ejpmr, 2020,7(9), 127-138

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

A REVIEW: PARKINSON'S DISEASE

Vidya Shirsath* and Yogeshwary Bhongade

MVP'S College of Pharmacy Nashik. Maharastra, India.

***Corresponding Author: Vidya Shirsath**

MVP'S College of Pharmacy Nashik. Maharastra, India.

Article Received on 14/07/2020 **Article Revised on 04/08/2020** **Article Accepted on 24/08/2020**

ABSTRACT

Parkinson's disease is a common movement disorder seen in neurological practice, but the diagnosis is Management is challenging. Diagnosis is clinical and sometimes difficult, considering a large number of motor and non-motor symptoms in patients with PD. Medical treatment of PD patients is difficult, as are the options. Medications are limited and levodopa is the mainstay of treatment. However, levodopa-induced dyskinesia (LID) is commonly observed in Parkinson's disease patients treated with levodopa. This side effect is usually found after a long duration of treatment, but occasionally this can be seen even after a few days or months treatment. Different types of surgical approaches, including unilateral pallidotomy and deep brain stimulation, they have given excellent results in patients with PD, who cannot be given only medications.

KEYWORD: Deep brain stimulation, dopaminergic drugs, Parkinson's disease.

INTRODUCTION

Parkinson's disease (PD) is chronic progressive neurodegenerative disorder characterized by premature premature death of dopaminergic neurons in the noun nigra pars compact (SNpc) and widespread presence of alpha synuclein (aSyn), an intracellular protein. Basal dopamine deficiency the nodes lead to the classic parkinsonian motor symptoms namely bradykinesia, tremor, stiffness and Posterior postural instability. Even PE is associated with non-motor symptoms, which may precede motor symptoms of more than a decade. These non-motor symptoms become bothersome symptoms in later stages of PD. Currently the pillar of PD management is pharmacological therapy; however, these symptomatic therapies they have important limitations in advanced disease. Many disabilities will develop later in course of disease, including non-motor disease symptoms, dopamine resistant motor symptoms and long-term motor complications of dopamine therapy. Although there have been notable progress in medical and surgical treatment for PD, definitive disease modification therapy lacks. However, researchers are confident who will be able to identify the potential goals for disease modification. In this review, we will discuss epidemiology, clinical characteristics, pathophysiology, diagnosis, and management (medical and surgical) of PD. Experimental therapies have so far yielded only limited test results and will not be discussed here.

Epidemiology

The incidence and prevalence of PD increases with advanced age, being present in 1% of people older than 65 years.[1] Early-onset Parkinson's disease (EOPD) is defined as the onset of parkinsonian features before age 40. It represents 3-5% of all cases of PD. It is classified as "youth" (which occurs before the age of 21) and "juvenile onset" (YOPD, which occurs in the age group between 21 and 40 years).[2] PD is twice as common in men as in women in most populations.[3,4] A protective effect of female sex hormones is observed. The presence of genetic mechanisms associated with gender and / or gender-specific differences in exposure to environmental risk factors could explain this male preponderance.[3,4] There are no large and homogeneous epidemiological data on PD in India. Razdan et al., Reported a prevalence rate of 14.1 per 100,000 among a population of 63,645 inhabitants of rural Kashmir in northern India. The prevalence rate for 60 years was 247 / 100,000.[5] A low prevalence rate of 27 / 100,000 has been reported from Bangalore in southern India, and 16.1 / 100,000 from rural Bengal in eastern India.[6,7] Bharucha et al., Reported a high gross prevalence rate of 328.3 / 100,000 among a population of 14,010 Parsis living in colonies in Mumbai, Western India.[8]

PATHOPHYSIOLOGY

PD Genetics

The genetic forms of PD represent only 5-10% of all cases.[9,10] The presence of a family history, early onset of the disease, and specific clinical characteristics (eg, dystonia as a presenting symptom) raise suspicions of the presence of the genetic form of the disease in a patient . A genetic basis can be seen in> 10% of people with YOPD and the percentage of genetically defined cases increases to> 40% if the onset of the disease is older than 30 years.[11,12] Major genes identified and demonstrated

to be causal in PD include Parkin (PARK2), Leucine-rich repetitive Chinase2 (LRRK2 / PARK8), Alpha synuclein (SNCA-PARK1 / PARK4), inductive kinase induced by PTEN Putin 1 (PINK1 / PARK6), DJ1 (PARK 7), C-terminal ubiquitin hydrolase as 1 (UCH-L1) and ATPase type 13A2 (ATP13A2).[9,10,13]

Genetics of PD in India

Mutations reported in the Parkin gene are the highest and vary between 1.96% and 39.1% among the Indian case series.[14] Mutations are absent in SNCA and less frequent in DJ1, PINK1 and LRRK2.[14] Mutations in the Parkin gene have been implicated in causing early-onset autosomal recessive PE (RA) and vary considerably between individuals from different geographic locations in India.[15-19] Chaudhary et al., In 2006, observed that Parkin mutations represented 14.3% of cases of familial PD, 6.9% of cases of young onset (age of onset ≤40 years) and 5.9% of cases of late onset. (age of onset ≥41 years) Sporadic PD.[16] Padmaja MV et al., In 2012, Parkin mutations reported 68% of early-onset cases in a study conducted in South India.[19] It is not possible to differentiate young Parkin-positive Parkin patients from Parkin-negative patients only because of their clinical characteristics.[9,10] DJ-1 mutations (observed in Parkinsonism AR) are responsible for the early onset of PD symptoms with a benign course. These mutations are characterized by a good response to levodopa and are generally associated with the presence of dystonia. The prevalence of DJ1 (AR) mutations in PD patients is modest (~ 5%) in the Indian population.[20] Two other Indian studies examined the prevalence of DJ1 mutations in PD patients.[21,22] One study reported a prevalence of 3.9% of DJ1 variants,[21] while another study was unable to identify pathogenic mutations.[22]

LRRK 2 (Autosomal Dominant Parkinsonism [AD]) is the most common cause of 'familial' and 'sporadic' PD worldwide, with a mutation frequency of 5-7% in patients with a family history of PD.[23] LRRK2 mutations, however, have been observed less frequently in India.[24-28] The most frequent and best studied LRRK2 mutation is the replacement of glycine with serine at position 2019 (c.6055G> A).[29] The study by Vijayan B et al. He was unable to find any contribution of the G2019S mutation to the pathogenesis of PD.[25] Punia et al. from India (made up of a heterogeneous population), who reported LRRK2 mutations in <0.1% of PD cases.[27] A point mutation of the SNCA gene causes the early onset of PE (AD) and its overexpression causes the development of symptoms of PE in old age in the fourth or fifth decade in affected limbs.[9,10] SNCA mutations, however, rarely contribute to PD in India.[24,30] A limited study with 100 cases of PD in northern Karnataka, India, suggested that SNCA mutations may be population-specific and, therefore, may not play a causal role in all populations studied.[31] The PINK1 gene, which encodes a mitochondrial complex, has been implicated in the cause of an AR form of parkinsonism.[32] The contribution of PINK1 variants in the case of DP is limited in India.[33,34] Tamali Halder et al., Observed that 1.8% (2/106) of PD patients in North India harbor PINK1 variants.[34] In 2016, Sudhaman et al., Discovered a new frame change mutation in the podocalissin-like gene (PODXL) as a probable cause of early-onset Parkinsonism (RA) in an Indian family, where the Parkin mutation test The PINK1 and DJ1 genes were negative.[35] New mutations are identified daily and added to the causal spectrum of genetic PD. However, the contribution of genetic testing in the treatment of Parkinson's disease is limited and there is no influence of positive genetic testing in treatment decision making.

