Parkinson's Disease: Diagnosis, Therapeutics & Management

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Introduction

Parkinson disease is a chronic, progressive neurodegenerative movement which affects about 1% of population over the age of 60. In Parkinson disease there is loss of dopaminergic neurons in substantia nigra\(^{[1],[2]}\) which affects nerve cells (neurons) in an area of the brain near the neck. These nerve cells normally produce dopamine, a chemical that transmits signals between areas in the brain. These signals coordinate smooth, balanced muscle movement. Parkinson’s disease causes the neurons to die, leading to a lack of dopamine in the brain. With the loss of dopamine, patients lose the ability to control their body movements.\(^{[3]}\)

People with PD classically present with the symptoms and signs associated with parkinsonism, namely hypokinesia (ie poverty of movement), bradykinesia (ie slowness of movement), rigidity and rest tremor. Parkinsonism can also be caused by drugs and less common conditions such as progressive supranuclear palsy (PSP) and multiple system atrophy (MSA). Although PD is predominantly a movement disorder, other impairments frequently develop, including psychiatric problems such as depression and dementia. Autonomic disturbances and pain may later ensue, and the condition progresses to cause significant disability and handicap with impaired quality of life for the affected person. Family and carers may also be affected indirectly.\(^{[2]}\)

Parkinson affects various functional activities such as balance, walking, speech, handwriting, typing, fastening buttons, driving, and many other simple, or complex but familiar and routine activities.\(^{[4]}\) Early in the course of the disease, the most obvious symptoms are movement-related, including shaking, rigidity, slowness of movement and difficulty with walking and gait. Later, cognitive and behavioural problems may arise, with dementia commonly occurring in the advanced stages of the disease. Other symptoms include sensory, sleep and emotional problems. PD is more common in the elderly with most cases occurring after the age of 50. The main motor symptoms are collectively called parkinsonism, or a "parkinsonian syndrome".

Parkinson's disease is often defined as a Parkinsonian syndrome that is idiopathic (having no known cause), although some atypical cases have a genetic origin. Many risk and protective factors have been investigated. The clearest evidence is for an increased risk of PD in people exposed to certain pesticides and a reduced risk in tobacco smokers. The pathology of the disease is characterized by the accumulation of a protein called alpha-synuclein into inclusions called Lewy bodies in neurons, and from insufficient formation and activity of dopamine produced in certain neurons of parts of the midbrain. Diagnosis of typical cases is mainly based on symptoms, with tests such as neuroimaging being used for confirmation. Modern treatments are effective at managing the early motor symptoms of the disease, mainly through the use of levodopa and dopamine agonists. As the disease progresses and dopamine neurons continue to be lost, a point eventually arrives at which these drugs become ineffective at treating the symptoms and at the same time produce a complication called dyskinesia, marked by involuntary writhing movements. Diet and some forms of rehabilitation have shown some effectiveness at alleviating symptoms. Surgery and deep brain stimulation have been used to reduce motor symptoms as a last resort in severe cases where drugs are ineffective. Research directions include a search of new animal models of the disease and investigations of the potential usefulness of gene therapy, stem cell transplants and neuroprotective agents. The disease is named after the English doctor James Parkinson, who published the first detailed description in An Essay on the Shaking Palsy in 1817. The main motor symptoms are collectively called parkinsonism, or a "parkinsonian syndrome". Parkinson's disease is often defined as a parkinsonian syndrome that is idiopathic (having no known cause), although some atypical cases have a genetic origin. Many risk and protective factors have been investigated. The clearest evidence is for an increased risk of PD in people exposed to certain pesticides and a reduced risk in tobacco smokers. The pathology of the disease is characterized by the accumulation of a protein called alpha-synuclein into inclusions called Lewy bodies in neurons, and from insufficient formation and activity of dopamine produced in certain neurons of parts of the midbrain. Diagnosis of typical cases is mainly based on symptoms, with tests such as neuroimaging being used for confirmation. Modern treatments are effective at managing the early motor symptoms of the disease, mainly through the use of levodopa and dopamine agonists. As the disease progresses and dopamine neurons continue to be lost, a point eventually arrives at which these drugs become ineffective at treating the symptoms and at the same time produce a complication called dyskinesia, marked by involuntary writhing movements. Diet and some forms of rehabilitation have shown some effectiveness at alleviating symptoms. Surgery and deep brain stimulation have been used to reduce motor symptoms as a last resort in severe cases where drugs are ineffective. Research directions include a search of new animal models of the disease and investigations of the potential usefulness of gene therapy, stem cell transplants and neuroprotective agents. The disease is named after the English doctor James Parkinson, who published the first detailed description in An Essay on the Shaking Palsy in 1817. The main motor symptoms are collectively called parkinsonism, or a "parkinsonian syndrome".
Parkinsonian brain varies from one individual to another. The anatomical distribution of the Lewy bodies is often directly related to the expression and degree of the clinical symptoms of each individual. Diagnosis of typical cases is mainly based on symptoms, with tests such as neuroimaging being used for confirmation. Modern treatments are effective at managing the early motor symptoms of the disease, mainly through the use of levodopa and dopamine agonists. As the disease progresses and dopaminergic neurons continue to be lost, a point eventually arrives at which these drugs become ineffective at treating the symptoms and at the same time produce a complication called dyskinesia, marked by involuntary writhing movements. Diet and some forms of rehabilitation have shown some effectiveness at alleviating symptoms. Surgery and deep brain stimulation have been used to reduce motor symptoms as a last resort in severe cases where drugs are ineffective. Research directions include investigations into new animal models of the disease and of the potential usefulness of gene therapy, stem cell transplants and neuroprotective agents. Medications to treat non-movement-related symptoms of PD, such as sleep disturbances and emotional problems, also exist. Several major organizations promote research and improvement of quality of life of those with the disease and their families. Public awareness campaigns include Parkinson's disease day (on the birthday of James Parkinson, April 11) and the use of a red tulip as the symbol of the disease.[8]

