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Latest Treatment and Management Strategies for the Management of Parkinson Disease

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ABSTRACT:

In the treatment of Parkinson's disease (PD), significant progress has been achieved. As a follow-up to experimental therapy, a great number of promising therapies are developing for Parkinson's disease. The most effective drug to manage Parkinson's symptoms remains Levodopa but it is also associated with severe complications such as wear-off effects, levodopa-induced dyskinesia and other motor problems. Inhibitors of catechol-o-methyl-transferase, dopamine agonists, and non-dopaminergic therapy may be used in conjunction with or in conjunction with Parkinson disease. The neurosurgical treatment is discussed briefly and is based on deep brain stimulation. Although it is important to note that new medicines are not necessarily better than conventional therapy, and that treating options have to be personalized and adapted to the individual patient's needs, while the review attempts to highlight the recent progress in the treatment of Parkinson's disease.

KEYWORDS: Parkinson's disease, levodopa, medical treatment, pallidotomy, deep brain stimulation.

1.0 INTRODUCTION

1.1 General Introduction

The symptom diagnosis of Parkinson's disease (PD) has been central to dopamine levodopa substitution therapy for nearly 40 years. While this drug remains the "gold standard", a number of additional dopaminergic medicines were developed to give PD patients alternatives. Practical problems in PD management include the degree of initiation of and the combination of treatment required to cure a disease and the role of parenteral therapy and advanced disease surgery. Although levodopa provides effective symptom relief at all levels, many have recommended alternative drugs for initiation in the correct patients with the risk of motor complications [1]. In earlier and more advancing diseases, dopamine agonists and monoamine oxidase (MAO) B inhibitors provide an efficient motor relief for PD and are associated to a low risk of motor complications. They are not so powerful as levodopa, however. Parenteral or levodopa agonists have a valuable mechanism or alternative to activity.

The initiation and use of medications must be adapted to specific patient needs as an important concept in the treatment of PD. When first diagnosed, many patients will still function. Their need for symptomatic therapy depends on their effects on work and home performance; their life expectancy, their quality of life and their comorbidities must also be taken into account. The fact that the average life expectancy from diagnosis to death is 17 years in patients with DC emphasizes the need for a long-term treatment strategy for the majority of patients. Due to the question of adverse effects and the duration of neuronal dysfunction from onset and death to clinical symptoms in PD it is not understood whether the type of medication used initially and subsequently may also affect the form. This may be for many decades in the monogenic forms of family PD [2]. The pre-symptomatic latent period is approximately six years, according to recent research using intermittent PD serial imagery severe nigral

dopaminergic loss is not known to be prior to symptoms, though degeneration from 60 % to 70% is believed to be approximate. In clinical research, the score of the Unified Parkinson Disease Rating Scale deteriorates by around 8 to 10 points in the first year and is associated with a substantial decrease in quality of life. This is a result of a significant decline in clinical size.

PD treatment was traditionally rejected until symptoms affect function in the workplace or social or domestic environment sufficiently. This vision originated and developed during the Levodopa period and became known teaching, but is possibly worth re-assessing in view of the now available variety of new treatments [3]. We proposed to enhance motor function and short-term quality of life early vs. later symptomatic care, and to maintain the benefit in the long term, maybe through a disease change impact on compensatory mechanisms. Others believe that the initiation still needs to be delayed.

