ABSTRACT

Parkinson is a pathological condition occurred due to degenerative disorder of central nervous system affecting the motor system. It results due to death of dopamine-generating cells in region of midbrain. It affects body movements including shivering of arms, legs, face, limb stiffness, slow motility, impaired functions in balance and coordination between body parts. Other common symptoms are depression, emotional breakdown, dysregulation of mood, speech problems, urinary problems, sleeplessness and skin problems. At present, there is no permanent cure for this disease and certain drugs available that helps in relieving from parkinsonism e.g. levodopa, pramipexole, dopamine agonists, MAO-B inhibitors, COMT inhibitors. Among them, levodopa and pramipexole are used initially to treat Parkinson. Levodopa is the most effective that get metabolized to dopamine in the brain by replacing biosynthetic precursor. It is also called as L-DOPA. In early onset of symptoms easily respond to L-DOPA treatment. Due to L-DOPA treatment, common symptoms such as motor disturbances, hallucinations, memory problems and confusion makes are respond well to consider Levodopa act as a standard treatment. Pramipexole is a non-ergot dopamine agonist which is effective in the treatment of this disease and major symptoms like fluctuations, dyskinesias, neuroprotection, dysregulation of mood, cardiac valvulopathy and somnipathy respond well when used with levodopa in combination with carbidopa. Common side effects called dyskinesia occurred less when mediation with pramipexole is used as compared to treatment with levodopa. On other side, medication with levodopa lead to less occurrence in signs of edema. So, Levodopa and pramipexole are effective in dopaminergic therapy with divergent drug efficacy.
KEYWORDS: Parkinson's disease; Levodopa; Pramipexole; dopamine; dopamine agonists; MAO-B inhibitors; COMT inhibitors.

INTRODUCTION
Parkinson’s disease is a chronic and progressive movement disorder and approximately one million people in the US are suffered from parkinsonism. Parkinson’s disease involves the malfunction and death of vital nerve cells in the brain, called neurons in the area of the brain called the substantia nigra which secretes a chemical called dopamine that transmit signals to brain that controls body movement and coordination. As parkinson’s disease progresses, the amount of dopamine produced in the brain decreases, leaving a person unable to control movement normally (Fig 1).[1] The main motor symptoms are collectively called “parkinsonian syndrome” which is idiopathic (having no known cause), although some atypical cases have a genetic origin.[2]

![Brain Regions Affected by Parkinson's Disease](image)

Fig 1: Brain regions affected by Parkinson’s disease

Many risk and protective factors have been investigated that the increased risk of parkinson’s disease in people was coined who are exposed to certain pesticides and a reduced risk was reported in tobacco smokers. The pathology of the diseases is characterized by the accumulation of alpha-synuclein into protein inclusions called Lewy bodies in neurons which leads to reduced secretion of dopamine in midbrain. Lewy bodies are the pathological hallmark of the idiopathic disorder and their distribution throughout the Parkinsonian varies from one individual to another and was also found to be in the brain stem and the olfactory bulb. Effective treatment was given with L-DOPA and Pramipexole.[3,4] Oxidative stress-related changes, including free radical damage to DNA, proteins, and fats, have been
observed in the brains of individuals with parkinson’s disease having mutations that affect mitochondrial function.\cite{4,5} Parkinson plus syndromes are observed also with cognitive difficulties or sleep problems such as multiple system atrophy, progressive supranuclear palsy, corticobasal degeneration and dementia.\cite{6} The drugs are commonly used for treating motor symptoms are levodopa (usually combined with a dopa decarboxylase inhibitor or COMT inhibitor) and dopamine agonists and MAO-B inhibitors to improve dopaminergic function.\cite{7} When medications are not enough to control symptoms, then, surgery and deep brain stimulation can be done and palliative care is provided to improve quality life of diseased patients.\cite{8,9}

Fig 2: A Lewy body (stained brown) in a brain cell of the substantia nigra in Parkinson's disease. The brown colour is positive immunohistochemistry staining for alpha-synuclein.

A triplication of the normal alpha-synuclein gene on one copy of chromosome 4 (a chromosome is a threadlike structure of a protein and the genetic material DNA) was identified in the family history of diseased patients to produce too much of the normal alpha-synuclein (Fig 2).\cite{9,10} Other genes also found to be linked to parkinson’s disease which are parkin, DJ-1, PINK1 and LRRK2. DJ-1 and PINK1 cause rare and found to be with mutation at early-onset of Parkinson’s disease to increase susceptibility to cellular stress.\cite{10} Mutations in LRRK2 were originally identified in several English and Basque families as a cause of a late-onset parkinson's disease.\cite{11} Common symptoms are associated with Parkinson’s disease are facial tremor, movement rigidity, bradykinesia and posture insability.\cite{12} A decreased activity in the basal ganglia might be prove helpful aid in diagnosing Parkinson's disease and brain CT scans are sometimes used to rule out disorders.\cite{13} Drug therapy used to treat Alzheimer's disease and multiple cerebral infarction, sometimes, lead to drug-induced
parkinsonism and Parkinson plus syndromes such as progressive supranuclear palsy and multiple system atrophy which must be ruled out. Anti-Parkinson's medications are typically found to be less effective to control the motor symptoms in Parkinson plus syndromes.\cite{14}

