



ISSN: 2319-9490

## REVIEW ARTICLE

### CURRENT APPROACHES FOR THE TREATMENT OF PARKINSON'S DISEASE: A SYSTEMATIC REVIEW

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Received 26<sup>th</sup> October, 2018; Accepted 19<sup>th</sup> November, 2018; Published 25<sup>th</sup> December, 2018

#### ABSTRACT

**Background:** PD is progressive in nature, and so patients face increased difficulties with activities of daily living (ADL) and various aspects of mobility such as gait, transfers, balance, and posture. Ultimately, this leads to decreased independence, inactivity, and social isolation, resulting in reduced quality of life. Balance dysfunction and postural instability in Parkinson's disease are among the most relevant determinants of an impaired quality of life. Physiotherapy interventions are essential to reduce the level of disability by treating balance dysfunction and postural instability. **Methods:** A systematic literature search of the Cochrane Library, PubMed/Medline, PEDro, Rehadat, and Rehab Trials were performed. The selected RCTs, which investigated the effects of conventional physiotherapy treatments in the management of postural instability and balance dysfunction in Persons with Parkinson's disease. Important characteristics and outcomes were extracted, summarized and analyzed. **Results:** The effects of postural adjustment, fall prevention strategies, and balance training exercises on near falls and quality of life. The results showed that Physiotherapy interventions have a positive effects on the reduction in fall event and balance improvement. A range of approaches to movement rehabilitation are used, which aim to enhance quality of life by maximizing physical ability and minimizing problems related to Parkinson's over the whole course of the disease. **Conclusion:** The results of the review articles concluded that physiotherapy interventions like balance training combined with muscle strengthening, the range of movement, walking training exercise is effective in improving balance in patients with PD and more effective than balance exercises alone.

**Key words:** Parkinson's disease, balance dysfunction, postural instability, Physiotherapy.

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**Citation: Dr. Parul Sharma, P.T. 2018.** "Current approaches for the treatment of parkinson's disease: a systematic review" *International Journal of Current Research in Life Sciences*, 7, (12), 2883-2886.

#### INTRODUCTION

Parkinson's disease (PD) was first described by Dr. James Parkinson in 1817 as a "shaking palsy." It is a chronic, progressive neurodegenerative disease characterized by both motor and non-motor features. The term parkinsonism is a symptom complex used to describe the motor features of PD, which include resting tremor, bradykinesia, and muscular rigidity. PD is the second most common neurodegenerative disorders. The Parkinson's Disease Foundation reports that approximately 1 million Americans currently have the disease. The incidence of PD in the U.S. is approximately 20 cases per 100,000 people per year (60,000 per year), with the mean age of onset close to 60 years. The prevalence of PD is reported to be approximately 1% in people 60 years of age and older and increases to 1% to 3% in the 80-plus age group. Research suggests that the pathophysiological changes associated with PD may start before the onset of motor features and may include a number of non-motor presentations, such as sleep disorders, depression, and cognitive changes. Gender differences pertaining to the incidence of PD are reflected in a

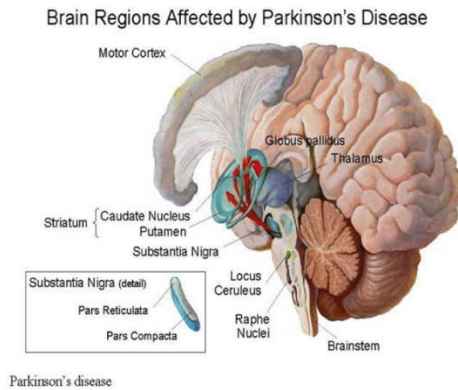
3:2 ratio of males to females, with a delayed onset in females attributed to the neuro-protective effects of estrogen on the dopaminergic system. Numerous risk factors and genetic mutations are associated with PD. Risk factors for the disease include oxidative stress, the formation of free radicals, and a number of environmental toxins e.g. Elevated cholesterol, Environmental toxins, Carbon disulfide, Cyanide, Herbicides, Methanol and organic solvents Pesticides, Head trauma, High caloric intake, Increased body mass index, Inflammation associated with activation of microglia etc. The variable prevalence of PD throughout the world suggests that environmental and genetic factors along with ethnic differences may all play a role in disease pathogenesis. Biomedical research in individuals with PD continues and may help to identify additional risk factors and to guide future prevention and treatment decisions.

#### Pathophysiology

PD is a disorder of the extrapyramidal system, which includes motor structures of the basal ganglia, and is characterized by the loss of dopaminergic function and consequent diminished motor function, leading to clinical features of the disease. The histo-pathological features of PD include the loss of pigmented dopaminergic neurons and the presence of Lewy

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bodies (LBs), intracellular cytoplasmic aggregates composed of proteins, lipids, and other materials. LBs have also been identified as major hallmarks associated with chronic neurodegenerative diseases, including PD. In patients with PD, LBs are found in dopaminergic neurons in the substantia-nigra as round bodies with radiating fibrils.