A region-specific selective loss of dopaminergic (DAergic) neuromelanin-containing neurons from the pars compacta of the substantia nigra (SNpc) is the pathological hallmark of PD. However, cell loss in the locus coeruleus, dorsal nuclei of the vagus, raphe nuclei, nucleus basalis of Meynert, and some other catecholaminergic brain stem structures including the ventrotegmental area also exists.[9] This neuronal cell loss is accompanied by intraneuronal inclusions: the Lewy body (LB). α-synuclein represents one of the most abundant proteins found in LBs, and it may play a pivotal role in the progression of PD. Since the degree of DAergic neuronal loss correlates with the severity of PD, levodopa (L-dopa), a chemical precursor of dopamine (DA) is the most effective drug for the symptomatic treatment of PD. Unfortunately, the clinical efficacy often declines after long-term levodopa replacement therapy (DA replacement therapy; DRT), and additionally, disabling adverse effects appear, most notably motor fluctuation such as the wearing-off or on-off phenomenon and dyskinesia. DA receptor agonists are even regarded as first choice in de novo and young PD patients to delay onset of levodopa therapy. They are also used as combination therapy together with levodopa to retard the development of motor complications in advanced stages of PD. DA receptor agonists appear to act by not only direct stimulation of postsynaptic DA receptors but also presynaptic receptors. However, DA receptor agonists may be slightly less potent medicines than levodopa and may be poorly tolerated by older PD patients. Additionally, long-term therapy with traditional ergot DA receptor agonists may result in valvular heart disease. A lack of spontaneity or reduced motivation (i.e., anhedonia) is the most troublesome issue in the therapy of advanced stage of PD patients. Medicines with high affinity for the DA receptors potentially improve these symptoms, however, hedonistic dysregulation syndrome or DA dysregulation syndrome (DDS) has emerged as a serious issue in PD with long-term DRT.[10]

1.1 PHYSIOLOGICAL CHARACTERIZATION OF DOPAMINE RECEPTOR

DA is a prototypical slow neurotransmitter that plays significant roles in a variety of not only motor functions but also cognitive, motivational, and neuroendocrine. All members of receptors share a number of structural characteristics such as

(1) seven hydrophobic transmembrane stretches
(2) significant amount of amino acid sequence identity between different subfamily within these transmembrane regions and posttranslational modifications such as glycosylation and phosphorylation.
(3) conserved amino acid residues that are involved in interaction of G-protein and in binding agonists.

On the basis of biochemical, pharmacological, and physiological criteria, DA receptors have been classified into two subfamilies, termed D1 and D2. Genes encoding members of the DA receptor family are part of a larger superfamily of genes comprising the G protein-coupled superfamily receptors (GPCRs). G protein-related actions of GPCRs are mediated by a subset of the heteromeric G protein subtypes. In general, G proteins consist of three protein subunits α, β, and γ. The α-subunits are functionally classified into several classes such as G_{α1}, G_{α2}, G_{α3}, G_{α4}, G_{α5}, and G_{α12} and determine actions of GPCRs. Upon ligand binding, G_{α} proteins release GDP and newly bind GTP, then βγ-complex dissociates from α-subunit. Both the α-subunit and the βγ-complex can transduce the signal to activate a number of effector systems. For example, the activation of G_{α} subunit stimulates adenylate cyclase (AC), whereas the activation of G_{α} subunit inhibits AC.
The D1 subfamily, including D1 and D5, are generally coupled to G\textsubscript{ai} and stimulate the production of cAMP and activate protein kinase A (PKA) (Table). The D2 subfamily, including D2, D3, and D4, are coupled to G\textsubscript{ai} and G\textsubscript{aii} and downregulate the production of cAMP via inhibiting AC, resulting in a decrease in PKA activity (Table). One of a PKA substrate, DA and cAMP-regulated phosphoprotein 32-kDa (DARPP-32) is known to be involved in DA receptor signaling. DARPP-32 is a multifunctional phosphoprotein and acts as an integrator involved in the modulation of cell signaling in response to multiple neurotransmitters, including DA. Activated DARPP-32 inhibits protein phosphatase 1 (PP1) and results in activation of mitogen-activated protein (MAP) kinases, such as extracellular signal-regulated kinase (ERK) and MAP/ERK kinase (MEK). MAP kinases play a pivotal role in the regulation of synaptic plasticity and have been shown to be signaling intermediates that are involved in the regulation of DA-associated behavior.

see illustration 1

The D1 receptor subfamily is expressed in multiple brain regions, including the cortex, hippocampus, amygdala, and most intensively, the striatum, olfactory bulb, and substantia nigra. In the cortex and hippocampus, D1 receptors are expressed in a predominately localized in shafts (Table). D5 receptors coexpress D1 receptors in cortical pyramidal neurons, and are predominantly localized in shafts (Table). The expression and localization of D2 receptor subfamily have also been investigated at the cellular and subcellular levels. There are two major D2 receptor variants that have been termed D2L and D2S. D2L contains an additional 29 amino acids in the third cytoplasmic loop. D2L and D2S expressed mainly postsynaptically and presynaptically, respectively. D2S might function as an autoreceptor that decreases DA release, resulting in decreased locomotor activity; however, activation of postsynaptic D2 receptors stimulates locomotion. D2 receptors, the predominant subtype of this class, are expressed in the pituitary gland and basal ganglia (striatum and substantia nigra) and localized in both pre- and postsynaptic structures. Presynaptically, D2 receptors are associated with both forebrain projecting DAergic afferents and glutamatergic terminals in the striatum and prefrontal cortex (PFC). Postsynaptically, D2 receptors are concentrated in shafts and spines of both cortical pyramidal neurons and striatopallidal neurons. While both D1 and D2 receptors are abundant in the striatum, the expression pattern of D1 and D2 receptors in the axon terminals, dendrites, and spines are obviously different by electron microscopic analysis. These findings indicate segregated circuit via D1 and D2 receptors in the striatum. D3 receptors are expressed in the olfactory tubercle, nucleus accumbens, striatum, and substantia nigra. Importantly, D3 receptors are also found in limbic system such as hippocampus, septum, or mammillary nuclei of the hypothalamus. The D4 receptors, known to have an unusually high affinity for the atypical neuroleptic clozapine, are localized in the frontal cortex, medulla, amygdala, hypothalamus, mesencephalon, and nucleus accumbens. It has been shown that lower level of D4 receptor expression is detected in the basal ganglia. In the rat central nervous system, the relative abundance of the DA receptors is D1 > D2 > D3 > D5 > D4.

