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·Review·

Progression of motor symptoms in Parkinson's disease

Ruiping Xia[1], Zhi-Hong Mao[2]

[1]*Department of Physical Therapy, School of Pharmacy and Health Professions, Creighton University, Omaha, Nebraska, USA*

[2]*Department of Electrical and Computer Engineering and Department of Bioengineering, University of Pittsburgh, Pittsburgh, Pennsylvania, USA*

Abstract: Parkinson's disease (PD) is a chronic progressive neurodegenerative disease that is clinically manifested by a triad of cardinal motor symptoms – rigidity, bradykinesia and tremor – due to loss of dopaminergic neurons. The motor symptoms of PD become progressively worse as the disease advances. PD is also a heterogeneous disease since rigidity and bradykinesia are the major complaints in some patients whereas tremor is predominant in others. In recent years, many studies have investigated the progression of the hallmark symptoms over time, and the cardinal motor symptoms have different rates of progression, with the disease usually progressing faster in patients with rigidity and bradykinesia than in those with predominant tremor. The current treatment regime of dopamine-replacement therapy improves motor symptoms and alleviates disability. Increasing the dosage of dopaminergic medication is commonly used to combat the worsening symptoms. However, the drug-induced involuntary body movements and motor complications can significantly contribute to overall disability. Further, none of the currently-available therapies can slow or halt the disease progression. Significant research efforts have been directed towards developing neuroprotective or disease-modifying agents that are intended to slow the progression. In this article, the most recent clinical studies investigating disease progression and current progress on the development of disease-modifying drug trials are reviewed.

Keywords: Parkinson's disease; progression; motor symptoms; disease modification; treatment

1 Introduction

Parkinson's disease (PD) is a chronic neurodegenerative disease with a relentlessly progressive course[1,2]. It is also the most common form of movement disorder and the second most common neurodegenerative disorder, currently affecting an estimated five million[3] people worldwide[4]. The incidence and prevalence of PD are expected to increase exponentially as the population ages. Its pathological hallmark is the loss of pigmented dopaminergic neurons in the substantia nigra pars compacta, leading to various motor symptoms such as bradykinesia, rigidity, rest tremor, and postural instability at a later stage of the disease[5,6]. These symptoms are frequently referred to as cardinal motor symptoms, which become progressively worse as the disease advances. Increasing the dose of dopaminergic medication is a common approach against the worsening symptoms. However, the benefits of higher doses are offset by the side-effects, such as dyskinesia, motor fluctuations, confusion, and hallucination[7]. After 10–20

Corresponding author: Ruiping Xia
Tel: +1402-280-5946; Fax: +1402-280-5692
E-mail: ruipingxia@creighton.edu
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years of disease history, 40%–75% of patients with PD die, and about 50% of those who survive require nursing-home care[8,9].

The clinical diagnosis of PD is based on a combination of cardinal motor symptoms: bradykinesia, rigidity, and rest tremor. A positive response to dopamine-replacement therapy may further confirm the initial diagnosis, since a great majority of patients with PD exhibit a good initial response to levodopa[5]. In general, patients with PD do not necessarily experience all the cardinal motor features at diagnosis. Many clinical studies have indicated that the distinctions among the cardinal motor symptoms are significant although they share similarities and common origins[10]. The rate and the type of symptom progression are heterogeneous across patients and through the course of disease within the same patient. The heterogeneity among patients is reflected by two major sub-types: akinetic-rigid and tremor-dominant[10-13]. Further, different clinical phenotypes exhibit different prognoses with a faster progression in patients with bradykinesia and rigidity and a milder progression in those presenting with tremor-dominant disease.

During the past 10–20 years, there has been an increasing recognition of non-movement-related symptoms. Thus far, our understanding of PD has been evolving from the traditional pathologic concept of a disease entity of primarily motor features to a more dynamic approach involving multiple entities. There is generally a wide spectrum of non-motor symptoms involving multiple pathologies and entities, including but not limited to autonomic, gastrointestinal, neuropsychiatric, and sensory symptoms[14]. Accumulating evidence shows that non-motor symptoms can occur at any stages of the disease process, with some occurring prior to the onset of motor symptoms, e.g. altered olfactory function and erectile dysfunction[14]. Non-motor symptoms have gradually emerged and been accepted as an integral part of PD.