1.2 Pathology, etiology and pathogenesis

The pathological hallmark of PD is cell loss within the substantia nigra particularly affecting the ventral component of the par's compacta. By the time of death, this region of the brain has lost 50–70% of its neurons compared with the same region in unaffected individuals. The earliest documented pathological changes in PD [4] have been observed in the medulla oblongata/pontine tegmentum and olfactory bulb. In these early stages—Braak stages 1 and 2—patients are pre-symptomatic. As the disease advances—Braak stages 3 and 4—the substantia nigra, areas of the midbrain and basal forebrain become involved. Finally, the pathological changes appear in the neocortex. This pathological staging is based on the distribution of lewy bodies. Lewy bodies are the pathological hallmark of PD. They are a-synuclein-immunoreactive inclusions made up of a number of neurofilament proteins together with proteins responsible for proteolysis. These include ubiquitin, a heat shock protein which plays an important role in targeting other proteins for breakdown. Mutations in the a-synuclein gene are responsible for some familial forms of PD in which lewy bodies are also seen. Mutations in the parkin protein produce a parkinsonian syndrome without lewy bodies in juvenile cases suggesting that the parkin protein plays an important role in the development of the lewy body. It has been shown that parkin facilitates the binding of ubiquitin (ubiquination) to other proteins such as the a-synuclein interacting protein synphilin-1 leading to the formation of lewy bodies [5]. Lewy bodies are found in PD and Dementia with lewy bodies (DLB), but are not a pathological hallmark of any other neurodegenerative disease. The identification of single gene defects in PD has focused interest on the ubiquitin-proteasome system (UPS) as one potential candidate in the development of cell death [6]. The UPS is important for intracellular proteolysis and a large number of intracellular processes that maintain the viability of cells. It does this by removing unwanted proteins that are no longer required by the cell. Failure of the UPS leads to the abnormal aggregation of proteins including a-synuclein which are a major component of lewy bodies. One of the first sites for LB deposition in early PD is the olfactory bulb. It is, therefore, of interest that a disturbance in smell and taste is often one of the earliest clinical features in PD raising the possibility that LB formation may be integral for the activation of pathways leading to neuronal dysfunction and death. The link between UPS and neurodegeneration has been strengthened by the discovery of mutations in genes which code for several ubiquitin-proteasome pathway proteins in PD.