Neuropathology

The pathophysiology of Parkinson's disease involves the loss or degeneration of dopaminergic neurons in the noun nigra pars compact (SNpc) and Lewy accumulation bodies, which are abnormal intracellular aggregates containing proteins, such as alpha-synuclein (aSyn) and ubiquitin.[36,37] 60-70% of neurons in SNpc are lost before symptoms appear.[38] Research has revealed that the pathogenic process in PD involves regions of the peripheral and central nervous system in addition to the dopaminergic neurons of SNpc. Lewy body pathology begins in brain stem cholinergic and monoaminergic neurons and in olfactory system neurons, but involves limbic and neocortical brain regions with disease progression.[39,40] Loss of dopaminergic neurons initially limited to SNpc has become more frequent since end-stage disease was established[41,42] Changes in the motor circuit in PD Selective loss of dopaminergic neurons in the striatum causes impaired motor control in people with PD. The motor circuit for PD consists of corticostriatal views of the primary motor cortex, the additional motor area, the cingulate motor cortex, and the premotor cortex, ending in the dendrites of the mid-striatal spinal neurons.[43,44] The direct pathway is a monosynaptic connection between the median spiny neurons that express dopamine D1 receptors and the GABAergic (gamma-butyric-ergic acid) neurons in the internal pale globe (Gpi) and the noun nigra pars reticulata (SNpr) The "indirect" pathway originates from median spiny neurons that express D2 receptors, which project into the external pale globe (Gpe) and reach the Gpi through the subthalamic nucleus (STN) as a glutamatergic relay. Through these two pathways, the striatal dopamine tone Regulates the GABAergic output activity of the basal ganglia. There is a reduction in D1-mediated direct pathway activity and an increase in D2-mediated indirect pathway activity, with a consequent net increase in the rate of activation of basal ganglia exit neurons (GABA), that excessively inhibit downstream of the thalamocortical and brain areas[43,44] Changes in cerebellar activity and in the interaction between the basal ganglia and the cerebellum contribute to the pathophysiology of tremor in PD.[45] Abnormalities of balance and gait are due to dysfunction of the outlet of the basal ganglia through projections in the midbrain locomotive region (peduncle-pontine and wedge-shaped nuclei).[46]

Intestine and EP

The parasympathetic nerves and the enteric nervous system are among the structures most affected by aSyn pathology. Brain-gut-microbiota axis dysfunction in PD may be associated with non-motor symptoms that are evident before classical motor symptoms, supporting the hypothesis that the disease process extends from the intestine to the brain.[47] Gut microbiomes play an important role in regulating movement disorders, and abnormalities of the microbiota could be a risk factor for Parkinson's disease. Sampson et al., Using mice that overexpress aSyn, reported that alterations of the intestinal microbiota were required for the development of motor deficits, microglial activation, and aSyn pathology.[48] Antibiotic treatment has improved, while microbial recolonization has promoted pathophysiology in adult animals, suggesting that postnatal signaling between the gut and the brain modulates the onset and course of the disease.[48] Oral administration of specific microbial metabolites [eg, short chain fatty acids (SCFA)] in germ-free mice has favored the development of neuroinflammation and motor symptoms. Research has shown that alterations in the intestinal microbiome are related to several clinical characteristics.

A recent Finnish study has shown that alterations in the composition of the microbiota, in particular the abundance of Enterobacteriaceae, is positively associated with the severity of postural instability and gait difficulty in PD patients.[49] Keshavarzian et al., E Unger et al., Noted that the feces of PD patients contained fewer short-chain fatty acids (SCFA), including butyrate, which produce bacteria that could exert anti-inflammatory properties.[50,51] An increase in intestinal permeability and dysfunction in intestinal symbiosis have also been proposed as mechanisms responsible for the development and progression of PD.[52] Recently, Hill-Burns et al. They observed a significantly modified abundance of numerous taxa in 197 patients with Parkinson's disease. They demonstrated the independent effects of PD drugs on these microbiomes, thus providing additional clues in the pathophysiology and treatment of PD.[53]

Clinical Diagnosis and Natural History

Parkinson's disease is clinically defined by the presence of bradykinesia in combination with at least one other manifestation: muscle stiffness, tremor at rest, or postural instability (the latter is a feature of the more advanced form of the disease).[54] Motor symptoms begin unilaterally and asymmetry persists throughout the disease. Non-motor symptoms are seen in a large proportion of patients. Some of these non-motor symptoms may anticipate the onset Cardinal motor symptoms for years.[55] These non-motor symptoms include sleep disorders [eg, frequent awakening, rapid eye movement (RBD) sleep behavior, and daytime sleepiness], hyposmia, autonomic function disorders [orthostatic hypotension, urogenital dysfunction, and constipation], cognitive decline, mood disorders and pain.[55] The Sydney multicenter study on Parkinson's disease reported dementia (83%), hallucinations (74%), symptomatic hypotension (48%), constipation (40%) and urinary incontinence (20%) in 71% of PD patients who survived> 20 years after the onset of the disease.[56] Gait freezing, postural instability, fall, and suffocation were reported in 81%, 87%, and 48% of patients, respectively.[56]

Although there is no consensus on the classification of PD subtypes, clinical observations suggest the existence of two main subtypes: PD with dominant tremor (with relative absence of other motor symptoms) and non-dominant PD with tremor (which includes the phenotypes described as rigid akinetic syndrome and postural instability gait disorder, PIGD). PD with dominant tremor is often associated with a slower rate of progression and lower functional disability than Parkinson's disease without tremor.[57] Almost 90% of PD patients experience non-motor symptoms during the course of the disease that generally do not respond well to dopamine therapy.[58] Mood disorders and constipation nearly double an individual's risk of developing Parkinson's disease in later years.[59] Idiopathic RBD carries a high risk of developing PD and other synucleotinopathies.[60] The average latency between the appearance of RBD and the appearance of parkinsonian motor symptoms is 12-14 years.[61]

Autonomous symptoms (mentioned above) increase with age, with disease severity, and with higher doses of dopaminergic drugs. Urinary symptoms include urgency, frequency, nocturia, and urge incontinence, with more common urinary accumulation problems than emptying difficulties. Urinary symptoms are more frequent and occur earlier in multi-system atrophy (MSA) than in PD.[62] Painful sensory symptoms were observed in two thirds of Parkinson's disease patients and are believed to be due to an abnormality in nociceptive therapy.[62] There is a six-fold increased risk of dementia (subcortical type) in patients with Parkinson's disease, and this occurs later in the course of the disease.[63] Up to 60% of PD patients develop dementia within 12 years of diagnosis.[63] Hyposmia occurs in approximately 90% of patients with early stage PE and anticipates typical motor symptoms over several years.[64] The onset of hyposmia may predict an increased risk of developing PD, and olfactory tests may help differentiate PD from other parkinsonian syndromes.

Image

Early PD is a diagnostic challenge with broad differential diagnoses consisting of diseases that are not associated with nigral degeneration or striatal dopamine deficiency. The commonly used clinical criteria in the United Kingdom for Brain Bank Parkinson's disease (UKPDSBB) are only 80% diagnostic accurate at the first visit after the development of early PD in a patient.[65] So functional Imaging is needed to confirm

the clinical diagnosis and to Understand the underlying pathophysiology.

Single-photon emission computed tomography 123 I-ioflupane [SPECT] (also known as DaTscan) is useful for evaluating the density of presynaptic dopaminergic terminals within the striatum, as it helps to differentiate PE from disorders that do not exist the presence of presynaptic dopaminergic terminal deficiency.[66,67] Positron emission tomography of positrons 18F-DOPAL-6-fluorine-3,4-dihydroxyphenylalin(18F-DOPA) assesses presynaptic dopaminergic integrity and accurately reflects monoaminergic disorders in PD. A retrospective analysis of 27 patients who underwent 18F-DOPA PET examination for suspected motor symptoms of PD showed that their sensitivity was 95.4% (95% confidence intervals [CI], 100% -75.3%), 100% specificity (95% CI: 100% -59.0%), positive predictive value (100% (95% CI, 100% -80.7%) and negative predictive value 87.5% (95% CI, 99.5% -50.5%).[68] [123I] N-□-fluoropropyl-2□-carbomethoxy-3□- (4-iodophenyl) nortropane (FP-CIT) is a selective and powerful [DAT] imaging agent for the dopamine transporter. The correlation between the values obtained in the FP-CIT single-photon emission computed tomography (SPECT) and the F-DOPA PET for striatal absorption in patients with different stages of PD has been demonstrated. reduction in the amount of endogenous dopamine concentration and this results in a reduction of the striatal bond of FP-CIT in the early stages of PE. Therefore, FP-CIT may be more sensitive than the F-DOPA scan to detect early striatal dopamine deficits. A study compared the sensitivity and specificity of the contralateral absorption of the striatum and the putaminal based on the results of FP-SPECT CIT and F-DOPA PET in patients with Parkinson's disease and healthy controls and found it to be 100% in the initial phase of the illness. When only the caudate absorption was considered, the specificity remained at 100% for FP-CIT but decreased to 90% for F-DOPA, while the sensitivity was 91% for both scanning techniques.[71] However, techniques that rely solely on dopamine imaging are not sufficient to diagnose Parkinson's disease because they do not reliably distinguish PD from other parkinsonian syndromes associated with nigral degeneration, such as atypical parkinsonism.