Despite the significant advances in medical research and the clinical management of PD during the past decades, slowing its progression remains major unmet need[1]. Dopamine-replacement therapy (levodopa and dopamine agonists) improves the motor symptoms and alleviates disability. In particular, levodopa remains the gold standard of drug therapy, but it is also associated with dyskinesia, i.e. drug-induced involuntary body movement and motor fluctuations[15-17]. These motor complications, which usually occur after a few years of levodopa treatment, can in turn have an adverse impact on patients' quality of life and contribute to the global disability. Further, symptomatic therapy with dopamine-replacement fails to slow down or stop the disease progression. Therefore, increasing efforts have recently been dedicated to developing therapeutic agents that potentially have neuroprotective or disease-modifying effects in PD patients. The present review provides an overview of clinical studies investigating the natural progression of motor symptoms through the course of PD. Furthermore, current progress on neuroprotective or disease-modifying drug trials is reviewed and discussed.

2 Progression of motor symptoms in PD

Several studies, including placebo-controlled clinical trials and the use of a longitudinal design[18-24], have been conducted to investigate the changes in motor symptoms of PD over a period of time. Motor symptoms are evaluated by the Motor Examination (Part III) of the Unified Parkinson's Disease Rating Scale (UPDRS)[25], with higher scores indicating a greater severity of disease. Data obtained during a 6- to 12-month placebo phase recommend changes in motor scores as the best indicator, as there is no treatment effect to confound interpretation of the results. The reported changes are consistent across several trials, with an increase of 8 to 10 points for the total UPDRS and an addition of 5 to 6 points for the motor scores alone[18-21]. Such a change is considered to be clinically significant due to its impact on functional disability in early PD[26]. Using cross-sectional analysis, a more recent study of 653 PD patients reported that the minimal clinically important differences were estimated to be 2.3 to 2.7 points on the UPDRS motor score and 4.1 to 4.5 points on the UPDRS total score[27]. These estimates are expected to assist in determining clinically meaningful changes in PD progression and the response to therapeutic interventions.

These studies examined the progression of several motor symptoms as an entirety. Using a longitudinal approach, Louis *et al*.[23] investigated disease progression by quantifying the rate of change of the cardinal motor symptoms (bradykinesia, rigidity, tremor, and postural instability) altogether as well as separately in 237 PD patients using the Motor Section of the UPDRS. Patients were evaluated at baseline and at yearly intervals for up to eight years. The results showed that the total motor scores increased at an annual rate of 1.5% and at more than double that rate (3.6%) in those who died during the follow-up period. In addition, the sub-scores for bradykinesia, rigidity and gait impairment progressed at similar annual rates of 2.0%–3.1%, whereas the tremor sub-score remained relatively constant over time. This finding had been previously suggested[24] and was subsequently confirmed by a clinical drug trial known as the Deprenyl and α-Tocopherol Antioxidative Treatment of Parkinsonism (DATATOP) study[28]. More recently, Schupbach *et al.*[29] examined the progression of motor symptoms in early, untreated PD patients for a period of 12 months, by using the Motor Section of the UPDRS as well as a modified segmental rating of motor signs including all major joints. Each patient received comprehensive evaluations of motor symptoms at baseline and follow-up at 6 and 12 months. They reported that rigidity progressed faster than akinesia/bradykinesia and tremor, based on the UPDRS-III and the modified segmental rating of motor signs.

Neuroimaging data and pathological reports have provided the underlying explanations for these clinical observations. It has been shown that tremor-dominant patients present a slower progression in which there is better preservation of the nigro-striatal pathway, whereas a faster progression occurs in the akinetic-rigid type that is accompanied by severe cell loss in the substantia nigra pars compacta[13,30]. As evaluated by fluoropropyl-carbomethoxy-iodophenyl-tropane (FP-CIT) single photon emission computed tomography (SPECT) (a sensitive tool for quantifying the striatal density of the dopamine transporter and used for clinical purposes), tremor-dominated patients showed consistently higher FP-CIT uptake in all the examined regions as compared to the akinetic-rigid group. In addition, several cross-sectional imaging studies showed a strong correlation of the dopamine transporter with global measures of motor symptoms and with specific cardinal motor features, most notably with bradykinesia and rigidity[31-34]. In contrast, most studies showed no correlation between dopamine transporter binding and rest tremor or action tremor[32-34]. More recently, a study in over 60 patients showed that FP-CIT uptake in the contralateral caudate and contralateral putamen had significant correlations with rigidity and bradykinesia, as assessed by the UPDRS motor scores. But the FP-CIT uptake in either caudate or putamen had no correlation with the tremor score[13]. This is consistent with the evidence that reductions of striatal density of the dopamine transporter are significantly correlated with the severity of rigidity and akinesia/bradykinesia but not with tremor[13,33-37]. Moreover, accumulating evidence consistently shows that the correlation between the motor symptom of each clinical sub-type and neuronal loss, as measured by neuroimaging, varies remarkably, and there are distinctive patterns in the progression of motor symptoms among different phenotypes of PD. Such variation suggests that different pathophysiological processes and nigro-striatal pathways are represented by various subtypes of PD.