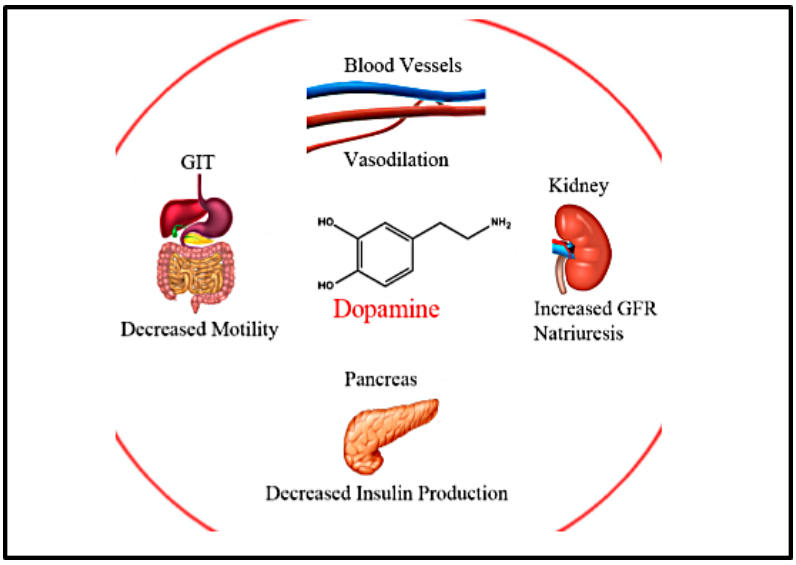

Figure 1: Select peripheral actions of dopamine

1.3 Genetics of PD [7,8]

Although PD is usually a sporadic disease, there are a growing number of single gene mutations which have been identified. At the time of writing, 11 genes have been mapped by genetic linkage with six genes identified: a-synuclein (SNCA), ubiquitin C-terminal hydrolase like 1 (UCH-L1), parkin (PRKN), LRRK 2, PINK 1 and DJ-1 genes. These single gene defects with the notable exception of LRRK 2 are responsible for only a small number of patients with PD, though more importantly their identification and the proteins that they encode for are providing significant insight into the disease mechanisms that may be responsible for PD and other neurodegenerative diseases. A point mutation of the SNCA gene leads to the early onset of PD in affected members in an autosomal dominant pattern. Of interest, duplication or triplication of the SNCA gene in affected members leads to PD symptoms developing at a later age in the fourth or fifth decades raising the possibility that overexpression of SNCA may be a factor in sporadic disease. The LRRK 2 gene (PARK8) is the most common cause of familial or the so-called 'sporadic' PD to date [9]. The frequency of LRRK2 mutations in patients with a family history of PD is 5–7%. The heterozygous mutation, 2877510 g→A, produces a glycine to serine amino acid substitution at codon 2019 (Gly2019 ser). This LRRK2 G2019S mutation is the most commonly described, accounting for the majority of familial cases and up to 1.6% of cases of idiopathic PD, though the prevalence seems to be very variable. The LRRK2 gene encodes for a protein named dardarin (derived from the basque word for tremor; the original families described came from Spain and England). Lewy bodies have been identified in some LRRK 2 cases. Many of the LRRK2 patients reported have typical features of PD with onset in middle or late onset. Symptoms at onset may be typical of idiopathic PD characterized by unilateral bradykinesia and rigidity, with tremor present in some but not all patients. A number of single gene mutations, e.g. parkin and DJ-1 with an autosomal recessive pattern of inheritance, may have a clinical pattern of earlier age of onset, a more benign course with good response to levodopa and the presence of dystonia. However, it is not possible to identify parkin positive young onset PD patients from parkin negative patients on clinical features alone. There has been a great deal of research into mitochondrial genetics and function in PD. Abnormalities in Complex 1 of the oxidative phosphorylation enzyme pathway is the most consistent finding, having been detected in PD brains, blood platelets and skeletal muscle, although defects in other complexes have also been reported [10]. It appears that the cells of the par's compacta are particularly susceptible to oxidative damage. Mitochondrial DNA studies have as yet failed to identify a convincing gene mutation to explain the oxidative phosphorylation defects in PD. However, it seems likely that a mitochondrial defect may play a role in the pathways leading to cell dysfunction and death. The PINK1 gene codes for a mitochondrial complex and has been shown to be responsible for an autosomal recessive form of PD, though is not a major risk factor for sporadic disease.

2.0 INITIAL THERAPY

The main therapeutic possibilities for the motor symptoms of PD are dopamine medicines, e.g. levodopa, the dopamine agonists and the MAO-B inhibitors, all of which have adequate clinical data. The use of these and the design of the best long-term approach for PD patients (Figure 2) are significant considerations.

2.1 Producing Effective Symptom Control

Dopaminergic medications that both improve bradykinesia and rigidity in PD in varying degrees, although trembling is more refractive. The most potent dopaminergic medication is still Levodopa, but dopamine agonists can also provide effective control. Together with two studies on dopamine agonist immunology levodopa showed a three to five points rating of the Unified Parkinson's Disease Rating Scale over the corresponding agonist, but the motor controls of both patients' and physicians' groups were considered satisfactory [11]. Monoamine oxidase B inhibitors have the benefit of early disease monotherapy and adjuvant therapy but are not as active as levodopa and dopamine agonists.