**MEDICATIONS**

Medication used in treatment of parkinson’s disease fall into three categories. The first category includes drugs that increase the level of brain dopamine and levodopa is commonly used drug that cross the blood-brain barrier and changed into dopamine. Rest other drugs only mimic dopamine either prevent or slow its breakdown (Fig 3).\cite{15}

![Treatment Algorithm for Parkinson’s Disease](image)

**Fig 3: Treatment for Parkinson’s disease**

The second category of drugs affects other neurotransmitters in the body in order to early onset of the respective disease e.g. anticholinergic drugs interfere with production or uptake of the neurotransmitter acetylcholine which reduce tremors. The third prescribed category of drugs is used to control the non-motor symptoms of the disease called antidepressants.\cite{15,16}

**PHARMACOLOGICAL TREATMENT OF PARKINSON’S DISEASE**

The effective drugs which are used to treat motor symptoms are Levodopa, dopamine agonists, and MAO-B inhibitors. The effective treatment approach varies depending on the diseased stage. Two phases are usually distinguished with an initial phase in which patient has already developed some motor disability required pharmacological treatment and a second stage in which the patient develops motor complications related to responding
levodopa medication to attain an optimal cognition between good management of symptoms and drug induced side effects resulting into enhancement of dopaminergic function. The start of L-DOPA treatment may be delayed by using other medications such as MAO-B inhibitors and dopamine agonists to reduced the onset of dyskinesias (Fig 4).\cite{3,16,17}

**Fig 4: Mode of action of anti-parkinson therapies**

**LEVODOPA MEDICATION**

After levodopa treatment, neurons is started to use levodopa to make dopamine and replenish the brain's reduced supply to easily pass through the blood-brain barrier combined with carbidopa to reduce or eliminate the tremors and other motor symptoms of early onset of symptoms of parkinson’s disease\cite{18}. Levodopa usually helps to control bradykinesia and body rigidity. Levodopa/carbidopa can have a variety of side effects including nausea, hypotension and restlessness. The nausea and vomiting caused by levodopa are reduced by using the effective concentration of levodopa and carbidopa. Long-term use of levodopa sometimes also causes hallucinations, dyskinesia and psychosis in some patients (Fig 5).\cite{9,12,15,19}
DOPAMINE AGONISTS MEDICATION

Dopamine agonists have a similar effect to levodopa since they bind to dopaminergic postsynaptic receptors which include apomorphine, pramipexole, ropinirole, and rotigotine, mimic the role of dopamine in the brain. They may be used alone or with levodopa for treating early onset of symptoms of Parkinson’s disease. Their potential side effects are coined including drowsiness, sudden sleep, hallucinations, confusion, dyskinesias, edema (swelling due to excess fluid in body tissues), nightmares and vomiting. In rare cases, they can cause an uncontrollable desire to gamble, hypersexuality and compulsive shopping. Agonists at higher doses have also been associated to a wide variety of impulse-control disorders especially in younger diseased patients.[8,15,20]

PRAMIPEXOLE MEDICATION

Treating with pramipexole results in less occurrence of dyskinesias as compared to treatment with levodopa. With levodopa there is reduction in signs of freezing, edema etc. that provide better control of symptoms. Both options i.e. Levodopa and pramipexole are effective in dopaminergic therapy but both act with different efficacies. Pramipexole is a non-ergot dopamine agonist which is effective in this disease. This helps in treating major symptoms like fluctuations, dyskinesias, neuroprotection, risk for development of dysregulation of sleep and mood and cardiac valvulopathy.[8,12,15,22]
MAO-B INHIBITORS
These drugs inhibit the enzyme monoamine oxidase B or MAO-B which breaks down of brain dopamine. MAO-B inhibitors cause dopamine to accumulate in surviving nerve cells and reduce the symptoms of parkinson’s disease. NINDS (National Institute of Neurological Disorders and stroke) have reported that selegiline (also called deprenyl) can delay the need for levodopa therapy by up to a year or more. Selegiline has tolerated side effects such as nausea, orthostatic hypotension or insomnia as compared to L-DOPA when used alone or with L-DOPA. It must be taken under the physician prescription and must not be taken with the antidepressant, especially with fluoxetine or the sedative, meperidine which can have lethal effects like stroke. The drug rasagiline (also called azilect) is used in treating the motor symptoms of parkinson’s disease with or without levodopa.[12,15,21]