It has long been suggested that DA dysfunction plays a major role in the pathogenesis of schizophrenia. Antipsychotics such as chlorpromazine and haloperidol act primarily as D2 receptor antagonists (Table). These D2 receptor blockades are effective in attenuating positive symptoms of schizophrenia (e.g., hallucinations and delusions) associated with acute episodes as well as preventing psychotic relapse. Wong et al. demonstrated that D2 receptor density in the caudate nucleus is elevated in drug-naïve schizophrenia patients with positron emission tomography (PET) study. Breier et al. also showed that patients with schizophrenia compared with healthy volunteers had significantly greater amphetamine-related reductions in radioligand \([^{11}C]\) raclopride-specific binding ratio with PET. This result indicates that schizophrenia is associated with elevated amphetamine-induced synaptic DA concentrations (Table a). Studies also showed that increased striatal DA synthesis capacity in unmedicated schizophrenia patients. These results indicated that the pool of releasable DA is increased in patients with schizophrenic psychosis. Kramer et al. demonstrated that a selective D4 receptor agonist L-745870 is ineffective in patients with schizophrenia.

1.2 GENETIC MANUPULATION OF DOPAMINE RECEPTOR

The facts regarding the contribution of D1- and D2-type DA receptors in the genesis of the behavioral and neurochemical Parkinsonian phenotype have been provided by classic pharmacological approaches. Recently, genetically modified mice of DA receptors are also clarifying the significance of specific effects of DA-related neuronal physiology and pathophysiology.
In 1994, Xu et al. and Drago et al. generated D1 receptor-deficient mice. Xu et al. demonstrated that these mice also appear to exhibit a general behavioral hyperactivity during both phases of light-dark cycle; however, Drago et al. described that the locomotor activity of knockout mice did not differ significantly from that of normal control except for displaying a significant decrease in rearing behavior. Test for akinesia were normal. Moreover, Gantois et al. used a Cre/Lox transgenic approach to generate an animal model in which D1 receptor-expressing cells are progressively ablated in the postnatal brain. Whereas no differences in locomotor activity were found between the mutated mice and control, mutant showed hyperactivity in a novel environment. Abnormal oral behaviors such as chewing and sifting, limb-clasping dystonic posture, and spontaneous seizure are also found in mutant mice. Increased locomotor activity of D1 receptor-deficient mice is cancelled with a D1/D5 receptor antagonist SCH 23390, indicating that D1 and D5 receptors can exert distinct and complex physiological actions in locomotor activity.

In contrast to disruption of D1 receptor subfamily, spontaneous PD-like locomotor impairment is found in D2 receptor subfamily knockout mice. D2 receptor-deficient mice exhibit significantly reduced spontaneous movements in behavioral tests. However, Kelly et al. demonstrated that striatal tissue content of monoamines and their metabolites from C57BL/6 congenic strain of D2 receptor mutant mice did not differ from those of wild type, and they found no evidence for supersensitive D1, D3, or D4 DA receptors in the D2 receptor knockout mice. Recently, Tinsley et al. showed that LB-like cytoplasmic inclusions containing α-synuclein and ubiquitin were present in substantia nigra neurons of older D2 receptor knockout mice (>18 months old). Diffuse cytosolic α-synuclein immunoreactivity in nigral neurons increased with age in both wild-type and knockout mice, most likely because of redistribution of α-synuclein from striatal terminals to substantia nigra cell bodies. Gene and protein expression studies showed endoplasmic reticulum (ER) stress and changes in trafficking and autophagic pathways, indicating that these changes were accompanied by a loss of DA terminals in the dorsal striatum. Wang et al. showed behavioral alteration in the D2L receptor-deficient mice. The knockout mice display reduced locomotor activity and rearing behavior and reduced sensitivity to haloperidol-induced catalepsy. These results indicate that D2L might have a bigger impact on certain types of motor functions, and blockade of D2L might contribute more than blockade of D2S to the extrapyramidal side effects (or parkinsonism) that are commonly associated with typical antipsychotic drugs. In addition, D2 receptor plays a pivotal role in the striatal processing of motor information received from the cortex in the generation of striatal synaptic plasticity. Whereas tetanic stimulation of corticostratal fibers produced long-term potentiation (LTP) in the D2 receptor-null mice, long-term depression (LTD) is usually recorded in wild-type mice. The LTP in knockout mice is blocked by an NMDA receptor antagonist, indicating that D2 receptor is involved in the formation of striatal LTD and exerts a negative control in the expression of an NMDA-mediated long-term LTP at corticostratal synapses. Adenosine A2A receptors (A2AR) are known to coexpress D2 receptors in striatopallidal neurons, and A2AR-D2 receptor interaction modulates DA-mediated signaling. A2AR selective antagonist, (E)-1,3-diethyl-8-(3,4-dimethoxystyryl)-7-methyl-3,7-di hydro-1Hpurine-2,6-dione (KW-6002, Istradefylline), exhibits anti-Parkinsonian activities. Aoyama et al. demonstrated that locomotor impairment can be relieved by KW-6002 treatment in D2 receptor knockout mice. Furthermore, the level of the expression of enkephalin and substance P is elevated to normal levels after A2AR antagonist treatment. These results show that A2AR and D2 receptor have antagonistic and independent activities in controlling neuronal and motor functions in the basal ganglia.