Standard magnetic resonance imaging (MRI) has a marginal role in establishing the diagnosis of PD; however, very high and high field magnetic resonance imaging (7 Tesla) combined with advanced techniques such as diffusion tensor imaging are explored to determine an early diagnosis of Parkinson's disease.[72] Magnetic resonance imaging helps to identify patients with symptomatic parkinsonism and also helps to show specific changes in the basal ganglia and infra-tentator structures in patients with atypical parkinsonism.[73] Sympathetic myocardial denervation, evaluated with PET or SPECT using noradrenergic tracers, is seen in PD, but not in patients with atypical parkinsonism or other PD mimics.[74]

Cerebrospinal fluid (CSF) and blood tests

Currently, there is no clinically useful CSF-based test for the diagnosis of PD. Several studies have been conducted that have evaluated protein levels in the cerebrospinal fluid (eg, levels of different syn-synuclein species) but the sensitivity and specificity of these tests were low.[75] Although lower plasma apolipoprotein A1 levels are often associated with increased severity of motor symptoms, its utility as a blood biomarker has not been established to date.[76] The main obstacle in PD research is the absence of good biomarkers with high sensitivity and specificity to diagnose the disease in the initial phase or even in the prodromal phase; and no single measure currently meets all the necessary criteria for a biomarker in PD.[77] Disease modifying therapies would be more effective if patients were diagnosed and treated during this prodromal period. Possible clinical markers include RBD diagnosed by polysomnography and olfactory dysfunction measured by standard methods, such as the University of Pennsylvania Odor Identification Test.[61]

Pharmacological management

The main objective of PD research is to develop a therapy that modifies the disease that can slow down or stop the neurodegenerative process. However, there is no definitive therapy that modifies the disease to achieve this.

Dopaminergic therapy

The American Academy of Neurology (AAN) recommends starting one of the following available drug therapies once patients develop a functional disability.[78] Available medical therapies for the treatment of motor symptoms include levodopa / carbidopa, dopamine agonists (both ergot and non-ergot), monoamine oxidase-B (MAO-B) inhibitors, injectable dopamine agonist (apomorphine), catechol-O-methyltransferase (COMT) inhibitors, N-methyl-D-aspartate receptor (NMDA) inhibitors and anticholinergics. In later stages of Parkinson's disease, the drug supply may be supplemented by alternative routes[79-82] (eg, intrajuncture infusions, subcutaneous injections, or transdermal patches). Continuous motor fluctuations and dyskinesias indicate the patient's candidacy for deep brain stimulation (DBS). Dopaminergic therapy is highly effective in bradykinesia and stiffness, but MAO B monoamine inhibitors are only moderately effective. Dopamine and levodopa agonists help reduce disease progression and disability. Tremor responds to anticholinergic drugs like trihexyphenidyl, but has a poor and inconsistent response to dopamine replacement therapy.[83,84]

Levodopa and new formulations of Levodopa

The mechanism for the main motor symptoms in PD is striatal dopamine depletion due to loss of the dopaminergic neuron in the SNpc. The administration of

levodopa to replace striatal dopamine has been a breakthrough in the treatment of Parkinson's disease, and since then multiple additional targets have been identified for dopaminergic therapies. Levodopa is considered a standard therapy and almost all patients require this particular treatment during their illness.[85] Long-term use of levodopa is complicated by motor fluctuations and dyskinesias. The mechanisms underlying these motor complications are still unclear. An accepted hypothesis for this manifestation is the participation of presynaptic and postsynaptic mechanisms that ultimately lead to stimulation of the non-physiological pulsatile striatal dopamine receptor, causing several maladaptive neurons. responses[86,87] Irregular administration of the drug due to the short half-life of levodopa, as well as the variability in its absorption and transport of the blood-brain barrier, play an important role in the development of motor complications.[82]

The bioavailability of levodopa can be improved by developing more effective oral formulations (eg, extended-release formulations) or by developing innovative routes of administration (eg, intestinal infusion, transcutaneous administration via mini-pumps or by inhalation). RYTARY / IPX066 is a new oral formulation of levodopa-carbidopa (LD / CD) that combines immediate and prolonged release of LD / CD. This has been approved in the United States and the European Union. IPX066 is composed of LD / CD microspheres designed to dissolve at various rates, allowing rapid absorption and prolonged release of levodopa over a long period of time. Studies have shown that administration of IPX066 improved symptoms in patients with early and advanced PE.[88-93] A significant improvement in unified Parkinson's disease rating scale (UPDRS) scores without the development of bothersome dyskinesias has been reported using this preparation compared to other levodopa formulations.[88-93]

Levodopa-carbidopa intestinal gel (LCIG) is an approved therapy for hospitalized patients with advanced PD. LCIG is administered continuously from a percutaneous endoscopic gastrojejunostomy tube (PEG-J), through a portable infusion pump. It reduces fluctuations in plasma L-dopa levels and therefore reduces motor complications.[80,81,94] Recently, researchers are evaluating the "accordion pill" (AP09004), an extended-release LD / CD formulation with gastro-retentive properties.[95-97] Other formulations of levodopa currently active in the studies include ND-0612, ODM-101, CVT-301, and Cyclops. ND-0612 is a proprietary liquid formulation of LD / CD that allows subcutaneous administration through a small patch pump device; and, ODM-101 is a new oral formulation of levodopa / carbidopa / entacapone that contains a higher amount of carbidopa (65 or 105 mg).[98-100] CVT-301 and cyclops are levodopa inhalation powders. Because they have a rapid onset of action, they are promising candidates for the treatment of Parkinson's disease.[101,102]

Although levodopa provides the highest levels of symptomatic relief, MAO-B inhibitors / dopamine agonists may be considered an initial therapy to delay subsequent complications. A randomized trial of newly diagnosed PD patients failed to show the long-term benefits of levodopa-saving therapy.[103] However, this study had limitations characterized by a lack of generalization, as patients <60 years of age, who were at high risk of developing dyskinesias, were not well represented.[104]

Dopamine agonists

Dopamine receptors primarily target the D2 family of receptors. The initial members of this drug family were derivatives of ergoline. Ergoline drugs have posed cardiac and lung safety problems and the agents currently used are all non-ergolinic drugs, for example pramipexole, ropinirole, apomorphine, pyribedil, rotigotine. Dopamine agonists induce less stimulation of the pulsatile striatal dopamine receptor than levodopa and can significantly reduce the risk of motor complications when used as initial monotherapy.[84,105,106] Apomorphine has D1 and D2 receptor activity and a potency equal to that of levodopa.[66] Continuous subcutaneous infusion of apomorphine reduces fluctuations in motor response and levodopa-induced dyskinesias.[107] Another medication, rotigotine, is available as a transdermal patch formulation that allows continuous release of the medication.[79]

Both levodopa and dopamine agonists are associated with nausea, daytime sleepiness, and edema, but side effects are more common with dopamine agonists. Dopamine agonists are known to cause impulse control disorders and drug-induced hallucinations (especially in the elderly with cognitive impairment), and are therefore best avoided in high-risk groups.