Although amyloid beta 1-42 is associated with Alzheimer's disease (AD) and its pathology, recent data suggest that cerebral spinal fluid containing this biomarker may predict cognitive decline in PD as well. These data are consistent with previous research, which reported that the pathology of AD contributes to cognitive impairment in PD and may have relevance in predicting the cognitive decline associated with PD. The differential diagnosis of PD should include a comprehensive history and physical examination. Difficult or questionable cases should be referred to a movement-disorder specialist for further evaluation. There are no definitive tests to confirm the diagnosis of PD; therefore, a clinical diagnosis requires the clinician to review the patient's history, to assess symptoms, and to rule out alternative diagnoses. The cardinal motor features of PD—described as the “classical triad”—include a 4-Hz to 6-Hz resting tremor, “cogwheel” rigidity, and brady-kinesia. These cardinal features are often reported as the first clinical findings of the disease. A fourth feature, postural instability, occurs in approximately 50% of PD patients within five years of diagnosis.

#### Typical appearance of Parkinson's disease



- Bradykinesia - Occurs in 80% to 90% of patients, Slowness of movement, Decreased amplitude of movement. Episodes of “freezing” are an extreme manifestation of PD and usually occur in advanced disease.
- Rigidity - Occurs in 80% to 90% of patients, Resistance to passive movement in both flexor and extensor muscles with limb relaxed, Often accompanied by “cogwheel” phenomenon. The rigidity of PD can affect other body parts besides the limbs, such as the face, which can display a “masked” expression (hypomimia).
- Tremor at rest - Common initial symptom (70% to 90% of patients), Often resolves with action or during sleep, Primarily distal, involving hands, May also involve jaw, tongue, lips, chin, or legs
- Other - Dysarthria, dystonia & Postural instability - Predisposes patients to falls and injuries, Occurs in later stages of Parkinson's disease, Results from loss of postural reflexes.

Additional diagnostic aids may include neuropsychiatric testing, sleep studies, and vision exams secondary to visual changes reported in some PD patients, such as abnormal color vision due to changes in intra-retinal dopaminergic transmission. Drug-induced parkinsonism (DIP) should be considered in the differential diagnosis of PD because it is one of the few reversible causes of the disorder. Identifying DIP is important in order to avoid treating patients inappropriately and therefore necessitates a complete medication evaluation in all patients suspected of having PD. High-risk populations for DIP include elderly women, patients with multiple comorbidities, and patients taking multiple medications at high doses for extended periods. The drugs most commonly associated with DIP include those with dopamine receptor-blocking properties, such as the antipsychotic agents haloperidol, thiothixene, and risperidone. If PD patients require antipsychotic agents, those with a lower risk for DIP, such as quetiapine and clozapine, are recommended. A challenge in diagnosing PD is that the disorder's clinical motor features may not present until approximately 50% to 80% of dopaminergic neurons are lost.

Unfortunately, at this point significant disease progression may already exist.

Adding to this problem is the need to identify subtle motor features that can easily go unrecognized, such as the absence of arm swing or jerking motions.

Further complicating an early diagnosis is the presence of non-motor comorbidities, including depression, anxiety, fatigue, constipation, anosmia, and sleep disorders, which the clinician may not recognize as being associated with PD. Early recognition of these features and their possible association with PD may facilitate an earlier diagnosis. Out Of these three core features, tremor is most often recognized by patients and caregivers.

#### Clinical Tool

The most commonly used scale for assessing the clinical status of patients with PD, including both motor and non-motor symptoms, is the Unified Parkinson's Disease Rating Scale (UPDRS). Increases of 2.5 and 4.3 points in the UPDRS motor

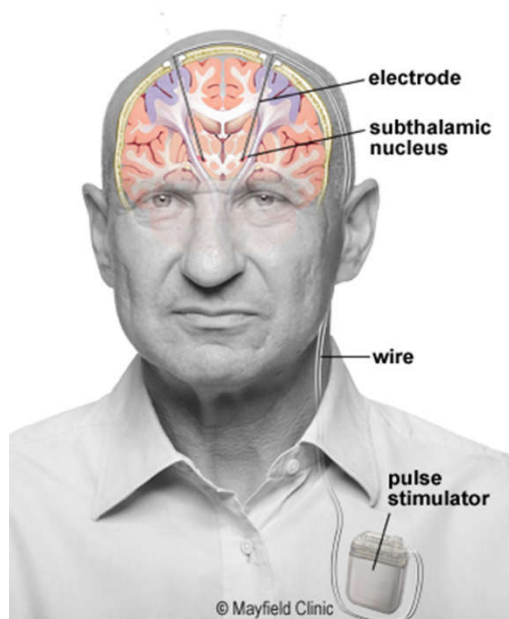
and total scores, respectively, have been recognized as clinically relevant.