Although D3 receptor-deficient mice do not exhibit parkinsonism, it is quite important to elucidate specific behavioral alteration in the knockout mice for understanding clinical features of pharmacotherapeutic DA receptor agonists in the treatment of PD. D3 mutant mice exhibit hyperactivity in novel and exploratory environment and rearing behavior. These mutant mice demonstrated that both D1- and D2-receptor-binding sites are present in the dorsal and ventral striatum and the distributions and the densities of both binding sites in the mutants and controls are qualitatively and quantitatively similar. Importantly, hyperactivity of mutant mice is caused by response to combinations of D1 and D2 receptor subfamily agonists, cocaine, and amphetamine. Carta et al. also showed that acute administration of cocaine resulted in increasing mRNA level of c-fos and dynorphin in the dorsal and ventral striatum of D3 receptor knockout mice, indicating D3 receptor plays a role on gene regulation in the DA system. Moreover, Schmauss found that c-fos mRNA levels expressed in response to D1 agonist or methamphetamine administration is significantly blunted in D3 receptor-deficient (and also D2 receptor-deficient) mice. D3 receptor mutants exhibit deficits in their
spatial working memory, and methamphetamine pretreatment does not rescue this memory deficit of D3 mutants. These results indicate that the constitutive inactivation of D3 receptors leads to a decrease in agonist-promoted D1 receptor activity. D'Agata et al. have investigated parkin expression profile in D3 knockout mice. Parkin protein has an E3 ubiquitin-ligase activity, and loss of parkin function may result in accumulation of unnecessary molecules that lead to the degeneration of neurons. Real-time PCR analysis showed a different quantitative expression of parkin gene in mutant compared to control mice. Furthermore, immunoreactivity of parkin showed a higher intensity in D3 receptor knockout mice compared to wild type by Western blot analysis using parkin mouse monoclonal antibody. Karasinska et al. generated mice lacking both D1 and D3 receptors and investigated psychostimulant-induced behavior. Administration of cocaine increased locomotor activity in wild-type and D3 knockout mice, failed to stimulate activity in D1 knockout mice, and reduced activity in D1/D3 knockout mice. Karasinska et al. discussed the significance of expression level of phosphorylated cAMP-responsive element-binding protein (pCREB) in the striatum. CREB is activated by phosphorylation in striatal regions following D4 receptor activation. Striatal pCREB levels following acute cocaine were increased in D3 mutant mice and decreased in D1 and D1/D3 mutant mice. The change of locomotor activity of D3 mutant mice is controversial. Jung et al. demonstrated that the activity of D2/D3 double mutants is significantly reduced not only when compared to wild type but also when compared to single D2 receptor mutants. They indicated that a relatively long observation period for locomotor activity is needed in D3 mutant mice because of their rapidly habituating hyperactivity.

D4 knockout mice show significantly reduced exploration behavior and rearing activity. Extent of improvement of locomotor activity is dramatically increased in D4 receptor-deficient mice than that of wild type of littermate following the administration of ethanol, cocaine, and amphetamine, indicating that knockout mice are more responsive to the locomotor stimulants than wild type. Falzone et al. described that the absence of D4 receptor increases avoidance behavior to unconditioned stimuli and does not impair behavioral reactions to fear-conditioned stimuli in two different approach/avoidance conflict paradigms. These results indicate that D4 receptor could play a pivotal role in the DAergic modulation of cortical signals triggered by environmental stimuli, because D4 receptor is physiologically expressed at highest levels in the prefrontal cortex and is the predominant D2-like receptor localized in this brain area.

Classification

The term parkinsonism is used for a motor syndrome whose main symptoms are tremor at rest, stiffness, slowing of movement and postural instability. Parkinsonian syndromes can be divided into four subtypes according to their origin: primary or idiopathic, secondary or acquired, hereditary parkinsonism, and parkinson plus syndromes or multiple system degeneration. Parkinson's disease is the most common form of parkinsonism and is usually defined as “primary” parkinsonism, meaning parkinsonism with no external identifiable cause. In recent years several genes that are directly related to some cases of Parkinson's disease have been discovered. As much as this can go against the definition of Parkinson's disease as an idiopathic illness, genetic parkinsonism disorders with a similar clinical course to PD are generally included under the Parkinson's disease label. The terms "familial Parkinson's disease" and sporadic Parkinson's disease can be used to differentiate genetic from truly idiopathic forms of the disease.

PD is usually classified as a movement disorder, although it also gives rise to several non-motor types of symptoms such as cognitive difficulties or sleep problems. Parkinson plus diseases are primary parkinsonisms which present additional features. They include multiple system atrophy, progressive supranuclear palsy, corticobasal degeneration and dementia with Lewy bodies.

In terms of pathophysiology, PD is considered a synucleinopathy due to an abnormal accumulation of alpha-synuclein protein in the brain in the form of Lewy bodies, as opposed to other diseases such as Alzheimer's disease where the brain accumulates tau protein in the form of neurofibrillary tangles. Nevertheless, there is clinical and pathological overlap between tauopathies and synucleinopathies. The most typical symptom of Alzheimer's disease, dementia, occurs in advanced stages of PD, while it is common to find neurofibrillary tangles in brains affected by PD. Dementia with Lewy bodies (DLB) is another synucleinopathy that has similarities with PD, and especially with the subset of PD cases with dementia. However the relationship between PD and DLB is complex and still has to be clarified. They may represent parts of a continuum or they may be separate diseases.
Brain & Its Movement

When a person initiates a movement, information from the senses, from parts of the brain that control planning, and from other brain regions travels to a region called the striatum. The striatum then interacts with other areas of the brain — the substantia nigra, globus pallidus, and thalamus — to send out signals that control balance and coordination. These signals travel to the cerebellum, which controls muscle coordination, and then finally down the spinal cord to peripheral nerves in the limbs, head, and torso, where they control the muscles.

The molecules that carry information through the brain and spinal cord are called neurotransmitters. Neurotransmitters are special chemicals produced by neurons that accumulate in tiny sacs at the end of nerve fibers. When stimulated, these sacs release neurotransmitters into the gap between neurons, called a synapse. The neurotransmitters cross the synapse and attach to proteins called receptors on the neighboring cell. These signals change the properties of the receiving cell. If the receiving cell is also a neuron, it will carry the signal on to the next cell. If the receiving cell is a muscle fiber, it will react to the stimulation by contracting, which creates movement.[9]

But in Parkinson Disease the primary area of brain is affected which is substantia nigra which contains a specialized set of neurons that send signals in the form of a neurotransmitter called dopamine. The signals travel to the striatum via long fibers called axons. The activity of this pathway controls normal movements of the body. When neurons in the substantia nigra degenerate, the resulting loss of dopamine causes the nerve cells of the striatum to fire excessively. This makes it impossible for people to control their movements, leading to the primary motor symptoms of Parkinson disease.[9]

Etiology

4.1 ENVIRONMENTAL FACTOR
Most people with Parkinson’s disease have idiopathic Parkinson’s disease (having no specific known cause). In most of the cases these disease is generally caused by various environmental factors. A small proportion of cases, however, can be attributed to known genetic factors. Other factors have been associated with the risk of developing PD, but no causal relationship has been proven. PD traditionally has been considered a non-genetic disorder in around 15% of individuals. At least 5% of people are now known to have forms of the disease that occur due to a mutation of one of several specific genes.