COMT INHIBITORS
COMT stands for catechol-O-methyltransferase which is an enzyme that leads to breaks down of dopamine. The drug entacapone and tolcapone can decrease prolonged beneficial effects of levodopa medication in diseased patients. The most common side effects of COMT-inhibitors treatment are diarrhea, nausea, sleep disturbances, dizziness, urine discoloration, abdominal pain, hypotension, hallucination and liver dysfunction.[12,15,23]

OTHER MEDICATIONS
Parkinson’s disease has been afflicted humans for thousands of years and was mentioned in ancient details of medical history when it was treated with variety of plant-based treatments having naturally occurring L-DOPA such as Mucuna pruins (velvet bean).[24] As well as, genetic research on parkinson’s disease is still going on to know the factual truth of mutational orientated medical compliances.[11,12] Other pharmacologic treatment remains the mainstay for its treatment with new delivery methods (such as inhaled dopamine and intestinal gel) are available to allow better control of early onset of symptoms of parkinson’s disease.[6,13,14] Rehabilitation therapy is showing promising results and may even affect the course of the disease by stimulating the production of protective neurotransmitters naturally to support the drug induced beneficial effects in diseased patients.[8,9] Apart all, the medical management of parkinson’s disease is complex which required knowledge of multiple medications that interact in sometimes unforeseen ways along with drug supportive brain stimulation and gene therapy trials which are done under way for focusing the track of the dopamine pathway in diseased patients.[11-14,19-23] Now these days, upcoming advanced
medical revolution of using stem cell therapy appears promising for various life threatening
diseases but results are currently inconclusive.\textsuperscript{[25]} Impulse control disorders are typically
managed by reducing or eliminated the dopaminergic medication, particularly dopamine
agonists to be given with L-DOPA with evidence-based management of some nonmotor
symptoms including cognitive ability changes by a paucity of high-quality positive results at
all stages of parkinson’s disease.\textsuperscript{[26,27,28]} As well as, medical management of this disease must
require the consideration of the role of patient health care expenditures to reduce the deep
brain stimulation including changes in societal cognitive behavior, stress and depression
during the medication of patients of Parkinson’s disease.\textsuperscript{[29,30]}

\textbf{CONCLUSION}

Hence, it is coined out form this informative brief study that parkinson’s disease is a
neurodegenerative movement disorder with changing. During its clinical management and
medications, various clinical problems emerge as potential therapeutic goals to achieve the
best treatment of this disease with well known different pharmacological agents such as
levodopa, pramipexole, dopamine agonists, MAO-Inhibitors and COMT-inhibitors. The
appearance of motor complications during drug based medications are found to be more
delicate and difficult to achieve the approachable and satisfactory treatment of this disease.
The advanced stage of parkinson’s disease is found to be notable by clinical problems that are
often dopamine nonresponsive and available options lacking of the support of a good-quality
research evidence. Therefore, cornerstone of symptomatic treatment for Parkinson disease is
only dopamine replacement therapy with criterion standard of symptomatic L-DOPA therapy,
the metabolic precursor of dopamine in combination with carbidopa, a peripheral
decarboxylase inhibitor as promising and trustworthy therapeutic tool which provides the
greatest symptomatic benefit with the fewest short-term adverse effects. Dopamine agonists
such as pramipexole and ropiniroleand monoamine oxidase (MAO)-B inhibitors inhibitors
such as rasagiline and selegiline can be used as monotherapy to improve early onset of
symptoms this disease or as adjuncts to levodopa in patients whose response to levodopa is
going to be deteriorating and experiencing fluctuations in their response to levodopa.
Catechol-\textit{O} -methyl transferase (COMT) inhibitors inhibitors such as entacapone and
tolcapone may be used to increase the peripheral half-life of levodopa in patients, thereby
delivering more levodopa to the brain over a longer time with consistent beneficial prolonged
effects. Anticholinergic medications can be used for the treatment of controlling tremor.
However, these medications are not particularly effective for bradykinesia, rigidity, gait
disturbance, or other features of advanced Parkinson disease and cognitive side effects are common. Therefore, anticholinergics are usually reserved for the treatment of tremor that is not adequately controlled with dopaminergic medications. Researchers are developing a variety of new surgical and non-surgical therapies for Parkinson's disease. These new therapies show great promise for improving the quality and length of life in Parkinson's patients. While some experimental therapies are already helping patients in clinical trials, scientists must find ways to refine these therapies and answer the questions surrounding their use. Other therapies, such as genetic engineering require much more preclinical research before they can become available for trials. Improved understanding of Parkinson's disease and development of valid biomarkers for disease progression will aid study of these therapies and perhaps lead to new ones.

REFERENCES