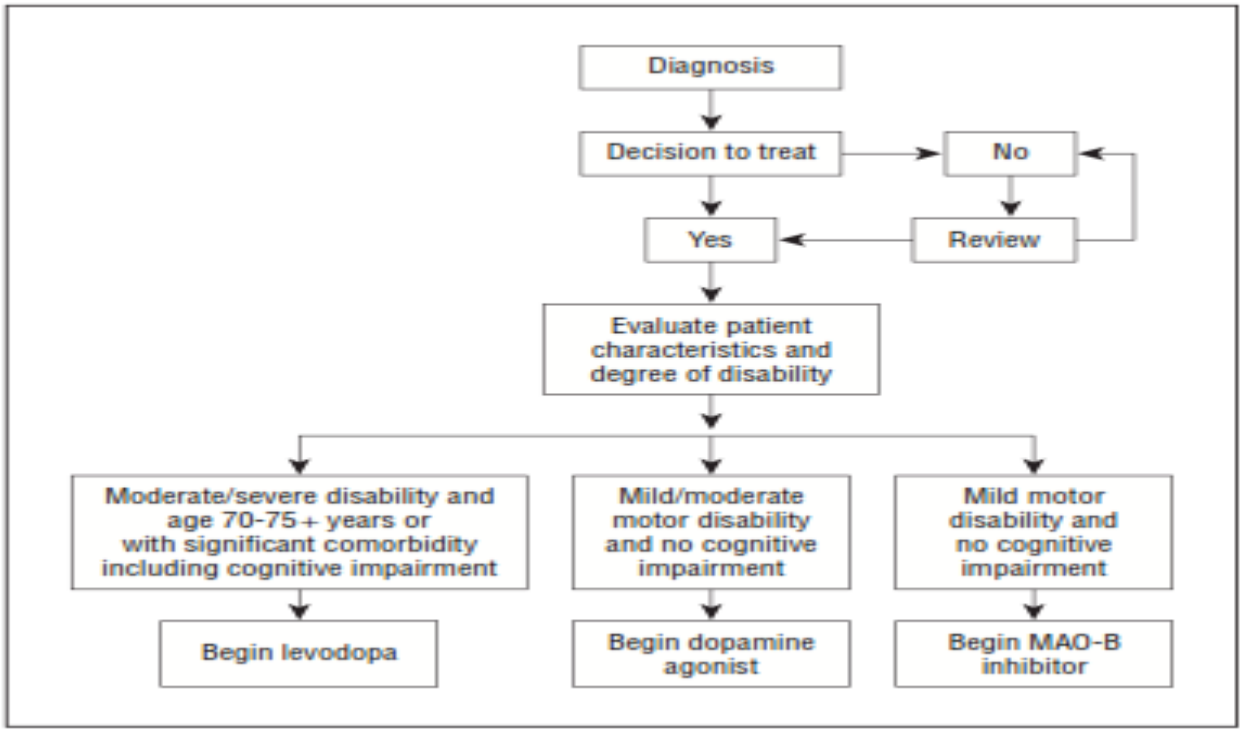

Figure 2: Pathway of decision to begin Parkinson's Disease for drug treatment

2.2 Delaying Motor Complications

Motor complications include both wearing off and dyskinesia. The latter rate develops at about 10 % annually but in young adult PD at a much faster rate, so that 70% are affected after 3 years. Early dyskinesia may be mild and may not interfere with general activity but they contain further complications which can affect the quality of life significantly. The cause of motor problems is not well known, but it appears to be associated with the effects of a short-term pulsative striatum stimulation. As a result, treatment strategies that require more continuous dopamine stimulation have been established, thus restoring stimulation of the dopamine receptor to a more constant (physiological) level [12]. These include the use of long-term medicines such as ropinirole and pramipexole from

the dopamine agonist, delaying the introduction of short-term medicines such as levodopa, or increasing half-life as an alternative and the development of new systems for supply.

3.0 COMBINATION THERAPY FOR ADVANCING DISEASE

As PD progresses, the provision of effective symptom control becomes more challenging and additional drugs may need to be added. Long-term follow-up indicates that levodopa supplementation will be required of those who begin to receive a dopamine agonist about half at 3 years, and 2/3 at 5 years. For those who started to receive an agonist (pramipexole) and supplemented with levodopa alone, quality of life analysis was similar over 4 years. This study has shown that engine function with four years of treatment is better than baseline, while quality of life analysis shows baseline degradation. Selegiline has been able to postpone the need for additional care for nine to 12 months in patients with early disorders [13].