4.2 GENETIC FACTOR
Mutations in specific genes have been conclusively shown to cause PD. These genes include alpha-synuclein (SNCA), ubiquitin carboxy-terminal hydrolase L1 (UCH-L1), parkin (PRKN), leucine-rich repeat kinase 2 (LRRK2 or dardarin), PTEN-induced putative kinase 1 (PINK1), DJ-1 and ATP13A2. In most cases, people with these mutations will develop PD. With the exception of LRRK2, however, they account for only a small minority of cases of PD. The most extensively studied PD-related genes are SNCA and LRRK2. Mutations in genes including SNCA, LRRK2 and glucocerebrosidase (GBA) have been found to be risk factors for sporadic PD. Mutations in GBA are known to cause Gaucher’s disease. Genome-wide association studies, which search for mutated alleles with low penetrance in sporadic cases, have yielded few positive results, but such studies have been few in number and their size small. The role of the SNCA gene is important in PD because the alpha-synuclein protein is the main component of Lewy bodies. Missense mutations of the gene (in which a single nucleotide is changed), and duplications and triplications of the locus containing it have been found in different groups with familial PD. Missense mutations are rare. On the other hand, multiplications of the SNCA locus account for around 2% of familial cases. Multiplications have been found in asymptomatic carriers, which indicate that penetrance is incomplete or age-dependent. The LRRK2 gene (PARK8) encodes for a protein called dardarin. The name dardarin was taken from a Basque word for tremor, because this gene was first identified in families from England and the north of Spain. Mutations in LRRK2 are the most common known cause of familial and sporadic PD, accounting for up to 10% of individuals with a family history of the disease and 3% of sporadic cases. More than 40 different mutations of the gene have been found to be related to PD. All these mutations directly affect the dopaminergic neurons and causes loss of dopaminergic system in the body.

Sign & Symptoms

5.1 PRIMARY SYMPTOMS OF PARKINSON DISEASE
Bradykinesia: slowness in voluntary movement such as standing up, walking, and sitting down. This
happens because of delayed transmission signals from the brain to the muscles. This may lead to difficulty initiating walking, but when more severe can cause “freezing episodes” once walking has begun.\(^5\)\(^{[10]}\)

**Tremors:** often occur in the hands, fingers, forearms, foot, mouth, or chin. Typically, tremors take place when the limbs are at rest as opposed to when there is movement.

**Rigidity:** otherwise known as stiff muscles, often produce muscle pain that is increased during movement.

**Poor balance:** happens because of the loss of reflexes that help posture. This causes unsteady balance, which oftentimes leads to falls.

### 5.1.1 Motor

Four motor symptoms are considered **cardinal in PD:** tremor, rigidity, slowness of movement, and postural instability

**Tremor** is the most apparent and well-known symptom. It is the most common around 30% of individuals with PD do not have tremor at disease onset, most develop it as the disease progresses. It is usually a rest tremor: maximal when the limb is at rest and disappearing with voluntary movement and sleep. It affects to a greater extent the most distal part of the limb and at onset typically appears in only a single arm or leg, becoming bilateral later. Frequency of PD tremor is between 4 and 6 hertz (cycles per second).

A feature of tremor is “pill-rolling”, a term used to describe the tendency of the index finger of the hand to get into contact with the thumb and perform together a circular movement. The term derives from the similarity between the movement in PD patients and the earlier pharmaceutical technique of manually making pills.

**Bradykinesia** (slowness of movement) is another characteristic feature of PD, and is associated with difficulties along the whole course of the movement process, from planning to initiation and finally execution of a movement. Performance of sequential and simultaneous movement is hindered. Bradykinesia is the most disabling symptom in the early stages of the disease. Initial manifestations are problems when performing daily tasks which require fine motor control such as writing, sewing or getting dressed. Clinical evaluation is based in similar tasks such as alternating movement. Bradykinesia is not equal for all movements or times. It is modified by the activity or emotional state of the subject, to the point that some patients are barely able to walk yet can still ride a bicycle. Generally patients have less difficulty when some sort of external cue is provided.

**Rigidity** is stiffness and resistance to limb movement caused by increased muscle tone, an excessive and continuous contraction of muscles. In parkinsonism the rigidity can be uniform (lead-pipe rigidity) or ratchety (cogwheel rigidity). The combination of tremor and increased tone is considered to be at the origin of cogwheel rigidity. Rigidity may be associated with joint pain; such pain being a frequent initial manifestation of the disease. In early stages of Parkinson’s disease, rigidity is often asymmetrical and it tends to affect the neck and shoulder muscles prior to the muscles of the face and extremities. With the progression of the disease, rigidity typically affects the whole body and reduces the ability to move.\(^8\)

**Postural instability** is typical in the late stages of the disease, leading to impaired balance and frequent falls, and secondarily to bone fractures. Instability is often absent in the initial stages, especially in younger people. Up to 40% of the patients may experience falls and around 10% may have falls weekly, with number of falls being related to the severity of PD. Other recognized motor signs and symptoms include gait and posture disturbances such as festination (rapid shuffling steps and a forward-flexed posture when walking), speech and swallowing disturbances including voice disorders, mask-like face expression or small handwriting, although the range of possible motor problems that can appear is large.