Further, several studies have demonstrated that the progression of motor symptoms has a nonlinear pattern over the course of disease. The progression is faster in patients at the early stage of disease (Hoehn and Yahr[38] stages 1–2.5) than in patients with a longer disease duration (Hoehn and Yahr stages 3–5)[39,40]. This nonlinear pattern can be explained as follows. First, clinical measures of motor impairment might have easily reached saturation at the advanced stages of the disease, possibly due to a ceiling effect of the UPDRS. Second, a clinicopathological study using a longitudinal design also presented similar findings of an exponential decline of nigral cell counts associated with PD over time[41]. In an earlier study by Fearnley *et al.*[42], the micro-structure of the substantial nigra was examined in 20 patients with varying disease durations and 36 control cases. The findings also showed an exponential loss of

pigmented neurons, with a 45% loss in the first decade in the patient group whereas in the control cases, there was a linear decline of pigmented neurons at a rate of 4.7% per decade with aging in the substantia nigra pars compacta[42]. Moreover, the nonlinear progression of PD was also supported by a longitudinal cohort study using neuroimaging[43]. In that study, 31 parkinsonian patients with a wide spectrum of disease durations and severity were examined by serial PET imaging of striatal fluorodopa F 18 activity at a baseline visit and a follow-up visit, with a mean interval of 64.5 ± 22.6 months between. The results suggest that the neurodegenerative process in PD follows a negative exponential course and slows down with increasing disease duration.

3 Non-motor symptoms in PD

The motor symptoms of PD have dominated the clinical picture of the disease. However, many patients with PD also experience a series of non-motor-related symptoms that can be presented at different stages of the disease. The non-motor symptoms, which have attracted increasing attention during the past couple of decades, are now considered as important elements in the clinical spectrum. Typical non-motor symptoms include but are not limited to, sleep disturbances, anxiety, depression, constipation, fatigue, change or loss of smell, hallucination, and a progressive decline of cognitive ability that may lead to dementia[14].

The recognition of non-motor symptoms in PD has stimulated much interest in research to better understand the disease process, as well as their impact on patients' quality of life. Several studies have shown that non-motor symptoms can significantly impair the quality of patients' lives and may precipitate institutionalization[44,45]. Further, it is now known that a variety of non-motor symptoms can precede the cardinal motor features and diagnosis of PD by a number of years[46]. The stage with non-motor symptoms is often referred to as the premotor phase. In particular, efforts are being dedicated to testing the significance of rapid eye movement-related sleep disorder and olfactory dysfunction as potential biomarkers or precursors to identify individuals at an increased risk of developing the motor symptoms, before substantial loss of dopaminergic neurons occurs[47,48].

Apart from the association of these symptoms with the premotor phase, various non-motor symptoms frequently develop in the majority of patients who are at moderate or advanced stages of PD. Non-motor symptoms can be manifested within five years of disease onset, as indicated by a patient self-reported questionnaire[49]. The common clinical signs include cognitive decline and dementia, pain, and psychosis.

4 Relationship between motor and non-motor symptoms in PD

The motor symptoms have been recognized since its first description by James Parkinson in 1817. Disability is most commonly associated with the cardinal motor symptoms which are often referred to as the primary symptoms of PD. Further, motor symptoms are more extensively investigated, and their impact on patients' functional mobility and quality of life is well-established[50-52]. On the other hand, evidence also suggests that non-motor symptoms have significant impacts on patients' quality of life[53,54]. The findings on motor and non-motor symptoms can be investigated both clinically and from the patients' perspectives.

A recent study in 462 patients showed that both motor and non-motor symptoms contribute to health status, as measured by the PD questionnaire[55-57]. Motor signs, depression, anxiety, cognition, and other non-motor symptoms are the top five symptom domains that determine patients' health status[55]. In general, the worst symptoms deemed by patients are often different from what is perceived by clinicians. To investigate the prevalence of the most troublesome symptoms in PD experienced and perceived by patients, Politis *et al*.[58] assessed 265 patients by asking each to name and rank the three worst symptoms experienced in the previous six months. The patients were stratified into two groups according to the duration of disease. Subjects with less than six years of disease were classified into the early PD group while those who had

more than six years of symptoms were considered to be in the advanced group. In the early group, the cardinal motor symptoms (slowness, tremor, and stiffness) were the highest-ranked symptoms, followed by pain, loss of smell/taste and mood. Patients in the advanced group ranked fluctuating response to medication, mood, and drooling as the worst complaints, followed by sleep problems, tremor, and pain. The findings from this study suggested that the cardinal motor symptoms are the most prevalent complaints in patients with early PD. Wearing-off or fluctuating responses to medication was the most troublesome complaint in advanced group. The wearing-off phenomenon usually refers to an earlier than expected reappearance of the cardinal motor symptoms. Besides motor-related symptoms, the non-motor symptoms pose greater challenges to patients' daily lives at an advanced stage of the disease.