### Current Regimen for Treatment

Current effective therapy regimen: Deep brain stimulation and infusion techniques

### Deep brain stimulation

Both sided deep brain stimulation (DBS) of the sub-thalamic nuclei reduces the dosages of dopaminergic drugs, improves motor symptoms and motor complications, but not speech, gait or postural dysfunction. This method may cause social adjustment problems, depression and cognitive disturbances. Depression might occur in the postoperative phase but there is no clear evidence for DBS induced depression in the long term.



#### Deep brain stimulation (DBS)

The DBS system is used to help control tremors and chronic movement disorders, like Parkinson's disease. Tiny electrodes are connected via a subcutaneous wire to a neurostimulator implanted under the skin near the clavicle.

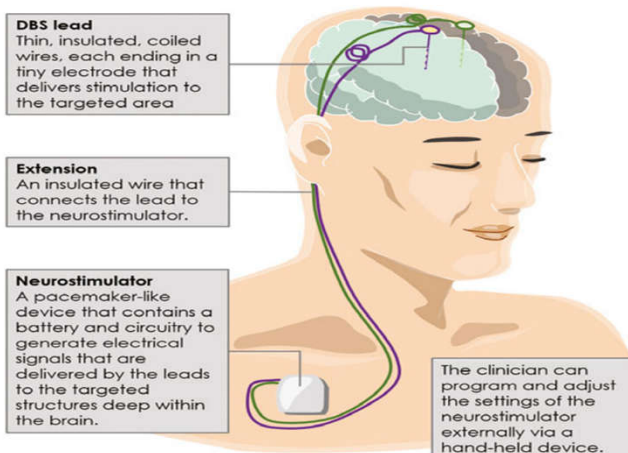


Figure 4 Components of the Deep Brain Stimulation system

DBS is a rather intensive treatment in which electrodes are implanted into a certain areas of the brain. DBS often targets brain areas critical for movement such as the subthalamus. The electrodes placed in the brain can then send electrical impulses to ameliorate motor dysfunction. The beneficial effects of DBS

on motor function have been well documented, but there is less attention on non-motor symptoms. Overall, DBS has shown promising effects on non-motor symptoms such as anxiety and depression. Additionally, there is also evidence that DBS can improve sleep quality, musculoskeletal pain, urinary symptoms, gastrointestinal symptoms (gastric emptying and constipation), weight loss and odor discrimination. The beneficial effects of deep brain stimulation on motor function have been well documented, but there is less attention on non-motor symptoms. A new brain area is being targeted with DBS, specifically for Parkinson disease dementia. A recently published study used DBS surgery on the nucleus basalis of Meynert. The nucleus basalis of Meynert is the most important source for releasing the neurotransmitter, acetylcholine, to other brain areas critical for cognitive functioning, such as the neocortex. The rationale of this study is based on the fact that in the parkinsonian brain there is a significant deficit in brain activity related to acetylcholine. In animal models, low-frequency stimulation of the nucleus basalis of Meynert has been shown to enhance cholinergic innervation of the cortex. Although the study using nucleus basalis of Meynert DBS surgery didn't show improvement in the primary cognitive outcomes, the procedure was well tolerated, opening up the possibility of DBS surgery for patients with PDD. Of interest, the authors observed a significant reduction in visual hallucination in 2 patients and decreased in the severity and frequency of dyskinesia in 3 patients, which require further exploration.

### Focused Ultrasound Subthalamotomy

Prior to the development of DBS, ablative neurosurgery was widely used to treat movement disorders. Ablative neurosurgery involves the removal of a specific brain area. DBS is preferred over ablative neurosurgery due to its reversibility and documented efficacy for PD treatment. It is our responsibility, as physicians, to obtain newest medical information and to select therapies that are most suitable for each patient. A new technique has been developed for ablating specific brain areas. Gamma-knife and MRI-guided focused ultrasound (MRgFUS), allows for deep brain ablating without opening the skull. The U.S. Food and Drug Administration have now approved MRgFUS for patients with essential tremor. A pilot study using focused ultrasound subthalamotomy in patients with PD showed that it was effective, well tolerated and the adverse events seemed to be mostly mild and transient. This new technique will possibly become another treatment option in the future for patients who don't want their brain to be opened. However, more studies with long term follow up are mandatory for confirming MRgURS's efficacy and adverse effect.

### Final Thoughts

PD is a heterogeneous disorder and every patient is unique. As more and more new drugs, devices and techniques are being developed, individualized treatment tailoring each patient's symptoms and needs has never been so important. It is our responsibility, as physicians, to obtain the latest medical information and to select therapies that are most suitable for each patient.

### Infusion techniques

The present infusion systems administer dopaminergic drugs continuously. Apomorphine is mostly administered in

combination with other oral anti-parkinsonian drugs. Rarely, axonal polyneuropathy occurs, which is often associated with vitamin B-12 deficiency.

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