### 5.1.2 Neuropsychiatric

Parkinson’s disease can cause **neuropsychiatric disturbances** which can range from mild to severe. This includes disorders of speech, cognition, mood, behaviour, and thought. Cognitive disturbances can occur in the initial stages of the disease and sometimes prior to diagnosis, and increase in prevalence with duration of the disease. The most common cognitive deficit in affected individuals is **executive dysfunction**, which can include problems with planning, cognitive flexibility, abstract thinking, rule acquisition, initiating appropriate actions and inhibiting inappropriate actions, and selecting relevant sensory information. Fluctuations in attention and slowed cognitive speed are among other cognitive difficulties. Memory is affected, specifically in recalling learned information. Nevertheless, improvement appears when recall is aided by cues. Visuospatial difficulties are also part of the disease, seen for example when the individual is asked to perform tests of facial recognition and perception of the orientation of drawn lines.\(^5\)

A person with PD has two to six times the risk of
suffering dementia compared to the general population. The prevalence of dementia increases with duration of the disease. Dementia is associated with a reduced quality of life in people with PD and their caregivers, increased mortality, and a higher probability of needing nursing home care. Behavior and mood alterations are more common in PD without cognitive impairment than in the general population, and are usually present in PD with dementia. The most frequent mood difficulties are depression, apathy and anxiety. Impulse control behaviors such as medication overuse and craving, binge eating, hypersexuality, or pathological gambling can appear in PD and have been related to the medications used to manage the disease. Psychotic symptoms—hallucinations or delusions—occur in 4% of patients, and it is assumed that the main precipitant of psychotic phenomena in Parkinson’s disease is dopaminergic excess secondary to treatment; it therefore becomes more common with increasing age and levodopa intake.[^5]

5.1.3 Other

In addition to cognitive and motor symptoms, PD can impair other body functions. Sleep problems are a feature of the disease and can be worsened by medications. Symptoms can manifest in daytime drowsiness, disturbances in REM sleep, or insomnia. Alterations in the autonomic nervous system can lead to orthostatic hypotension (low blood pressure upon standing), oily skin and excessive sweating, urinary incontinence and altered sexual function. Constipation and gastric dysmotility can be severe enough to cause discomfort and even endanger health. PD is related to several eye and vision abnormalities such as decreased blink rate, dry eyes, deficient ocular pursuit (eye tracking) and saccadic movements (fast automatic movements of both eyes in the same direction), difficulties in directing gaze upward, and blurred or double vision. Changes in perception may include an impaired sense of smell, sensation of pain and paresthesia (skin tingling and numbness). All of these symptoms can occur years before diagnosis of the disease[^5]

5.2 SECONDARY SYMPTOMS OF PARKINSON DISEASE

See Illustration 2

Pathology

6.1 ANATOMICAL PATHOLOGY

The basal ganglia, a group of "brain structures" innervated by the dopaminergic system, are the most seriously affected brain areas in PD. The main pathological characteristic of PD is cell death in the substantia nigra and, more specifically, the ventral (front) part of the pars compacta, affecting up to 70% of the cells by the time death occurs. Macrophagic alterations can be noticed on cut surfaces of the brainstem, where neuronal loss can be inferred from a reduction of melanin pigmentation in the substantia nigra and locus coeruleus. The histopathology (microscopic anatomy) of the substantia nigra and several other brain regions shows neuronal loss and Lewy bodies in many of the remaining nerve cells. Neuronal loss is accompanied by death of astrocytes (star-shaped glial cells) and activation of the microglia (another type of glial cell). Lewy bodies are a key pathological feature of PD.[^5]

6.2 PATHOPHYSIOLOGY

The primary symptoms of Parkinson’s disease result from greatly reduced activity of dopamine-secreting cells caused by cell death in the pars compacta region of the substantia nigra. There are five major pathways in the brain connecting other brain areas with the basal ganglia. These are known as the motor, ocular-motor, associative, limbic and orbitofrontal circuits, with names indicating the main projection area of each circuit. All of them are affected in PD, and their disruption explains many of the symptoms of the disease since these circuits are involved in a wide variety of functions including movement, attention and learning. Scientifically, the motor circuit has been examined the most intensively. A particular conceptual model of the motor circuit and its alteration with PD has been of great influence since 1980, although some limitations have been pointed out which have led to modifications. In this model, the basal ganglia normally exert a constant inhibitory influence on a wide range of motor systems, preventing them from becoming active at inappropriate times. When a decision is made to perform a particular action, inhibition is reduced for the required motor system, thereby releasing it for activation. Dopamine acts to facilitate this release of inhibition, so high levels of dopamine function tend to promote motor activity, while low levels of dopamine function, such as occur in PD, demand greater exertions of effort for any given movement. Thus the net effect of dopamine depletion is to produce hypokinesia, an overall reduction in motor output. Drugs that are used to treat PD,
conversely, may produce excessive dopamine activity, allowing motor systems to be activated at inappropriate times and thereby producing dyskinesias. [5]

Brain Cell Death

There is speculation of several mechanisms by which the brain cells could be lost. One mechanism consists of an abnormal accumulation of the protein alpha-synuclein bound to ubiquitin in the damaged cells. This insoluble protein accumulates inside neurones forming inclusions called Lewy bodies. According to the Braak staging, a classification of the disease based on pathological findings, Lewy bodies first appear in the olfactory bulb, medulla oblongata and pontine tegmentum, with individuals at this stage being asymptomatic. As the disease progresses, Lewy bodies later develop in the substantia nigra, areas of the midbrain and basal forebrain, and in a last step the neocortex. These brain sites are the main places of neuronal degeneration in PD, however, Lewy bodies may not cause cell death and they may be protective. In patients with dementia, a generalized presence of Lewy bodies is common in cortical areas. Neurofibrillary tangles and senile plaques, characteristic of Alzheimer's disease, are not common unless the person is demented. [11]

Other cell-death mechanisms include proteosomal and lysosomal system dysfunction and reduced mitochondrial activity. Iron accumulation in the substantia nigra is typically observed in conjunction with the protein inclusions. It may be related to oxidative stress, protein aggregation and neuronal death, but the mechanisms are not fully understood. Parkinson's disease is generally believed to be caused by environmental factors, but sometime hereditary parkinson disease have provides some valuable clues about the maechanism. Like other neurodegenerative disorders, the damage is cused by protein misfolding and aggregation, aided and a betted by three familiar villains, namely excitotoxicity, oxidative stress and apoptosis.

Diagnosis

**Stepwise Approach.** The diagnosis of Parkinson is clinical process. The following 3-step approach is suggested,

**8.1. IDENTIFICATION OF A PARKINSONIAN SYNDROME**
Commonly used criteria are the presence of bradykinesia and at least 1 of the following: muscular rigidity, 4- to 6-Hz resting tremor, and/or postural instability.