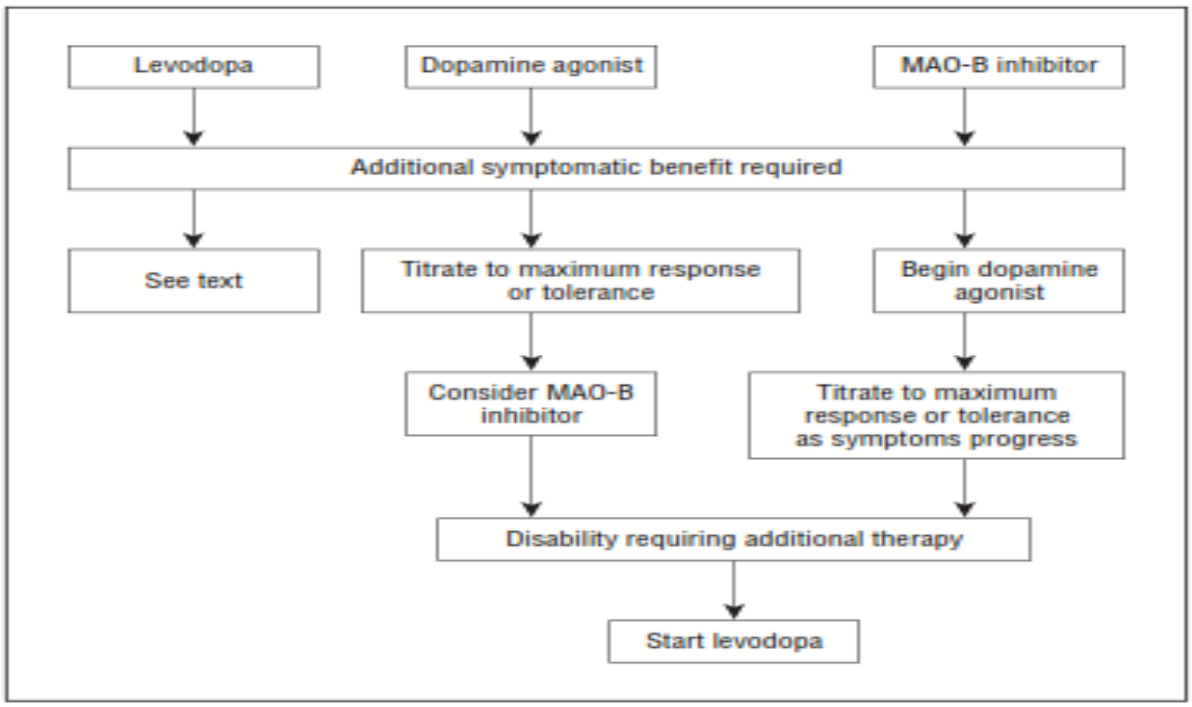

Figure 3: Decision process for the early Parkinson disease series and combination of drugs

The figures show that 46% of the 2-year-old and 32% of the 3-year-old patients still have rasagiline-alone control over their symptoms. Therefore, levodopa supplementary therapy is required for PD patients who begin to receive an agonist or MAO-B inhibitor at some stage. The addition of a dopamine agonist is the next logical step for those who have begun to obtain MAO-B inhibitors. A MAO-B inhibitor may be used to treat those who have already received a highly efficient or tolerated dose of an agonist and require further treatment. Levodopa is the following option for most of these patients (Figure 3).

4.0 TREATMENT OF ADVANCED DISEASE

Progressive degeneration of the neurons and the emergence of motor problems lead to complex treatment schemes (Figure 3). Advanced PD is also characterized by a poor engine control with frequent oscillations between on, on, and off or frozen dyskinesia. Amantadine has proven effectiveness in peak dose progress. The effective dose in 2 divided doses is 200 to 400 mg / day; dyskinesis can be decreased in frequency by about 24% to 56% and the impact