MAO B inhibitors

MAO B inhibition leads to an increase in synaptic dopamine concentration and symptomatic efficacy. Selegiline, an irreversible selective MAO B inhibitor, has been shown to be effective in addition to levodopa since the 1970s.[108] The results of the MONOCOMB study showed that selegiline monotherapy in early stage PD delayed disease progression. In advanced PE, selegiline had levodopa-saving qualities and was reasonably well tolerated in long-term use.[109] In a recent study in Japanese patients with early PD, selegiline monotherapy significantly reduced UPDRS scores part I + II + III.[110] Rasagiline, another irreversible MAO B inhibitor, is a well-known adjuvant therapy in patients with motor fluctuations.[105] A 3-year direct retrospective control study looking at the efficacy of MAO B inhibitors in Parkinson's disease reported the same efficacy in controlling motor symptoms in PD patients with optimized therapy.[111] MAO B inhibitor therapy was associated with a significant reduction in levodopa requirements and a lower frequency of dyskinesias.[111] Safinamide is a reversible MAOB inhibitor with

antiglutaminergic properties. Safinamide offers greater control over motor symptoms in advanced PE and improves quality of life.[112] In a recent randomized control study, safinamide, when used in addition to levodopa, improved activation time without causing dyskinesic discomfort and reduced the incidence of the "attrition" phenomenon.[113]

Catecohol Inhibitors: O-Methyl Transferase (COMT) Current levodopa preparations contain carbidopa or benserazide to prevent peripheral metabolism of dopamine, and therefore these drugs increase the bioavailability of the above drug. This shifts the peripheral metabolism of levodopa to a secondary pathway that involves COMT. Inhibition of the COMT pathway will further increase the bioavailability and half-life of levodopa, thereby helping patients with motor fluctuations.[114] Triple therapy with levodopa / carbidopa / COMT inhibitor increases activation time, reduces deactivation time and significantly improves quality of life.[115] The use of tolcapone is limited due to its side effects. Entocapone, a safer alternative, is currently available but less effective. In phase II studies, nebicapone was more effective than entacapone and safer than tolcapone.[116] Opicapone, in a once-daily oral dose regimen, has also been shown to reduce turn-off time and increase turn-on time without dyskinesia discomfort, in patients with advanced PE.[117]

Non-dopaminergic drug targets

Advanced symptoms of PD (both motor and non-motor) respond poorly to dopaminergic therapy. The reason may be an abnormality in other non-dopaminergic neurotransmitters such as acetylcholine, glutamate, norepinephrine, or serotonin.[118] Motor fluctuations, levodopa-induced dyskinesias, freezing gait, postural instability and falls, treatment-resistant tremor, swallowing, and speech disorders are among the symptoms requiring treatment with non-agents. dopaminergic. Lack of acetylcholine, due to degeneration of cholinergic neurons, causes dementia, gait abnormalities, and falls.[119] The donepezil study established for the treatment of falls is related to the hypothesis of the existence of an abnormal cholinergic system in PD that is responsible for frequent falls.[120] Rivastigmine, a cholinesterase inhibitor, is used for dementia associated with PD[121] The utility of rivastigmine in the treatment of gait abnormalities and frequent falls is being evaluated.[122]

Depression in PD patients responds to all types of antidepressant drugs and there is limited evidence to recommend tricyclic antidepressants on selective serotonin reuptake inhibitors. The role of noradrenergic drugs must be firmly established in clinical trials.[123] Psychotic symptoms in Parkinson's disease respond well to clozapine.[123,124] In addition to quetiapine, all other atypical neuroleptics worsen parkinsonism by blocking striatal D2 dopamine receptors. The recent positive effects obtained with the inverse agonist 5hydroxytryptamine 2A (HT2A), pimavanserin, strongly support the serotonergic effect of clozapine in the treatment of psychosis.[125]

Amantidine is an N-methyl-D-aspartate receptor (NMDA) antagonist used for levodopa-induced dyskinesias.[83,84,105] The guidelines differ regarding the effectiveness of amantadine in the treatment of levodopa-induced dyskinesias. The evidence-based review of the Movement Disorders Society reported that amantadine was "effective" in the treatment of dyskinesias, while the guidelines of the American Neurological Association (AAN) concluded that amantadine was "probably effective"[83,126] A recent controlled study investigated the efficacy and safety of 274 mg of ADS-5102 extended-release capsules (amantadine) (equivalent to 340 mg of amantadine hydrochloride) for levodopa-induced dyskinesia. The study reported a significant reduction in levodopa-induced dyskinesia and an improvement in shutdown times.[127]

PD patients have autonomic dysfunction problems, particularly in the advanced stage. Pharmacological therapy directed at the autonomic nervous system includes the use of mineralocorticoids, fludrocortisone, as well as the use of adrenergic agents (such as midodrine and ethylephrine), the precursor of norepinephrine (ie droroidepa) for the treatment of orthostatic hypotension; antimuscarinics (such as oxybutynin, tolterodine, or trospium chloride) for the treatment of urgency or urinary incontinence; and prokinetic medications to improve constipation.[84,123,128]

Tyrosine kinase inhibitors for the treatment of PD

Research has recently shown that the levels and activation of Abelson non-receptor tyrosine kinase (c-Abl) have been upregulated in the brain tissue of patients with Parkinson's disease. Karuppagounder et al., Evaluated the in vivo efficacy of a brain-penetrating c-PD tyrosine kinase inhibitor in the acute model of PD-1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP) and found that nilotinib prevented neuronal loss of dopamine and behavioral deficits after MPTP poisoning.[129] Nilotinib reduced c-Abl activation, Parkin substrate levels, and neuronal cell death. Imam et al. They tested the efficacy of INNO-406 (a second generation irreversible inhibitor of Abl kinase) and found that INNO-406 could prevent the progression of dopaminergic neuronal damage in a mouse model of C57 induced by toxins.[130] Researchers have shown that c-Abl inhibitors (nilotinib, imatinib and, to a lesser extent, bafetinib) could prevent loss of dopamine neurons, improve motor behavior, inhibit Cdk5 phosphorylation, regulate □-phosphorylation synuclein and reduce Parkin substrate levels.[131] Brain-permeable c-Abl inhibitors may serve as potential therapeutic agents for the treatment of Parkinson's disease and other neurodegenerative disorders.

Surgical treatment

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) or the internal pale globe (GPi) is a well-known treatment for patients with motor complications.[132-134] For the treatment of tremors, thalamic DBS is a viable option. Surgical treatment is preferred when motor fluctuations and dyskinesias become disabling despite the reactivity of motor symptoms to levodopa. The average time before DBS is performed is approximately 10-13 years after the diagnosis of Parkinson's disease has been established. The results of the EARLYSTIM study, a randomized multi-center control study, showed that DBS in the first course of the disease (average disease duration 7.5 years, with motor fluctuations for <3 years) could improve the patient's quality of life. and several The secondary result measures more than the best medical therapy.[135]

DBS is reversible and can be adjusted for disease progression. The presence of dementia, acute psychosis, and major depression are the exclusion criteria for DBS.[136] Bilateral STN DBS improves UPDRS II (activity of daily living) and UPDRS III (motor) scores by an average of 50-60% compared to preoperative OFF medical status. The daily dose of dopaminergic drugs is reduced by approximately 60% after the establishment of DBS, and dyskinesias decrease by 60-70%.[137,138] DBS of the subthalamic nucleus (STN) was associated with a reduction in the need for levodopa doses.[139] DBS mortality is <0.5%, and major adverse events include intracranial hemorrhage or device-related complications (such as lead infections and malfunction, among others).[140] The non-pharmacological therapies available for PD include exercise, education, support groups, speech therapy, and nutrition. The evidence provided by the literature recommends its use early in the course of the disease.

CONCLUSION

Parkinson's disease is one of the most common neurodegenerative diseases that affects the aging of the population and is associated with increased morbidity and mortality. It is necessary to know the manifestations of the disease, the treatments and the long-term progressive course of the disease for optimal case management. Terrible progress It was done to understand the neuropathology of Parkinson's disease and its progression throughout the nervous system. However, none of these treatments is curative. PD remains a progressive disorder that ultimately causes severe disability due to the increasing severity of motor problems and treatment-resistant non-motor symptoms. Changing the factors that lead to disease progression and further delaying your disability are the key unsatisfied issues that need to be addressed through current and future research efforts.

