



Pharmacotherapy for Parkinson's Disease in the Elderly

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Abstract

Parkinson's disease is a debilitating neurological disorder, named after Dr. James Parkinson, who first described the condition. Histopathologically, it is characterized by the loss of dopaminergic neurons and appearance of Lewy bodies in the brain. The major risk factor is age, although a genetic link has also been suggested. The major symptoms are tremor, bradykinesia, and muscle rigidity. Since there are no specific tests, diagnosis heavily relies on clinical observation and physical examination. The disease is particularly serious in the elderly and frail. The mainstay of pharmacotherapy is levodopa, which is still considered as the gold standard. However, rapid progress in research has uncovered new therapeutic approaches that could potentially revolutionize Parkinson's disease treatment in the near future.

Keywords: Parkinson; Bradykinesia; Tremor; Rigidity; Neurodegeneration, Levodopa

Introduction

Parkinson's disease was first described medically as a neurological disorder in 1817 by Dr. James Parkinson, who was a British surgeon with contributions in many fields of scientific endeavor, most notably, geology. He first reported

this condition in his clinical research work 'An Essay on the Shaking Palsy', where he first described 'paralysis agitans', which was later renamed Parkinson's disease. However, descriptions of this condition can be traced as far back as 1000 BC in ancient Indian and Chinese medical texts.



Figure 1: Dr. James Parkinson (1755 - 1824).

Parkinson's disease is the second most common neurodegenerative disorder, following Alzheimer's disease. Notably, both these conditions are most prevalent in the elderly and frail [1]. This condition is historically considered as a dopaminergic disorder. However, with significant advancements in medicine, it is now regarded as a complex multisystem syndrome that affects both the motor and non-motor arms of the nervous system. As the disease progresses, there is increased propensity for severe disability, morbidity, and hospitalization. Moreover, in late-stage disease, many overlapping symptoms can lead to severe complications [2].

Pathophysiology of Parkinson's Disease

The underlying pathological features of Parkinson's disease involve the loss of dopaminergic neurons in the substantia nigra of the brain and appearance of alpha-synuclein clumps, commonly known as Lewy bodies [3]. As a consequence, there is a deficiency in dopamine and surplus of acetylcholine, leading to motor symptoms. By the time symptoms become evident, 60-70% are already

lost [4]. Moreover, non-motor symptoms may be caused by neurotransmitters in non-dopaminergic areas of the brain [5].

Risk Factors for Parkinson's Disease

The major risk factor for Parkinson's disease is age and in most cases, the disorder occurs after 65 years and is slightly more prevalent in men [6]. A genetic cause has been found by some researchers, which accounts for 5-10% of Parkinson's patients who are mostly in the younger age group [7,8].

Clinical Symptoms of Parkinson's Disease

Besides the obvious motor symptoms, there are also some non-motor symptoms, including pain, depression, and fatigue. These often precede the appearance of motor symptoms and are classified under prodromal phase. In this phase, since the symptoms are non-specific and mild, diagnosis becomes difficult. Some of the clinical symptoms are highlighted in Table 1 [2,7].

| Major Symptoms | Features |
|---------------------------|---|
| Tremor | Usually resting and unilateral |
| Bradykinesia | Slowed movements |
| Muscle rigidity | Muscle stiffness, cramps, pain, flexed posture |
| Minor Symptoms | |
| Reduced facial expression | - |
| Speech changes | Reduced volume, monotonous tone |
| Micrographia | Small writing |
| Hyposmia | Reduced smell sensation |
| Dysphagia | Difficulty swallowing |
| Sialorrhea | Hypersalivation or drooling |
| Autonomic dysfunction | Orthostatic hypotension, constipation, urinary problems, sexual dysfunction, delayed gastric emptying, excessive sweating |
| Sleep disturbances | Insomnia, REM sleep behavior disorder, excessive daytime sleepiness |
| Neuropsychiatric symptoms | Apathy, anxiety, dementia, depression, psychosis |
| Gait disturbances | Shuffling walk, reduced arm swing, freezing posture, trips and falls |
| Fatigue | - |

Table 1: Clinical Symptoms of Parkinson's Disease.

Diagnosis of Parkinson's Disease

Since there is no specific diagnostic test for Parkinson's disease, clinical history of the patient, coupled with a thorough physical examination are crucial for making a definitive diagnosis [9]. Laboratory investigations and X-ray examination are not very useful, but may help to narrow-

down the other possible causes in the differential diagnosis.

Bradykinesia with resting tremor or muscular rigidity must be present in order to confirm the diagnosis [10]. Other associated symptoms that can support the diagnosis include unilateral onset and asymmetrical presentation [2,7].

Parkinson's Disease Manifestations in the Elderly

The clinical manifestations of Parkinson's disease in the elderly can be enhanced and progress quicker due to age-related physiological changes [3]. There may be multiple disabilities, coupled with old age complications, including frailty, delirium, dementia, and a greater propensity for trips and falls [1].

Many factors can be responsible for poor compliance to therapy in the elderly. These can include disabilities, intake of multiple drugs, complex drug regimens, adverse side effects, and higher prevalence of cognitive impairment. Some of the strategies that can be adopted to improve compliance include using simpler dosing regimens, using aids for dosing, as well as implementation of more education and counselling initiatives [11].

Management of elderly patients may prove to be difficult, both when they live independently or in long-term care facilities. In the former case, social isolation may take a toll on their health and well-being. For example, forgetfulness is likely to negatively impact their medication schedule,

resulting in missed doses. On the other hand, in long-term care settings, patients will not have the degree of freedom and independence that they would get at home. Moreover, caregivers are likely to be oblivious of the personal needs of the patients. As a result, the patients don't receive the optimal specialized care that they need [12]. The choice of treatment options is also restricted in the older age group. Coupled with this is the lack of research studies and clinical trials in this vulnerable population, which reduces our understanding of what treatment approaches are best for them.