**8. 2. EXCLUSION OF OTHER CAUSES OF PARKINSONISM**
Differentiation of PD from other causes of parkinsonism is paramount. This includes separation from secondary (symptomatic) forms and atypical (parkinson-plus) syndromes, which can often be challenging.

**8.2.1 SECONDARY OR SYMPTOMATIC**
This forms include drug-induced parkinsonism, most commonly related to antipsychotics and antiemetic agents; postinfectious parkinsonism (eg, sequelae of West Nile viral encephalitis); structural lesions, such as stroke or hydrocephalus; vascular lesions; metabolic conditions, including Wilson’s disease; trauma (post-traumatic parkinsonism); and toxic insults, such as those caused by carbon monoxide, manganese, or 1-methyl-4-phenyl 1,2,3,6-tetrahydropyridine (MPTP). Prescribed medications frequently implicated in the development of parkinsonism are haloperidol, risperidone, metoclopramide, and prochlorperazine.

**8.2.2 ATYPICAL (PARKINSON-PLUS) CONDITIONS**
It include Alzheimer’s disease with extrapyramidal signs; progressive supranuclear palsy; multiple system atrophy, such as Shy-Drager syndrome; corticobasal ganglionic degeneration; DLB; spinal cerebellar ataxias; striatonigral degeneration; and ALS/parkinsonismdementia complex of Guam.

**8.3. IDENTIFICATION OF SUPPORTIVE FEATURES**
Several supportive criteria can increase the positive predictive value of the clinical diagnosis of PD against the gold standard of pathology confirmation. At least 3 supportive features add greatly to diagnostic confidence. Important is a response to an adequate challenge of levodopa, which is required for clinical diagnosis of PD. Olfactory dysfunction may be highly useful in distinguishing PD from other types of parkinsonism.

Management

**9.1 DRUG TREATMENT**
There is no cure for Parkinson’s disease, but medications, surgery and multidisciplinary management can provide relief from the symptoms. The main families of drugs useful for treating motor symptoms are levodopa (usually combined with a
dopa decarboxylase inhibitor or COMT inhibitor), dopamine agonists and MAO-B inhibitors. The stage of the disease determines which group is most useful. Two stages are usually distinguished: an initial stage in which the individual with PD has already developed some disability for which he needs pharmacological treatment, then a second stage in which an individual develops motor complications related to levodopa usage. Treatment in the initial stage aims for an optimal tradeoff between good symptom control and side-effects resulting from enhancement of dopaminergic function. The start of levodopa (or L-DOPA) treatment may be delayed by using other medications such as MAO-B inhibitors and dopamine agonists, in the hope of delaying the onset of dyskinesias. In the second stage the aim is to reduce symptoms while controlling fluctuations of the response to medication. Sudden withdrawals from medication or overuse have to be managed. When medications are not enough to control symptoms, surgery and deep brain stimulation can be of use. In the final stages of the disease, palliative care is provided to enhance quality of life.

9.1.1. Levodopa

Levodopa has been the most widely used treatment for over 30 years. L-DOPA is converted into dopamine in the dopaminergic neurons by dopa decarboxylase. Since motor symptoms are produced by a lack of dopamine in the substantia nigra, the administration of L-DOPA temporarily diminishes the motor symptoms. Only 5–10% of L-DOPA crosses the blood-brain barrier. The remainder is often metabolized to dopamine elsewhere, causing a variety of side effects including nausea, dyskinesias and joint stiffness. Carbidopa and benserazide are peripheral dopa decarboxylase inhibitors, which help to prevent the metabolism of L-DOPA before it reaches the dopaminergic neurons, therefore reducing side effects and increasing bioavailability. They are generally given as combination preparations with levodopa. Existing preparations are carbidopa/levodopa (co-careldopa) and benserazide/levodopa (co-beneldopa). Levodopa has been related to dopamine dysregulation syndrome, which is a compulsive overuse of the medication, and punding. There are controlled release versions of levodopa in the form intravenous and intestinal infusions that spread out the effect of the medication. These slow-release levodopa preparations have not shown an increased control of motor symptoms or motor complications when compared to immediate release preparations.

Tolcapone inhibits the COMT enzyme, which degrades dopamine, thereby prolonging the effects of levodopa. It has been used to complement levodopa; however, its usefulness is limited by possible side effects such as liver damage. A similarly effective drug, entacapone, has not been shown to cause significant alterations of liver function. Licensed preparations of entacapone contain entacapone alone or in combination with carbidopa and levodopa.

Levodopa preparations lead in the long term to the development of motor complications characterized by involuntary movements called dyskinesias and fluctuations in the response to medication. When this occurs a person with PD can change from phases with good response to medication and few symptoms (“on” state), to phases with no response to medication and significant motor symptoms (“off” state). For this reason, levodopa doses are kept as low as possible while maintaining functionality. Delaying the initiation of therapy with levodopa by using alternatives (dopamine agonists and MAO-B inhibitors) is common practice. A former strategy to reduce motor complications was to withdraw L-DOPA medication for some time. This is discouraged now, since it can bring dangerous side effects such as neuroleptic malignant syndrome. Most people with PD will eventually need levodopa and later develop motor side effects.

9.1.2. Dopamine agonists

Several dopamine agonists that bind to dopaminergic post-synaptic receptors in the brain have similar effects to levodopa. These were initially used for individuals experiencing on-off fluctuations and dyskinesias as a complementary therapy to levodopa; they are now mainly used on their own as an initial therapy for motor symptoms with the aim of delaying motor complications. When used in late PD they are useful at reducing the off periods. Dopamine agonists include bromocriptine, pergolide, pramipexole, ropinirole, piribedil, cabergoline, apomorphine and lisuride.

Dopamine agonists produce significant, although usually mild, side effects including drowsiness, hallucinations, insomnia, nausea and constipation. Sometimes side effects appear even at a minimal clinically effective dose, leading the physician to search for a different drug. Compared with levodopa, dopamine agonists may delay motor complications of medication use but are less effective at controlling symptoms. Nevertheless, they are usually effective enough to manage symptoms in the initial years. They tend to be more expensive than levodopa. Dyskinesias due to dopamine agonists are rare in younger people who have PD, but along with other side effects,
become more common with age at onset. Thus dopamine agonists are the preferred initial treatment for earlier onset, as opposed to levodopa in later onset. Agonists have been related to a impulse control disorders (such as compulsive sexual activity and eating, and pathological gambling and shopping) even more strongly than levodopa.