REFERENCES

1. Goldman SM, Tanner C. Etiology of Parkinson's's disease. In: Jankovic J, Tolosa E, editors. Parkinson's's disease and movement disorders, 3rd ed. Baltimore, MD: Lippincott-Williams and Wilkins, 1998; 133-58.
2. Schrag A, Schott JM. Epidemiological, clinical, and genetic characteristics of early-onset Parkinson'sism, Lancet Neurol, 2006; 5: 355-63.
3. Baldereschi M, Di Carlo A, Rocca, WA, Vanni P, Maggi S, Perissinotto E, *et al*. Parkinson's disease and Parkinsonism in a longitudinal study: Two-fold higher incidence in men. ILSA Working Group. Italian Longitudinal Study on Aging. Neurology, 2000; 55: 1358-63.
4. Van Den Eeden SK, Tanner CM, Bernstein AL, Fross RD, Leimpeter A, *et al*. Incidence of Parkinson's disease: Variation by age, gender, and race/ethnicity. Am J Epidemiol, 2003; 157: 1015-22.
5. Razdan S, Kaul RL, Motta A, Kaul S, Bhatt RK. Prevalence and pattern of major neurological disorders in rural Kashmir (India) in 1986. Neuroepidemiology, 1994; 13: 113-9.
6. Gourie Devi M, Gururaj P, Satishchandra P. Bangalore urban and rural neurological survey. Report submitted to the Indian Council of Medical Research, 1995.
7. Das SK, Sanyal K. Neuroepidemiology of major neurological disorders in rural Bengal. Neurol India, 1996; 49: 47-58.
8. Bharucha NE, Bharucha EP, Bharucha AE, Bhise AV, Schoenberg BS. Prevalence of Parkinson's's disease in the Parsi community of Bombay, India. Arch Neurol, 1988; 45: 1321-3.
9. Warner TT, Schapira AH. Genetic and environmental factors in the cause of Parkinson's disease. Ann Neurol, 2003; 53: S16-S23.
10. Cookson MR, Xiromerisiou G, Singleton A. How genetics research in Parkinson's disease is enhancing understanding of the common idiopathic forms of the disease. Curr Opin Neurol, 2005; 18: 706-11.
11. Marder K, Tang M-X, Mejia-Santana H, Rosado L, Louis ED, Comella C, *et al*. Predictors of Parkin mutations in early onset parkinson's disease: The CORE-PD Study. Arch Neurol, 2010; 67: 731-8.
12. Alcalay R, Caccappolo E, Mejia-Santana H, Tang MX, Rosado L, Ross B, *et al*. Frequency of known mutations in early onset PD;Implication for genetic counseling: The CORE-PD study. Arch Neurol, 2010; 67: 1116-22.
13. Lesage S, Brice A. Parkinson's disease: From monogenic forms to genetic susceptibility factors. Hum Mol Genet, 2009; 18: R48-59.
14. Das SK, Ghosh B, Das G, Biswas A, Ray J. Movement disorders: Indian scenario: A clinico-genetic review. Neurol India, 2013; 61: 457-66.
15. Madegowda RH, Kishore A, Anand A. Mutational screening of the Parkin gene among South Indians with early onset Parkinson's disease. J Neurol Neurosurg Psychiatry, 2005; 76: 1588-90.
16. Chaudhary S, Behari M, Dihana M, Swaminath P V, Govindappa ST, Jayaram S, Singh S, et al. Parkin

mutations in familial and sporadic Parkinson's disease among Indians. Parkinsonism Relat Disord, 2006; 12: 239-45.
17. Biswas A, Gupta A, Naiya T, Das G, Neogi R, Datta S, et al. Molecular pathogenesis of Parkinson's disease: Identification of mutations in the Parkin gene in Indian patients. Parkinsonism Relat Disord, 2006; 12: 420-6.
18. Vinish M, Prabhakar S, Khullar M, Verma I, Anand A. Genetic screening reveals high frequency of PARK2 mutations and reduced Parkin expression conferring risk for Parkinsonism in North West India. J Neurol Neurosurg Psychiatry, 2010; 81: 166-70.
19. Padmaja MV, Jayaraman M, Srinivasan AV, Srisailapathy CR, Ramesh A. PARK2 gene mutations in early onset Parkinson's disease patients of South India. Neurosci Lett., 2012; 523: 145-7.
20. Abbas MM, Govindappa ST, Sudhaman S, Thelma BK, Juyal RC, Behari M, et al. Early onset Parkinson's disease due to DJ1 mutations: An Indian study. Parkinsonism Relat Disord, 2016; 32: 20-24.
21. Sanyal J, Sarkar B, Banerjee TK, Mukherjee SC, Ray BC, Raghavendra Rao V. Evaluating intra-genetic variants of DJ-1 among Parkinson's disease patients of Eastern India. Neurol Res., 2011; 33: 349-53.
22. Sadhukhan T, Biswas A, Das SK, Ray K, Ray J. DJ-1 variants in Indian Parkinson's disease patients. Dis Markers, 2012; 33: 127-35.
23. Gilks WP, Abou-Sleiman PM, Gandhi S, Jain S, Singleton A, Lees AJ, et al. A common LRRK2 mutation in idiopathic Parkinson's disease. Lancet, 2005; 365: 415-6.
24. Padmaja M V, Jayaraman M, Srinivasan AV, Srikumari Srisailapathy CR, Ramesh A. The SNCA (A53T, A30P, and E46K) and LRRK2 (G2019S) mutations are rare causes of Parkinson's disease in South Indian patients. Parkinsonism Relat Disord, 2012; 18: 801-2.
25. Vijayan B, Gopala S, Kishore A. LRRK2 G2019S mutation does not contribute to Parkinson's disease in South India. Neurol India, 2011; 59: 157-60.
26. Sanyal J, Sarkar B, Ojha S, Banerjee TK, Ray BC, Rao VR. Absence of commonly reported leucine-rich repeat kinase 2 mutations in Eastern Indian Parkinson's disease patients. Genet Test Mol Biomarkers, 2010; 14: 691-4.
27. Punia S, Behari M, Govindappa ST, Swaminnath PV, Jayaram S, Goyal V, et al. Absence/rarity of commonly reported LRRK2 mutations in Indian Parkinson's's disease patients. Neurosci Lett., 2006; 409: 83-88.
28. Sadhukhan T, Vishal M, Das G, Sharma A, Mukhopadhyay A, Das SK, et al. Evaluation of the role of LRRK2 gene in Parkinson's disease in an East Indian cohort. Dis Markers., 2012; 32: 355-62.
29. Paisan-Ruiz C. LRRK2 gene variation and its contribution to Parkinson's disease. Hum Mutat, 2009; 30: 1153-60.
30. Nagar S, Juyal RC, Chaudhary S, Behari M, Gupta M, Rao SN, et al. Mutations in the alpha-synuclein gene in Parkinson's disease among Indians. Acta Neurol Scand, 2001; 103: 120-22.
31. Kadakol GS, Kulkarni SS, Wali GM, Gai PB. Molecular analysis of □-synuclein gene in Parkinson's disease in North Karnataka, India. Neurol India, 2014; 62: 149-52.
32. Schapira AH. Mitochondria in the aetiology and pathogenesis of Parkinson's's disease. Lancet Neurol, 2008; 7: 97-109.
33. Biswas A, Sadhukhan T, Majumder S, Misra AK, Das SK, Variation Consortium IG, et al. Evaluation of PINK1 variants in Indian Parkinson's's disease patients. Parkinsonism Relat Disord, 2010; 16: 167-71.
34. Tamali Halder, Raj J, Sharma V, Das P. Novel P-TEN-induced putative kinase 1 (PINK1) variant in Indian Parkinson's disease patient. Neurosci Lett., 2015; 605: 29-33.
35. Sudhaman S, Prasad K, Behari M, Muthane UB, Juyal RC, Thelma BK. Discovery of a frameshift mutation in podocalyxin- like (PODXL) gene, coding for a neural adhesion molecule, as causal for autosomal-recessive juvenile Parkinsonism. J Med Genet, 2016; 53: 450-6.
36. Dickson DW, Braak H, Duda JE, Duyckaerts C, Gasser T, Halliday GM, et al. Neuropathological assessment of Parkinson's disease: Refining the diagnostic criteria. Lancet Neurol, 2009; 8: 1150-7.
37. Goedert M, Spillantini MG, Del Tredici K, Braak H. 100 years of Lewy pathology. Nat Rev Neurol, 2012; 9: 13-24.
38. Postuma RB, Gagnon JF, Montplaisir J. Clinical prediction of Parkinson's disease: Planning for the age of neuroprotection. J Neurol Neurosurg Psychiatry, 2009; 81: 1008-13.
39. Halliday, GM, McCann H. The progression of pathology in Parkinson's disease. Ann NY Acad Sci., 2010; 1184: 188-95.
40. Dijkstra, AA, Voorn P, Berendse HW, Dijkstra AA, Voorn P, Berendse HW, Groenewegen HJ;Netherlands Brain Bank, Rozemuller AJ, van de Berg WD. Stage-dependent nigral neuronal loss in incidental Lewy body and Parkinson's disease. Mov Disord 2014;29:1244-51. Stage-dependent nigral neuronal loss in incidental Lewy body and Parkinson's disease. Mov Disord, 2014; 29: 1244-51.
41. Damier P, Hirsch EC, Agid Y, Graybiel AM. The substantia nigra of the human brain. II. Patterns of loss of dopamine-containing neurons in Parkinson's disease. Brain, 1999; 122: 1437-48.
42. Fearnley JM, Lees AJ. Ageing and Parkinson's disease: Substantia nigra regional selectivity. Brain, 1991; 114: 2283-301.
43. Alexander GD, DeLong MR, Strick PL. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Annu Rev Neurosci, 1986; 9: 357-81.

