy*. 2015;17(5):665-679. doi:10.1016/j.jcyt.2015.02.001
141. Via AG, Frizziero A, Oliva F. Biological properties of mesenchymal Stem Cells from different sources. *Muscles Ligaments Tendons J*. 2012;2(3):154-162. Published 2012 Oct 16.
142. Tomita K, Madura T, Sakai Y, Yano K, Terenghi G, Hosokawa K. Glial differentiation of human adipose-derived stem cells: implications for cell-based transplantation therapy. *Neuroscience*. 2013;236:55-65. doi:10.1016/j.neuroscience.2012.12.066
143. Zuk PA, Zhu M, Ashjian P, et al. Human adipose tissue is a source of multipotent stem cells. *Mol Biol Cell*. 2002;13(12):4279-4295. doi:10.1091/mbc.e02-02-0105
144. Choi HS, Kim HJ, Oh JH, et al. Therapeutic potentials of human adipose-derived stem cells on the mouse model of Parkinson's disease. *Neurobiol Aging*. 2015;36(10):2885-2892. doi:10.1016/j.neurobiolaging.2015.06.022
145. Zhou Y, Sun M, Li H, et al. Recovery of behavioral symptoms in hemi-parkinsonian rhesus monkeys through combined gene and stem cell therapy. *Cytotherapy*. 2013;15(4):467-480. doi:10.1016/j.jcyt.2013.01.007
146. Hamblin MR. Shining light on the head: Photobiomodulation for brain disorders. *BBA Clin*. 2016;6:113-124. Published 2016 Oct 1. doi:10.1016/j.bbacli.2016.09.002
147. Babtan AM, Ilea A, Feurdean CN, et al. Biostimulation with low-level laser therapy and its effects on soft and hard tissue regeneration. Literature review. *J Mind Med Sci*. 2022;9(1):28-37. doi:10.22543/7674.91.P2837
148. Mitrofanis J. Why and how does light therapy offer neuroprotection in Parkinson's disease?. *Neural Regen Res*. 2017;12(4):574-575. doi:10.4103/1673-5374.205092
149. Liang HL, Whelan HT, Eells JT, Wong-Riley MT. Near-infrared light via light-emitting diode treatment is therapeutic against rotenone- and 1-methyl-4-phenylpyridinium ion-induced neurotoxicity. *Neuroscience*. 2008;153(4):963-974.
150. Ying R, Liang HL, Whelan HT, Eells JT, Wong-Riley MT. Pretreatment with near-infrared light via light-emitting diode provides added benefit against rotenone- and MPP+-induced neurotoxicity. *Brain Res*. 2008; 1243:167-173. doi:10.1016/j.brainres.2008.09.057
151. Ahrabi B, Tabatabaei Mirakabad FS, Niknazar S, et al. Photobiomodulation Therapy and Cell Therapy Improved Parkinson's Diseases by Neuro-regeneration and Tremor Inhibition. *J Lasers Med Sci*. 2022;13:e28. Published 2022 Jun 23. doi:10.34172/jlms.2022.28
152. Salehpour F, Gholipour-Khalili S, Farajdokht F, Kamari F, Walski T, Hamblin MR, DiDuro JO, Cassano P. Therapeutic potential of intranasal photobiomodulation therapy for neurological and neuropsychiatric disorders: a narrative review. *Rev Neurosci*. 2020 Apr 28;31(3):269-286. doi: 10.1515/revneuro-2019-0063
153. Liebert A, Bicknell B, Johnstone DM, Gordon LC, Kiat H, Hamblin MR. "Photobiomics": Can Light, Including Photobiomodulation, Alter the Microbiome?. *Photobiomodul Photomed Laser Surg*. 2019;37(11): 681-693. doi:10.1089/photob.2019.4628
154. Hamilton C, Hamilton D, Nicklason F, El Massri N, Mitrofanis J. Exploring the use of transcranial photobiomodulation in Parkinson's disease patients. *Neural Regen Res*. 2018 Oct;13(10):1738-1740. doi: 10.4103/1673-5374.238613
155. Reinhart F, Massri NE, Chabrol C, et al. Intracranial application of near-infrared light in a hemi-parkinsonian rat model: the impact on behavior and cell survival. *J Neurosurg*. 2016;124(6):1829-1841. doi: 10.3171/2015.5.JNS15735
156. Ma J, Shaw VE, Mitrofanis J. Does melatonin help save dopaminergic cells in MPTP-treated mice?. *Parkinsonism Relat Disord*. 2009;15(4):307-314. doi:10.1016/j.parkreldis.2008.07.008
157. Wallace BA, Ashkan K, Heise CE, et al. Survival of midbrain dopaminergic cells after lesion or deep brain stimulation of the subthalamic nucleus in MPTP-treated monkeys. *Brain*. 2007;130(Pt 8):2129-2145. doi:10.1093/brain/awm137