Pharmacotherapy Strategies for Parkinson's Disease

Still there is no cure for Parkinson's disease. However, current treatments are capable of managing the disease and significantly improving the symptoms. The mainstay of treatment is pharmacological in nature, although non-pharmacological approaches, including physiotherapy, occupational therapy, and speech therapy, may also be beneficial on a case-by-case basis [13,14].

| Pharmacological Agent | Adverse Effects (AEs) |
|---|--|
| Levodopa - dopa decarboxylase inhibitor | |
| Levodopa - carbidopa Levodopa - benserazide | Nausea, vomiting, orthostatic hypotension, hallucinations, motor fluctuations, dyskinesia |
| Dopamine agonists | |
| Non-ergot derivatives Pramipexole Rotigotine Apomorphine | Nausea, vomiting, orthostatic hypotension, edema, hallucinations, sleep attacks, impulse control disorders, rash, injection site reactions, sedation |
| Ergot derivatives Bromocriptine Cabergoline | Pleural, pericardial and retroperitoneal fibrosis, fibrotic valvular heart disease |
| Monoamine oxidase-B (MAO-B) inhibitors | |
| Rasagiline | Headache, arthralgia, nausea, vomiting, anorexia, exacerbation of levodopa AEs |
| Selegiline | Stimulant effects, dizziness, headache, confusion, agitation, exacerbation of levodopa AEs |
| Safinamide | Hypertension, nausea, vomiting, headache, exacerbation of levodopa AEs |
| Catechol-o-methyl transferase (COMT) inhibitors | |
| Entacapone | Diarrhea, dark-colored urine, exacerbation of levodopa AEs |
| N-methyl-D-aspartate antagonist | |
| Amantadine | Hallucinations, confusion, blurred vision, nausea, dry mouth, constipation |
| Anticholinergics | |
| Benzotropine Benzhexol | Cognitive impairment, hallucinations, nausea, blurred vision, urinary retention, constipation, falls |

Table 2: Pharmacotherapies for Parkinson's Disease in Elderly Patients.

It is recommended that until and unless the condition deteriorates and quality of life declines, medicines for motor symptoms should not be started. In fact, mild symptoms observed in the early stages of the disease do not require any treatment at all. The treatment goals vary among age groups. While the goal in the younger age group is to maintain an active lifestyle, in the older age group the goal is to maintain daily activities as normal as possible. Treatment should be started at the lowest dose possible, gradually increasing as per requirement. The major categories of pharmaceutical agents for the treatment of Parkinson's disease are listed in Table 2 [5,15].

Levodopa: The Gold Standard for Treating Parkinson's Disease

Levodopa is considered as the gold standard for treating Parkinson's disease. Notably, it is the most effective drug for

treating bradykinesia and rigidity, especially in the elderly and frail. Additionally, levodopa is an attractive option in the older age group due to its milder side effects, compared to other therapies [9,14].

Motor Complications of Parkinson's Disease

It should be noted that long-term use of levodopa can be associated with several complications. These include motor fluctuations, dyskinesia, and dystonia (Table 3) [15,16]. In fact, when levodopa is used for 6 years or more, dyskinesia and motor fluctuations can occur in up to 40% of Parkinson's patients [17].

Most patients usually experience these complications, although these are more common in younger adults.

| Complications | Features |
|--------------------|--|
| Motor fluctuations | Shifts between times of improved motor function and times of worsening Parkinsonian symptoms |
| Dyskinesias | Abnormal, involuntary movements typically appearing as fidgeting or restlessness |
| Dystonia | Abnormal muscle contractions often manifesting as painful muscle cramping and increased stiffness, generally occurring at trough levodopa levels during 'wearing-off' fluctuations, overnight or in the early morning before the first levodopa dose |

Table 3: Motor Complications of Parkinson's Disease.

Treatment Strategies for Motor Complications

Motor complications can be treated using several approaches. These include adjustment of the levodopa dose, regimen, or schedule, among others. This helps to optimize the amount of levodopa that is delivered to the brain, which is the key to effective therapy [5,16]. Optimization of levodopa can be brought about by administration during fasting state, small and frequent dosing, controlled-release formulations or adjunctive agents, such as dopamine agonists and COMT or MAO-B inhibitors. All these have been shown to improve motor fluctuations.

New Therapeutic Options

A novel therapeutic approach involves the use of vaccine to reduce deposition of alpha-synuclein protein [13]. Also, the tyrosine kinase inhibitor, nilotinib, has shown promise. Levodopa, specially formulated for inhalation is an attractive option for symptomatic relief. Cannabis-based therapies for both motor and non-motor symptoms are also becoming popular. Pimavanserin, a novel selective-serotonin inverse agonist, has been approved for treating psychosis in Parkinson's patients. In contrast to atypical antipsychotic agents, it does not exhibit dopamine blocking effects [18,19].

Concluding Remarks

Parkinson's disease is a complex neurological disorder that has many clinical challenges. Diagnosis is often difficult, especially in the early stages of the disease. Management of symptoms is challenging, particularly in advanced stages. Levodopa remains the gold standard for treating Parkinson's disease. However, other adjunctive therapies are often required. These include various drugs for controlling motor and non-motor complications. It is recommended that for optimal management, a personalized therapy approach should be used, involving a multidisciplinary team of medical experts.

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