44. Alexander G, Crutcher MD, De Long MR . Basal ganglia-thalamocortical circuits: Parallel substrates for motor, oculomotor, "prefrontal" and "limbic" functions. Prog Brain Res., 1990; 85: 119-46.
45. Dirkx MF, den Ouden H, Aarts E, Timmer M, Bloem BR, Toni I, et al. The cerebral network of Parkinson's tremor: An effective connectivity fMRI Study. J Neurosci, 2016; 36: 5362-72.
46. Windels F, Thevathasan W, Silburn P, Sah P. Where and what is the PPN and what is its role in locomotion? Brain, 2015; 138: 1133-4.
47. Mulak A, Bonaz B. Brain-gut-microbiota axis in Parkinson's disease. World J Gastroenterol, 2015; 21: 10609-20.
48. Sampson TR, Debelius JW, Thron T, Janssen S, Shastri GG, Khan ZE, et al. Gut microbiota regulate motor deficits and neuroinflammation in a model of Parkinson's disease. Cell., 2016; 167: 1469-80.
49. Scheperjans F, Aho V, Pereira PA, Koskinen K, Paulin L, Pekkonen E, et al. Gut microbiota are related to Parkinson's disease and clinical phenotype. Mov Disord, 2015; 30: 350-8.
50. Keshavarzian A, Green SJ, Engen PA, Voigt RM, Naqib A, Forsyth CB, et al. Colonic bacterial composition in Parkinson's disease. Mov Disord, 2015; 30: 1351-60.
51. Unger MM, Spiegel J, Dillmann KU, Grundmann D, Philippeit H, Bürmann J, et al. Short chain fatty acids and gut microbiota differ between patients with Parkinson's disease and age-matched controls. Parkinsonism Relat Disord, 2016; 32: 66-72.
52. Hasegawa S, Goto S, Tsuji H, Okuno T, Asahara T, Nomoto K, et al. Intestinal dysbiosis and lowered serum lipopolysaccharide-binding protein in Parkinson's's disease.PLoSONE, 2015; 10: e0142164.
53. Hill-Burns EM, Debelius JW, Morton JT, Wissemann WT, Lewis MR, Wallen ZD, et al. Parkinson's disease and Parkinson's disease medications have distinct signatures of the gut microbiome. Mov Disord, 2017; 32: 739-49.
54. Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease. A clinico-pathological study of 100 cases. J Neurol Neurosurg Psychiatry, 1992; 55: 181-4.
55. Chaudhuri KR, Schapira AH. Non-motor symptoms of Parkinson's's disease: Dopaminergic pathophysiology and treatment. Lancet Neurol, 2009; 8: 464-74.
56. Hely MA, Reid WG, Adena MA, Halliday GM, Morris JG. The Sydney multicenter study of Parkinson's's disease: The inevitability of dementia at 20 years. Mov Disord, 2008; 23: 837-44.
57. Jankovic J, McDermott M, Carter J, Gauthier S, Goetz C, Golbe L, et al. Variable expression of Parkinson's disease: A base-line analysis of the DATATOP cohort. The Parkinson's Study Group. Neurology, 1990; 40: 1529-34.
58. Lim SY, Lang AE. The nonmotor symptoms of Parkinson's disease-An overview. Mov Disord, 2010; 25(1): S123-S130.
59. Noyce AJ, Bestwick JP, Silveira-Moriyama L, Hawkes CH, Giovannoni G, Lees AJ, et al. Meta-analysis of early nonmotor features and risk factors for Parkinson's disease. Ann Neurol, 2012; 72: 893-901.
60. Salat D, Noyce AJ, Schrag A, Tolosa E. Challenges of modifying disease progression in pre-diagnostic Parkinson's disease. Lancet Neurol, 2016; 15: 637-48.
61. Postuma RB, Aarsland D, Barone P, Bum DJ, Hawkes CH, Oertel CH, et al. Identifying prodromal Parkinson's disease: Pre-motor disorders in Parkinson's disease. Mov Disord, 2012; 27: 617-26.
62. Lohle M, Storch A, Reichmann H. Beyond tremor and rigidity: Non-motor features of Parkinson's Disease. J Neural Transm (Vienna), 2009; 116: 1483-92.
63. Aarsland D, Beyer MK, Kurz MW. Dementia in Parkinson's disease. Curr Op Neurol, 2008; 21: 676-82.
64. Xiao Q, Chen S, Le W. Hyposmia: A possible biomarker of Parkinson's's disease. Neurosci Bull, 2014; 30: 134-40.
65. Rizzo G, Copetti M, Arcuti S, Martino D, Fontana A, Logroscino G. Accuracy of clinical diagnosis of Parkinson's disease: A systematic review and meta-analysis. Neurology, 2016; 86: 566-76.
66. Stoessl AJ, Lehericy S, Strafella AP. Imaging insights into basal ganglia function, Parkinson's disease, and dystonia. Lancet, 2014; 384: 532-44.
67. Politis M. Neuroimaging in Parkinson's disease: From research setting to clinical practice. Nat Rev Neurol., 2014; 10: 708-22.
68. Ibrahim N, Kusmirek J, Struck AF, Floberg JM, Perlman SB, Gallagher C, et al. The sensitivity and specificity of F‐DOPA PET in a movement disorder clinic. Am J Nucl Med Mol Imaging, 2016; 6: 102-9.
69. Ishikawa T, Dhawan V, Kazumata K, Chaly T, Mandel F, Neumeyer J, et al. Comparative nigrostriatal dopaminergic imaging with iodine‐123‐beta CIT‐ FP/SPECT and fluorine‐18‐FDOPA/PET. J Nucl Med., 1996; 37: 1760-5.
70. Eshuis SA, Maguire RP, Leenders KL, Jonkman S, Jager PL. Comparison of FP-CIT SPECT with F-DOPA PET in patients with de novo and advanced Parkinson's's disease. Eur J Nucl Med Mol Imaging, 2006; 33: 200-9.
71. Eshuis SA, Jager PL, Maguire RP, Jonkman S, Dierckx RA, Leenders KL, et al. Direct comparison of FP-CIT SPECT and F-DOPA PET in patients with Parkinson's disease and healthy controls. Eur J Nucl Med Mol Imaging, 2009; 36: 454-62.
72. Lehéricy S, Sharman MA, Santos CLD, Paquin R, Gallea C. Magnetic resonance imaging of the