158. Quirk BJ, Whelan HT. Near-infrared irradiation photobiomodulation: the need for basic science.

Photomed Laser Surg. 2011;29(3):143-144. doi: 10.1089/pho.2011.3014

159. Chung H, Dai T, Sharma SK, Huang YY, Carroll JD, Hamblin MR. The nuts and bolts of low-level laser (light) therapy. *Ann Biomed Eng*. 2012;40(2):516-533. doi:10.1007/s10439-011-0454-7
160. Moro C, Massri NE, Torres N, et al. Photobiomodulation inside the brain: a novel method of applying near-infrared light intracranially and its impact on dopaminergic cell survival in MPTP-treated mice. *J Neurosurg*. 2014;120(3):670-683. doi:10.3171/2013.9.JNS13423
161. Benabid AL, Chabardes S, Mitrofanis J, Pollak P. Deep brain stimulation of the subthalamic nucleus for the treatment of Parkinson's disease. *Lancet Neurol*. 2009;8(1):67-81. doi:10.1016/S1474-4422(08)70291-6
162. Ditthaphongphakdee S, Gaogasigam C. The effects of light touch cue on gait initiation in patients with Parkinson's disease. *J Bodyw Mov Ther*. 2021;26:187-192. doi:10.1016/j.jbmt.2020.08.009
163. Fraint A, Ouyang B, Metman LV, et al. Patient Knowledge and Attitudes towards Genetic Testing in Parkinson's Disease Subjects with Deep Brain Stimulation. *Parkinsons Dis*. 2019;2019:3494609. Published 2019 Apr 21. doi:10.1155/2019/3494609
164. Deuschl G, Schüpbach M, Knudsen K, et al. Stimulation of the subthalamic nucleus at an earlier disease stage of Parkinson's disease: concept and standards of the EARLYSTIM-study. *Parkinsonism Relat Disord*. 2013;19(1):56-61. doi:10.1016/j.parkreldis.2012.07.004
165. Perestelo-Pérez L, Rivero-Santana A, Pérez-Ramos J, Serrano-Pérez P, Panetta J, Hilarion P. Deep brain stimulation in Parkinson's disease: meta-analysis of randomized controlled trials. *J Neurol*. 2014;261(11): 2051-2060. doi:10.1007/s00415-014-7254-6
166. Daniels C, Krack P, Volkmann J, et al. Is improvement in the quality of life after subthalamic nucleus stimulation in Parkinson's disease predictable?. *Mov Disord*. 2011;26(14):2516-2521. doi:10.1002/mds.23907
167. Soulas T, Sultan S, Gurruchaga JM, Palfi S, Fénelon G. Depression and coping as predictors of change after deep brain stimulation in Parkinson's disease. *World Neurosurg*. 2011;75(3-4):525-532. doi: 10.1016/j.wneu.2010.06.015
168. Drapier S, Raoul S, Drapier D, et al. Only physical aspects of quality of life are significantly improved by bilateral subthalamic stimulation in Parkinson's disease. *J Neurol*. 2005;252(5):583-588. doi: 10.1007/s00415-005-0704-4
169. Schuepbach WM, Rau J, Knudsen K, et al. Neurostimulation for Parkinson's disease with early motor complications. *N Engl J Med*. 2013;368(7):610-622. doi:10.1056/NEJMoa1205158
170. National Institute for Health and Care Excellence. Parkinson's disease in adults. (NG71); London: NICE. 2017. Available at: https://www.nice.org.uk/guidance/ng71/chapter/Update-information
171. Herrington TM, Cheng JJ, Eskandar EN. Mechanisms of deep brain stimulation. *J Neurophysiol*. 2016; 115(1):19-38. doi:10.1152/jn.00281.2015
172. Mansouri A, Taslimi S, Badhiwala JH, et al. Deep brain stimulation for Parkinson's disease: meta-analysis of results of randomized trials at varying lengths of follow-up. *J Neurosurg*. 2018;128(4):1199-1213. doi:10.3171/2016.11.JNS16715