maintained by one year. Confusion and live reticular effects may be adverse. For parenteral dopaminergic treatment or surgery, a proportion of patients with complex diseases should be considered [14]. Intermittent or continuous apomorphine may enhance motor control and decrease or sometimes eliminate fluctuations significantly. Jejunal levodopa infusion is also able to minimize volatility considerably and can be given by percutaneous enteral gastrostomy. Parenteral patients must be carefully selected, but not so stringent as surgery guidelines [15]. Infusions of subcutaneous apomorphine are less economical and invasive than jejunal and are both suitable for surgery. PD Surgery has increasingly evolved and now involves deep brain and damaging lesions. Surgery provides the diagnosis of carefully chosen patients a big diagnosis option [16]. Candidates should have a clear diagnosis of PD and should have successfully responded to dopamine therapy. Surgery won't help those with Parkinsonism atypical. Their disorders are primarily motor problems and they should be cognitively healthy. Medical therapy manipulation should have tried to improve control. Pallidotomy can improve contralateral dyskinesia for a long time and improve patient bradykinesia and rigidity [17]. Deep brain stimulation (DBS) eliminates the need for severe brain damage and can be used for fairly healthy bilateral procedures. The stimulator can also be modified to maximize benefits and to minimize negative effects. Deep brain stimulation in both PD and dyskinesia in the subthalamic nucleus or globus pallidus interna improves all of the cardinal characteristics.

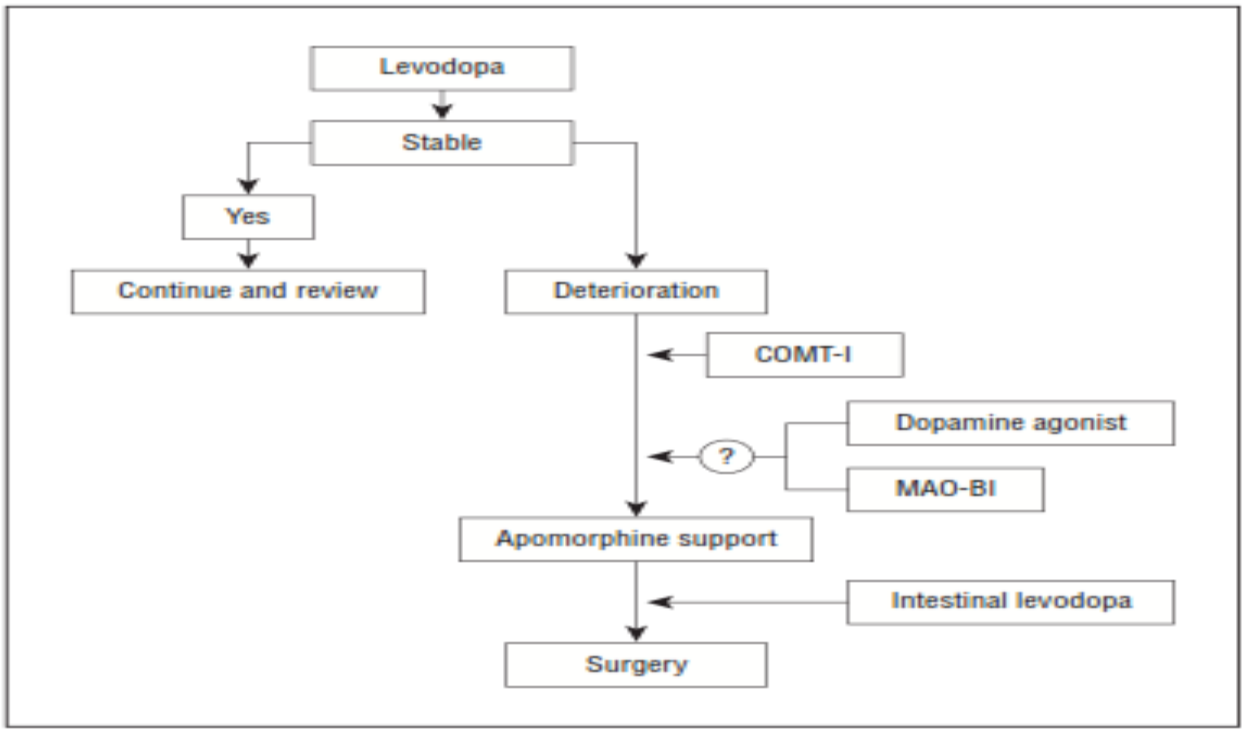

Figure 3. Decision pathway for treating Parkinson's disease progressive

Long-term studies indicate that DBS benefits last for more than 5 years, while impairment continues to rise year-on-year as a result of degeneration in non-dopaminergic locations [18]. Intracranial process, electrode device and stimulation may be linked to adverse effects with DBS. Problems occur in approximately 2% to 3% of cases including plumage, lead migration, infection and cutaneous erosion which sometimes require electrode replacement. A research has shown the sub thermal center of DBS to be stronger than conventional therapy for motor function and quality of life.