substantia nigra in Parkinson's's disease. Mov Disord, 2012; 27: 822-30.
73. Mahlknecht P, Hotter A, Hussl A, Esterhammer R, Schocke M, Seppi K. Significance of MRI in diagnosis and differential diagnosis of Parkinson's disease. Neurodegener Dis., 2010; 7: 300-18.
74. Treglia G, Cason E, Stefanelli A, Cocciolillo F, Di Giuda D, Fagioli G, et al. MIBG scintigraphy in differential diagnosis of Parkinsonism: A meta-analysis. Clin Auton Res., 2012; 22: 43-55.
75. Chen-Plotkin AS. Unbiased approaches to biomarker discovery in neurodegenerative diseases. Neuron, 2014; 84: 594-607.
76. Swanson CR, Berlyand Y, Xie SX, Alcalay RN, Chahine LM, Chen-Plotkin AS. Plasma ApoA1 associates with age at onset and motor severity in early Parkinson's disease patients. Mov Disord, 2015; 30: 1648-56.
77. Schapira AHV. Recent developments in biomarkers in Parkinson's disease. Curr Opin Neurol, 2013; 26: 395-400.
78. Miyasaki JM, Martin W, Suchowersky O, Weiner WJ, Lang AE. Practice parameter: Initiation of treatment for Parkinson's disease: An evidence-based review: Report of the quality standards subcommittee of the American Academy of Neurology. Neurology, 2002; 58: 11-17.
79. Antonini A, Bernardi L, Calandrella D, Mancini F, Plebani M. Rotigotine transdermal patch in the management of Parkinson's disease (PD) and its night-time use for PD-related sleep disorders. Funct Neurol, 2010; 25: 21-5.
80. Fernandez HH, Vanagunas A, Odin P, Espay AJ, Hauser RA, Standaert DG, et al. Levodopa-carbidopa intestinal gel in advanced Parkinson's disease open-label study: Interim results. Parkinsonism Relat Disord, 2013; 19: 339-45.
81. Olanow CW, Kieburtz K, Odin P, Espay AJ, Standaert DG, Fernandez HH, et al. Continuous intrajejunal infusion of levodopa-carbidopa intestinal gel for patients with advanced Parkinson's disease: A randomised, controlled, double-blind, double-dummy study. Lancet Neurol, 2014; 13: 141-49.
82. Poewe W., Antonini A. Novel formulations and modes of delivery of levodopa. Mov Disord, 2015; 30: 114-20.
83. Fox SH, Katzenschlager R, Lim S-Y, Ravina B, Seppi K, Coelho M, et al. The Movement Disorder Society evidence-based medicine review update: Treatments for the motor symptoms of Parkinson's disease. Mov Disord, 2011; 26: S2-41.
84. Connolly B, Lang AE. Pharmacological treatment of Parkinson's disease: A review. JAMA, 2014; 311: 1670-83.
85. LeWitt PA, Fahn S. Levodopa therapy for Parkinson's disease: A look backward and forward. Neurology, 2016; 86: S3-S12.
86. Olanow CW, Obeso JA, Stocchi F. Continuous dopamine-receptor treatment of Parkinson's disease: Scientific rationale and clinical implications. Lancet Neurol, 2006; 5: 677-87.
87. Cenci MA. Presynaptic mechanisms of l-DOPA-induced dyskinesia: The findings, the debate, and the therapeutic implications. Front Neurol, 2014; 5: 242.
88. Hauser RA, Ellenbogen AL, Metman LV, Hsu A, O'Connell MJ, Modi NB, et al. Crossover comparison of IPX066 and a standard levodopa formulation in advanced Parkinson's disease. Mov Disord, 2011; 26: 2246-52.
89. Hauser RA, Hsu A, Kell S, Espay AJ, Sethi K, Stacy M, et al. Extended-release carbidopa-levodopa (IPX066) compared with immediate-release carbidopa-levodopa in patients with Parkinson's disease and motor fluctuations: A phase 3 randomised, double‐blind trial. Lancet Neurol, 2013; 12: 346- 56.
90. Pahwa R, Lyons KE, Hauser RA, Fahn S, Jankovic J, Porcher E, et al. Randomized trial of IPX066, carbidopa/levodopa extended release, in early Parkinson's disease. Parkinsonism Relat Disord, 2014; 20: 142-8.
91. Stocchi F, Hsu A, Khanna S, Ellenbogen A, Mahler A, Liang G, et al. Comparison of IPX066 with carbidopa-levodopa plus entacapone in advanced PD patients. Parkinsonism Relat Disord, 2014; 20: 1335-40.
92. Waters CH, Nausieda P, Dzyak L, Spiegel J, Rudzinska M, Silver DE, et al. Long-term treatment with extended-release carbidopa-levodopa (IPX066) in early and advanced Parkinson's disease: A 9-month open-label extension trial. CNS Drugs, 2015; 29: 341-50.
93. Dhall R, Kreitzman DL. Advances in levodopa therapy for Parkinson's disease: Review of RYTARY (carbidopa and levodopa) clinical efficacy and safety. Neurology, 2016; 86: S13‐24.
94. Fernandez HH, Standaert DG, Hauser RA, Lang AE, Fung VS, Klostermann F, et al. Levodopa-carbidopa intestinal gel in advanced Parkinson's disease: Final 12-month, open-label results. Mov Disord, 2015; 30: 500-9.
95. LeWitt PA, Friedman H, Giladi N. Accordion pill carbidopa/ levodopa for improved treatment of advanced Parkinson's disease symptoms. Mov Disord, 2012; 27(1): S408.
96. Le Witt P, Friedman H, Giladi N. Sustained- release carbidopa-levodopa (accordian pill) in patients with advanced Parkinson's disease: Pharmacokinetic and clinical experience. Mov Disord, 2013; 28(1): S499.
97. LeWitt PA, Giladi N, Gurevich T. Accordion pill carbidopa/ levodopa (AP-CD/LD) for treatment of advanced Parkinson's disease (PD). Mov Disord, 2014; 29(1): S668.
98. Caraco Y, Oren S, LeWitt P. Constant therapeutic levodopa (LD) plasma concentrations maintained by continuous subcutaneous (SC) administration of ND-0612, a novel formulation of LD/carbidopa (CD). Mov Disord, 2013; 28(1): S452.