As described in Section 3, many patients with PD experience a wide variety of non-motor symptoms in addition to motor impairments[14,59]. Some non-motor symptoms can occur at the premotor stage whereas several other manifestations co-occur with motor symptoms. For example, the aforementioned study examining patients' perceptions of the three worst symptoms identified pain, mood and sleep problems to be the most troublesome non-motor impairments in both the early and advanced groups[58].

With respect to treatment, the classical triad of motor symptoms generally responds well to dopamine-replacement therapy. However, non-motor symptoms are not or not fully responsive to dopaminergic medication, suggesting that the non-motor symptoms might be mediated by non-dopaminergic pathways and non-nigrostriatal mechanisms, such as neurodegeneration of other transmitter systems in the cortex and brainstem, as well as genetic and psychosocial factors[60].

5 Therapeutic interventions for motor symptoms in PD

A variety of pharmacological and surgical interventions are available for the management of PD. Levodopa was the first major breakthrough in treatment, and remains the "gold standard" in the management of symptoms. Levodopa is converted into dopamine in the brain to replenish the brain's dwindling supply. In contrast to levodopa, dopamine agonists, whose introduction was a milestone in treatment, act directly on dopamine receptors in the brain, and thus can help alleviate the symptoms[6]. However, after a few years' treatment with levodopa, many patients begin to develop motor complications, which are broadly classified as "wearing-off reactions", "on-off reactions", and dyskinesia[7]. Surgical treatments have reportedly been effective in reducing symptoms and improving function. These include pallidotomy, thalamotomy, subthalamotomy, and high-frequency deep brain stimulation (DBS) via electrodes implanted in the globus pallidus, thalamus, or subthalamic nucleus[61,62].

Among the motor symptoms, bradykinesia and rigidity are most responsive to medication and surgical treatment, followed by tremor that also shows a positive response to the above interventions. Postural instability is generally not responsive to dopamine replacement. Numerous physiological studies have shown the effects of dopaminergic medications and DBS on reducing bradykinesia[63,64], rigidity[65-69], and tremor[70,71] in patients with PD. The occurrence of falls and gait dysfunctions associated with postural instability is an important determinant of patients' quality of life[72]. Given the poor responses of postural instability to drug and surgical interventions, numerous exercise interventions and rehabilitation programs have emerged and been evaluated with respect to their effectiveness on outcomes such as balance, strength, gait, walking speed, and physical function[73-75]. Clinical studies have shown beneficial effects of a variety of such programs (e.g. aerobic exercise, home-based exercise intervention, treadmill training with body weight support, and resistance training) on improving functional mobility in patients with PD[75-77]. The degree of improvement varies according to the type of intervention program, length of the program, as well as the frequency and duration of each training session.

These studies not only provide useful information in guiding clinicians to practice evidence-based decision-making in patient care but also lay a foundation for clinical application and implication. Each of the cardinal motor

symptoms can be used as an index to assess the efficacy of new pharmacological and surgical approaches or the effectiveness of new rehabilitation programs for PD patients, based on their responsiveness to each of the treatment regimes.

6 Current progress in disease modification in PD

Considerable research efforts have recently focused upon the development of neuroprotective and disease-modifying agents that are intended to slow the progression of PD. More than a dozen randomized, controlled clinical trials have been conducted to assess the potential neuroprotective effects for disease modification as summarized in a systematic review[78]. In that article, the authors reviewed 15 published studies on placebo-controlled trials which tested 13 putative neuroprotective agents and enrolled more than 4 000 participants. Among these trials were a few well-known large clinical trials, such as the DATATOP study[18] that was conducted at 28 clinical sites across North America, the Early versus Later Levodopa in PD (ELLDOPA) study[79] involving 32 sites in North America, and an international study on TCH346[80] that was carried out at 45 clinical sites.