173. Follett KA, Weaver FM, Stern M, et al. Pallidal versus subthalamic deep-brain stimulation for Parkinson's disease. *N Engl J Med*. 2010;362(22):2077-2091. doi:10.1056/NEJMoa0907083
174. Weaver FM, Follett KA, Stern M, et al. Randomized trial of deep brain stimulation for Parkinson disease: thirty-six-month outcomes. *Neurology*. 2012;79(1):55-65. doi:10.1212/WNL.0b013e31825dcdc1
175. Southwell DG, Rutkowski MJ, San Luciano M, et al. Before and after the veterans affairs cooperative program 468 study: Deep brain stimulator target selection for treatment of Parkinson's disease. *Parkinsonism Relat Disord*. 2018;48:40-44. doi: 10.1016/j.parkreldis.2017.12.013
176. Ramirez-Zamora A, Ostrem JL. Globus Pallidus Interna or Subthalamic Nucleus Deep Brain Stimulation for Parkinson Disease: A Review. *JAMA Neurol*. 2018; 75(3):367-372. doi:10.1001/jamaneurol.2017.4321
177. Tröster AI, Jankovic J, Tagliati M, Peichel D, Okun MS. Neuropsychological outcomes from constant current deep brain stimulation for Parkinson's disease. *Mov Disord*. 2017;32(3):433-440. doi: 10.1002/mds.26827
178. Odekerken VJ, Boel JA, Schmand BA, et al. GPi vs STN deep brain stimulation for Parkinson disease: Three-year follow-up. *Neurology*. 2016;86(8):755-761. doi:10.1212/WNL.0000000000002401
179. Liu Y, Li W, Tan C, et al. Meta-analysis comparing deep brain stimulation of the globus pallidus and subthalamic nucleus to treat advanced Parkinson disease. *J Neurosurg*. 2014;121(3):709-718. doi:10.3171/2014.4.JNS131711
180. Evidente VG, Premkumar AP, Adler CH, Caviness JN, Driver-Dunckley E, Lyons MK. Medication dose reductions after pallidal versus subthalamic stimulation in patients with Parkinson's disease. *Acta Neurol Scand*. 2011;124(3):211-214. doi:10.1111/j.1600-0404.2010.01455.x
181. Downar J, Blumberger DM, Daskalakis ZJ. Repetitive transcranial magnetic stimulation: an emerging treatment for medication-resistant depression. *CMAJ*. 2016;188(16):1175-1177. doi:10.1503/cmaj.151316

182. Reithler J, Peters JC, Sack AT. Multimodal transcranial magnetic stimulation: using concurrent neuroimaging to reveal the neural network dynamics of noninvasive brain stimulation. *Prog Neurobiol*. 2011;94(2):149-165. doi:10.1016/j.pneurobio.2011.04.004
183. Peinemann A, Reimer B, Löer C, et al. Long-lasting increase in corticospinal excitability after 1800 pulses of subthreshold 5 Hz repetitive TMS to the primary motor cortex. *Clin Neurophysiol*. 2004;115(7):1519-1526. doi:10.1016/j.clinph.2004.02.005
184. Huang YZ, Edwards MJ, Rounis E, Bhatia KP, Rothwell JC. Theta burst stimulation of the human motor cortex. *Neuron*. 2005;45(2):201-206. doi: 10.1016/j.neuron.2004.12.033
185. Chou YH, Hickey PT, Sundman M, Song AW, Chen NK. Effects of repetitive transcranial magnetic stimulation on motor symptoms in Parkinson disease: a systematic review and meta-analysis. *JAMA Neurol*. 2015;72(4):432-440. doi:10.1001/jamaneurol.2014.4380
186. Zhu H, Lu Z, Jin Y, Duan X, Teng J, Duan D. Low-frequency repetitive transcranial magnetic stimulation on Parkinson motor function: a meta-analysis of randomised controlled trials. *Acta Neuropsychiatr*. 2015;27(2):82-89. doi:10.1017/neu.2014.43
187. Matsumoto H, Ugawa Y. Repetitive transcranial magnetic stimulation for Parkinson's disease: A Review. *Brain Nerve*. 2017 Mar; 69(3): 219-225. doi: 10.11477/mf.1416200730.