99. Giladi N, Caraco Y, Gurevich T, Djaldetti R. Pharmacokinetics and safety of ND0612L (levodopa/carbidopa for subcutaneous infusion): Results from a phase II study in moderate to severe Parkinson's disease. Neurology, 2015; 84(P1): 187.
100. Muller T, Kuoppamaki M, Vahteristio M, Aho V. Novel levodopa product ODM-101 vs levodopa/carbidopa/entacapone in Parkinson's disease with response fluctuations. Mov Disord, 2013; 28: S146.
101. Lewitt PA, Hauser RA, Grosset DG, Stocchi F, Saint-Hilaire MH, Ellenbogen A, et al. A randomized trial of inhaled levodopa (CVT-301) for motor fluctuations in Parkinson's disease. Mov Disord, 2016; 31: 1356-65.
102. Luinstra M, Grasmeijer F, Hagedoorn P, Moes JR, Frijlink HW, de Boer AH. A levodopa dry powder inhaler for the treatment of Parkinson's disease patients in off periods. Eur J Pharm and Biopharm, 2015; 97: 22-29.
103. PD MED Collaborative Group. Long-term effectiveness of dopamine agonists and monoamine oxidase B inhibitors compared with levodopa as initial treatment for Parkinson's disease (PD MED): A large, open-label, pragmatic randomised trial. Lancet, 2014; 384: 1196-205.
104. Lang AE, Marras C. Initiating dopaminergic treatment in Parkinson's disease. Lancet, 2014; 384: 1164-1166.
105. Jankovic J, Poewe W. Therapies in Parkinson's disease. Curr Opin. Neurol, 2012; 25: 433-47.
106. Frankel JP, Lees AJ, Kempster PA, Stern GM. Subcutaneous apomorphine in the treatment of Parkinson's disease. J Neurol Neurosurg Psychiatry, 1990; 53: 96-101.
107. Katzenschlager R, Hughes A, Evans A, Manson AJ, Hoffman M, Swinn Let al. Continuous subcutaneous apomorphine therapy improves dyskinesias in Parkinson's disease: A prospective study using single-dose challenges. Mov Disord, 2005; 20: 151-7.
108. Birkmayer W, Riederer P, Ambrozi L, Youdim MB. Implications of combined treatment with 'Madopar' and L-deprenil in Parkinson's disease. A long-term study. Lancet, 1977; 1: 439-43.
109. Palhagen S, Heinonen E. Use of selegiline as monotherapy and in combination with levodopa in the management of Parkinson's disease: Perspectives from the MONOCOMB study. Progress inNeurotherapeutics and Neuropsychopharmacology, 2008; 3: 49-71.
110. Mizuno Y, Hattori N, Kondo T, Nemoto M, Origasa H, Takahashi R, et al. A randomized double-blind placebo-controlled phase III trial of selegiline monotherapy for early Parkinson's disease. Clin Neuropharmacol, 2017; 40: 201-7.
111. Cereda E, Cilia R, Canesi M, Tesei S, Mariani CB, Zecchinelli AL, et al. Efficacy of rasagiline and selegiline in Parkinson's disease: A head-to-head 3-year retrospective case-control study. J Neurol, 2017; 264: 1254-63.
112. deSouza RM, Schapira A. Safinamide for the treatment of Parkinson's disease. Expert Opin Pharmaco, 2017; 18: 937-43.
113. Schapira AH, Fox SH, Hauser RA, Jankovic J, Jost WH, Kenney C, et al. Assessment of safety and efficacy of safinamide as a levodopa adjunct in patients with Parkinson's disease and motor fluctuations: A randomized clinical trial. JAMA Neurol, 2017; 74: 216-24.
114. Muller T. Catechol-O-methyltransferase inhibitors in Parkinson's disease. Drugs, 2015; 75: 157-74.
115. Bonifácio MJ, Palma PN, Almeida L, Soares-da-Silva P. Catechol-O-methyltransferase and its inhibitors in Parkinson's disease. CNS Drug Reviews, 2007; 13: 352-79.
116. Learmonth DA, Vieira-Coelho MA, Benes J, Alves PC, Borges N, Freitas AP, et al. Synthesis of 1-(3,4-dihydroxy-5-nitrophenyl)- 2-phenyl-ethanone and derivatives as potent and long-acting peripheral inhibitors of catechol-O-methyltransferase. J Med Chem., 2002; 45: 685-95.
117. Rodrigues BF, Ferreira JJ. Opicapone for the treatment of Parkinson's disease. Expert Opin Pharmacother, 2017; 18: 445-53.
118. Kalia LV, Brotchie JM, Fox SH. Novel nondopaminergic targets for motor features of Parkinson's's disease: Review of recent trials. Mov Disord, 2013; 28: 131-44.
119. Yarnall A, Rochester L, Burn DJ. The interplay of cholinergic function, attention, and falls in Parkinson's's disease. Mov Disord, 2011; 26: 2496-503.
120. Chung KA, Lobb BM, Nutt JG, Horak FB. Effects of a central cholinesterase inhibitor on reducing falls in Parkinson's disease. Neurology, 2010; 75: 1263-9.
121. Emre M, Aarsland D, Albanese A, Byrne EJ, Deuschl G, De Deyn PP, et al. Rivastigmine for dementia associated with Parkinson's disease. N Engl J Med., 2004; 351: 2509-18.
122. Henderson EJ, Lord SR, Close JC, Lawrence AD, Whone A, Ben-Shlomo T. The respond trial—rivastigmine to stabilise gait in Parkinson's's disease a phase II, randomised, double blind, placebo controlled trial to evaluate the effect of rivastigmine on gait in patients with Parkinson's disease who have fallen. BMC Neurol, 2013; 13: 188.
123. Seppi, K, Weintraub D, Coelho M, Perez-Lloret S, Fox SH, Katzenschlager R, et al. The Movement Disorder Society evidence-based medicine review update: Treatments for the non-motor symptoms of Parkinson's disease. Mov Disord, 2011; 26: S42-S80.
124. Connolly B, Fox SH. Treatment of cognitive, psychiatric, and affective disorders associated

with Parkinson's disease. Neurotherapeutics, 2014; 11: 78-91.
125. Cummings J, Isaacson S, Mills R, William H, Chi-Burris K, Corbett A, et al. Pimavanserin for patients with Parkinson'sdisease psychosis: A randomised, placebo-controlled phase 3 trial. Lancet, 2014; 383: 533-40.
126. Pahwa R, Factor SA, Lyons KE, Ondo WG, Gronseth G, Bronte-Stewart H, et al. Practice parameter: Treatment of Parkinson's disease with motor fluctuations and dyskinesia (an evidence‐based review): Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology, 2006; 66: 983-95.
127. Oertel W, Eggert K, Pahwa R, Tanner CM, Hauser RA, Pahwa R, et al. Randomized, placebo-controlled trial of ADS-5102 (amantadine) extended-release capsules for levodopa-induced dyskinesia in Parkinson's disease (EASE LID 3). Move Disord, 2017; 32: 1701-9.
128. Perez-Lloret S, Rey MV, Pavy-Le Traon A, Rascol O. Emerging drugs for autonomic dysfunction in Parkinson's disease. Expert Opin Emerg Drugs, 2013; 18: 39-53.
129. Karuppagounder SS, Brahmachari S, Lee Y, Dawson VL, Dawson TM, Ko HS. The c-Abl inhibitor, nilotinib, protects dopaminergic neurons in a preclinical animal model of Parkinson's disease. Sci Rep., 2014; 4: 4874.
130. Imam SZ, Trickler W, Kimura S, Binienda ZK, Paule MG, Slikker W Jr, et al. Neuroprotective efficacy of a new brain‐penetrating C-Abl inhibitor in a murine Parkinson's disease model. PLoS one, 2013; 8: e65129.
131. Zhou, ZH, Wu YF, Wang X, Hahn YZ. The c-Abl inhibitor in Parkinson's disease. Neurol Sci., 2017; 38: 547-52.
132. Kalia SK, Sankar T, Lozano AM. Deep brain stimulation for Parkinson's disease and other movement disorders. Curr Opin Neurol, 2013; 26: 374-80.
133. Schuepbach WMM, Rau J, Knudsen K, Krack VP, Timmermann L, Halbig TD, et al. Neurostimulation for Parkinson's disease with early motor complications. N Engl J Med., 2013; 368: 610-22.
134. Manjunath M, Yadav R, Dwarakanath S, Jhunjhunwala K, Jafar A, Surathi P, Lenka A, Stezin A, Sampath S, Pal PK. Experience of pallidal deep brain stimulation in dystonia at a tertiary care centre in India: An initial experience. Neurol India, 2017; 65: 1322-9
135. Pandey S. When to do deep brain stimulation surgery in Parkinson disease? Early or late?. Neurol India, 2016; 64: 8-9.
136. Bronstein JM, Tagliati M, Alterman RL, Lozano AM, Volkmann J, Stefani A, et al. Deep brain stimulation for Parkinson's disease: An expert consensus and review of key issues. Arch Neurol, 2011; 68: 165-71.
137. Deuschl G, Agid Y. Subthalamic neurostimulation for Parkinson's disease with early fluctuations: Balancing the risks and benefits. Lancet Neurol, 2013; 12: 1025-34.
138. Pandey S, Sarma N. Deep brain stimulation: Current status. Neurol India, 2015; 63: 9-18.
139. Levine CB, Fahrbach KR, Siderowf AD, Estok RP, Ludensky VM, Ross SD, et al. Diagnosis and treatment of Parkinson's disease: A systematic review of the literature: Summary. 2003 May. In: AHRQ Evidence Report Summaries. Rockville (MD): Agency for Healthcare Research and Quality (US), 1998-2005; 57. Available from: https://www.ncbi.nlm.nih.gov/books/NBK11895. [Last accessed on 2018 Jan 22].
140. Voges J, Hilker R, Bötzel K, Kiening KL, Kloss M, Kupsch A, et al. Thirty days complication rate following surgery performed for deep-brain-stimulation. Mov Disord, 2007; 22: 1486-9.