The primary outcome measures applied in the above trials[78] were either "Time to levodopa or dopaminergic treatment" or "Change in UPDRS". The latter outcome assessment included different variables, e.g. both absolute changes in the UPDRS scores and changes in rate. The total UPDRS score was used in some trials whereas the sum of Parts II and III (i.e., activity of daily living and motor examination, respectively) was applied in other trials. The results from these trials showed various outcomes, with several trials demonstrating positive effects for neuroprotection, three negative effects, three equivocal effects and the remaining trials showing neither positive nor negative effect or a pilot trial. In brief, the disease-modifying effects of these putative agents remain inconclusive.

Further, the use of clinical UPDRS as the outcome measure of progression has potentially introduced a confounding factor related to the interpretation of data, because the UPDRS scores show improvement due to symptomatic benefits from dopaminergic treatments, consequently masking the underlying course of disease progression. In particular, this could be a concern when assessing patients who are in the early stages of the disease, in which cardinal motor symptoms such as rigidity and bradykinesia respond well to dopamine-replacement intervention[81]. In an attempt to overcome this barrier, neuroimaging data have been used as biomarkers to measure the progression in trials evaluating drugs with known symptomatic benefits on parkinsonian symptoms. The exemplar trials included measurement of changes in putamenal 18 F-fluoro-levodopa (^{18}F-Fdopa) uptake with positron emission tomography (PET) to assess the impact of drug treatment upon nigrostriatal integrity in the Requip as Early Therapy versus *L*-dopa-PET (REAL-PET) trial[82]. Over 160 patients with an early diagnosis of PD were enrolled and randomly assigned to treatment with either ropinirole or carbidopa/levodopa. PET imaging of ^{18}F-Fdopa uptake showed significantly less reduction in putamenal ^{18}F-Fdopa uptake in patients randomized to ropinirole (13%) compared to those on carbidopa/levodopa (20%) when assessed at the end of the two-year study. Such a difference is equivalent to a 34% slower loss of dopaminergic termini in the ropinirole group than in the carbidopa/levodopa group. Despite its potential as a surrogate biomarker, questions have arisen about the degree to which the imaging markers truly reflect nigrostriatal integrity and as to whether there was any blending effect on the imaging data resulting from the drug intervention[83].

A novel approach using a randomized delayed-start design has most recently been explored in an attempt to differentiate the disease-modifying effect from the symptomatic effect. In this type of study design, patients are randomly assigned to either putative drug or placebo group during Phase I of the study. All patients in both groups then receive the intervention drug in Phase II. This study design allows for testing whether an earlier intervention is more beneficial than a delayed intervention. A positive difference, if demonstrated, indicates the disease-modifying effect rather than the symptomatic effect, given that both

groups receive the same medication. The observed benefits can therefore be attributed to the early initiation of drug intervention, indicating the neuroprotective effect of the tested drug[84].

The first prospective clinical trial using this novel approach was the Attenuation of Disease Progression with Azilect Given Once-Daily (ADAGIO) study that was specifically designed to evaluate the potential of rasagiline for disease modification[85]. Rasagiline is an irreversible monoamine oxidase type-B (MAO-B) inhibitor used to treat early and advanced PD. A possible neuroprotective effect of rasagiline stemmed from laboratory studies in animal models of PD[86, 87]. In the double-blind, delayed-start trial of ADAGIO, a total of 1 176 early untreated PD patients were enrolled and randomly assigned into either the intervention or placebo group. The trial consisted of Phase I for 36 weeks followed by Phase II for another 36 weeks. The results showed consistently slower rates of worsening in the UPDRS scores associated with early-start treatment with rasagiline at 1 mg per day, suggesting a possible disease-modifying effect at this dose[85]. However, the authors pointed out that the results should be interpreted with caution due to concerns such as a high dropout rate during the placebo phase, potential misdiagnosis associated with early PD and other related factors. Despite these limitations, the ADAGIO trial is regarded as a landmark partly because of its use of a novel design that offers the best possible means to test putative neuroprotective agents at present.

7 Conclusion

The progression of motor symptoms in PD is closely associated with the progressive neurodegeneration in nigrostriatal pathways. In addition, multiple other factors contribute to the progression of global disability, converging from treatment-induced motor complications, evolution of axial motor symptoms poorly responsive to levodopa, and a large variety of non-motor symptoms. Significant advances have been made in increasing our understanding of the disease process and in clinical interventions. Effective treatment can be developed only if the origin and pathogenesis of PD have been revealed. Insights from animal and clinical studies have provided putative agents for neuroprotection or disease modification, with some having been tested in clinical trials and others on the way. Currently, therapeutic agents with a strong disease-modifying effect are not available. Substantial momentum in this area has, however, made it clear that therapeutic strategies with disease-modification potential are on the horizon.

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