5.0 The role of surgery in PD [19, 20, 21]

The use of surgery in PD dates back over 50 years. In the early 1950s, patients particularly those with severe tremor would on occasion be referred for ablative surgery usually to the contralateral thalamus. With the introduction of

levodopa, surgical treatment fell from vogue. It is somewhat ironic that the widespread recognition of levodopa-induced complications prompted surgeons and clinicians to revisit the area of surgical intervention. Initially, this concentrated on lesion surgery usually in the form of pallidotomy which was shown to be successful particularly for levodopa-induced dyskinesias. A further development came with the introduction of stimulators. This involved high-frequency deep brain stimulation (DBS) of discrete brain areas producing functional and reversible inhibition of the target site. A number of areas within the basal ganglia can be targeted. The procedure most commonly carried to reduce bradykinesia, tremor and rigidity and which also reduces drug-related motor complications is bilateral subthalamic stimulation. This can produce very dramatic benefit. The operation is technically difficult, but in experienced hands the risk of adverse events is low. However, the infrastructure and support team required to assess, carry out and monitor patients limits the availability of this form of treatment. Furthermore, there is concern about the increased incidence of psychiatric side effects, particularly depression following DBS. Patients with cognitive impairment or significant depression are, therefore, not suitable for this form of treatment. In terms of patients most suitable for treatment [22], STN DBS tends to be performed in patients under the age of 75 without significant systemic co-morbidity and in the absence of obvious structural abnormality on MR imaging. Patients should be levodopa-responsive who are disabled while ‘off’ and independent while ‘on’ with medication. Most patients will have had disease duration of at least 5 years to allow for other causes of atypical parkinsonism to become evident. Age seems to be less critical in Vim DBS performed for disabling tremor. Recent studies have suggested that DBS of the pedunculopontine nucleus may be beneficial in improving axial stability. Assessment of a patient for DBS requires assessment by an experienced multidisciplinary team.

6.0 CONCLUSION

Parkinson's disease is a clinically diagnosed neurodegenerative disorder based on its motor properties with commonly recognized non-motor symptoms. The etiology is unknown but comprises a combination of age and sex, the most frequent, of genetic and environmental factors. Increased mortality can include Parkinsonism frequency, Parkinsonism aggravation rate, weak response to levodopa, early gait disorder and Parkinsonism symmetry. Any of these featuring factors may explain a Parkinson plus syndrome being misdiagnosed as Parkinson's Idiopathic disorder, and in the differential diagnosis it is necessary to consider this difficulty. Several new therapies for patients with PD have become available and offer significant symptom control and long-term adverse effect profiles. The sequence of these medicines is an important consideration and depends on the particular patient's characteristics. Each phase of PD presents challenges to manage both short-term and long-term symptoms with the best risk benefits ratio. For all its imperfections as a pharmaceutical, orally administered L-dopa continues to be the major treatment option for managing PD [23].

7.0 FUTURE PROSPECTS

Many new medicines are being developed or will soon become available to PD patients. A variety of new medications will be introduced. There are two imminent arrivals in some countries, a transdermal (skin patch) rotigotine dopamine agonist delivery system and ropinirole preparation once a day. All these preparations for dopamine agonists have the ability to help regulate the PD motor symptoms and to increase patient adherence. Pramipexole once a day is now being tested in Phase III. No neuroprotective effect has yet been confirmed, although in some cases experimental laboratory and clinical studies have demonstrated a promise.

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