188. Khedr EM, Al-Fawal B, Abdel Wraith A, et al. The Effect of 20 Hz versus 1 Hz Repetitive Transcranial Magnetic Stimulation on Motor Dysfunction in Parkinson's Disease: Which Is More Beneficial?. *J Parkinsons Dis*. 2019;9(2):379-387. doi:10.3233/JPD-181540
189. Hai-Jiao W, Ge T, Li-Na Z, et al. The efficacy of repetitive transcranial magnetic stimulation for Parkinson disease patients with depression. *Int J Neurosci*. 2020;130(1):19-27. doi:10.1080/00207454.2018.1495632
190. Flamez A, Cordenier A, De Raedt S, et al. Bilateral low frequency rTMS of the primary motor cortex may not be a suitable treatment for levodopa-induced dyskinesias in late stage Parkinson's disease. *Parkinsonism Relat Disord*. 2016;22:54-61. doi: 10.1016/j.parkreldis.2015.11.009
191. Yokoe M, Mano T, Maruo T, et al. The optimal stimulation site for high-frequency repetitive transcranial magnetic stimulation in Parkinson's disease: A double-blind crossover pilot study. *J Clin Neurosci*. 2018;47:72-78. doi:10.1016/j.jocn.2017.09.023
192. Eggers C, Günther M, Rothwell J, Timmermann L, Ruge D. Theta burst stimulation over the supplementary motor area in Parkinson's disease. *J Neurol*. 2015;262(2):357-364. doi:10.1007/s00415-014-7572-8
193. Brys M, Fox MD, Agarwal S, et al. Multifocal repetitive TMS for motor and mood symptoms of Parkinson disease: A randomized trial. *Neurology*. 2016;87(18):1907-1915. doi:10.1212/WNL.0000000000003279
194. Sedlácková S, Rektorová I, Srovnalová H, Rektor I. Effect of high frequency repetitive transcranial magnetic stimulation on reaction time, clinical features and cognitive functions in patients with Parkinson's disease. *J Neural Transm (Vienna).* 2009;116(9):1093-1101. doi:10.1007/s00702-009-0259-0
195. Nardone R, De Blasi P, Höller Y, et al. Repetitive transcranial magnetic stimulation transiently reduces punding in Parkinson's disease: a preliminary study. *J Neural Transm (Vienna).* 2014;121(3):267-274. doi: 10.1007/s00702-013-1100-3
196. Merlo EM, MacKenzie Myles LA, Pappalardo SM. The VESPA Project: Virtual Reality Interventions for Neurocognitive and Developmental Disorders. *J Mind Med Sci*. 2022;9(1):16-27. doi:10.22543/7674.91.P1627
197. Benninger DH, Iseki K, Kranick S, Luckenbaugh DA, Houdayer E, Hallett M. Controlled study of 50-Hz repetitive transcranial magnetic stimulation for the treatment of Parkinson disease. *Neurorehabil Neural Repair*. 2012;26(9):1096-1105. doi: 10.1177/1545968312445636
198. Kim MS, Chang WH, Cho JW, et al. Efficacy of cumulative high-frequency rTMS on freezing of gait in Parkinson's disease. *Restor Neurol Neurosci*. 2015;33(4):521-530. doi:10.3233/RNN-140489
199. Shirota Y, Ohtsu H, Hamada M, Enomoto H, Ugawa Y; Research Committee on rTMS Treatment of Parkinson's Disease. Supplementary motor area stimulation for Parkinson disease: a randomized controlled study. *Neurology*. 2013;80(15):1400-1405. doi:10.1212/WNL.0b013e31828c2f66