**Apomorphine**, a non-orally administered dopamine agonist, may be used to reduce off periods and dyskinesia in late PD. It is administered by intermittent injections or continuous subcutaneous infusions. Since secondary effects such as confusion and hallucinations are common, individuals receiving apomorphine treatment should be closely monitored. Two dopamine agonists that are administered through skin patches (*lisuride* and *rotigotine*) have been recently found to be useful for patients in initial stages and preliminary positive results has been published on the control of off states in patients in the advanced state.

9.1.3. MAO-B inhibitors

MAO-B inhibitors (*selegiline* and *rasagiline*) increase the level of dopamine in the basal ganglia by blocking its metabolism. They inhibit monoamine oxidase-B (MAO-B) which breaks down dopamine secreted by the dopaminergic neurons. The reduction in MAO-B activity results in increased L-DOPA in the striatum. Like dopamine agonists, MAO-B inhibitors used as monotherapy improve motor symptoms and delay the need for levodopa in early disease, but produce more adverse effects and are less effective than levodopa. There are few studies of their effectiveness in the advanced stage, although results suggest that they are useful to reduce fluctuations between on and off periods. An initial study indicated that selegiline in combination with levodopa increased the risk of death, but this was later disproven.

9.1.4. Other drugs

Other drugs such as *amantadine* and *anticholinergics* may be useful as treatment of motor symptoms. However, the evidence supporting them lacks quality, so they are not first choice treatments. In addition to motor symptoms, PD is accompanied by a diverse range of symptoms. A number of drugs have been used to treat some of these problems. Examples are the use of *clozapine* for psychosis, *cholinesterase inhibitors* for dementia, and *modafinil* for daytime sleepiness. A 2010 *meta-analysis* found that *non-steroidal anti-inflammatory drugs* (apart from *acetaminophen* and *aspirin*), have been associated with at least a 15 percent (higher in long-term and regular users) reduction of incidence of the development of Parkinson's disease.

**Medications involved in Parkinson disease:**

- Although there is no cure for Parkinson's disease, a variety of medications is available to treat its symptoms. Current medical therapy is focused on improving movement.
  - **Levodopa** is the most commonly used drug for Parkinson's disease, and it remains the most efficacious to date. Levodopa replenishes dopamine. This drug helps the majority of patients, and is most effective in treating bradykinesia and rigidity. Carbidopa, an ingredient commonly pre-packaged with levodopa tablets, helps prevent or reduce some side effects of levodopa.

Other classes of Parkinson's drugs include:

- **MAO inhibitors** (such as *selegiline* and *rasagiline*), which act by preventing the early breakdown of dopamine in the brain
- **Dopamine agonists** (*ropinirole*, *pramipexole*, and *apomorphine*) that stimulate the dopamine receptors in the brain, thereby optimizing its function
- **COMT inhibitors** (*entacapone*, *tolcapone*) that are taken with levodopa to extend its effect

9.2. SURGERY AND DEEP BRAIN STIMULATION

In the treatment of Parkinson disease there neurosurgical techniques plays a vital role. These resulted not only from recognition of the shortcoming of medical treatment currently available, but also from an improved understanding of basal ganglia circuitry and better neuroimaging methods. Treatment motor symptoms with surgery was once a common practice, but since the discovery of levodopa, the number of operations declined. Studies in the past few decades have led to great improvements in surgical techniques, so that surgery is again being used in people with advanced PD for whom drug therapy is no longer sufficient. Surgery for PD can be divided in two main groups: *lesional* and *deep brain stimulation* (DBS). Target areas for DBS or lesions include the *thalamus*, the *globus pallidus* or the *subthalamic nucleus*. Deep brain stimulation (DBS) is the most commonly used surgical treatment. It involves the implantation of a medical device called a *brain pacemaker*, which sends electrical impulses to specific parts of the brain. DBS is recommended for people who have PD who suffer from motor fluctuations and tremor inadequately controlled by medication, or to those who are intolerant to medication, as long as they do not have
severe neuropsychiatric problems. Other, less common, surgical therapies involve the formation of lesions in specific subcortical areas (a technique known as pallidotomy in the case of the lesion being produced in the globus pallidus).

B) TARGET AREA FOR DEEP BRAIN STIMULATION

See Illustration 3

9.3. COMPLEMENTARY AND SUPPORTIVE THERAPY

9.3.1. Rehabilitation

There is some evidence that speech or mobility problems can improve with rehabilitation, although studies are scarce and of low quality. Regular physical exercise with or without physiotherapy can be beneficial to maintain and improve mobility, flexibility, strength, gait speed, and quality of life. However, when an exercise program is performed under the supervision of a physiotherapist, there are more improvements in motor symptoms, mental and emotional functions, daily living activities, and quality of life compared to a self-supervised exercise program at home. In terms of improving flexibility and range of motion for patients experiencing rigidity, generalized relaxation techniques such as gentle rocking have been found to decrease excessive muscle tension. Other effective techniques to promote relaxation include slow rotational movements of the extremities and trunk, rhythmic initiation, diaphragmatic breathing, and meditation techniques. As for gait and addressing the challenges associated with the disease such as hypokinesia (slowness of movement), shuffling and decreased arm swing; physiotherapists have a variety of strategies to improve functional mobility and safety. Areas of interest with respect to gait during rehabilitation programs focus on but are not limited to improving gait speed, base of support, stride length, trunk and arm swing movement. Strategies include utilizing assistive equipment (pole walking and treadmill walking), verbal cueing (manual, visual and auditory), exercises (marching and PNF patterns) and altering environments (surfaces, inputs, open vs. closed). Strengthening exercises have shown improvements in strength and motor function for patients with primary muscular weakness and weakness related to inactivity with mild to moderate Parkinson’s disease. However, reports show a significant interaction between strength and the time the medications was taken. Therefore, it is recommended that patients should perform exercises 45 minutes to one hour after medications, when the patient is at their best. Also, due to the forward flexed posture, and respiratory dysfunctions in advanced Parkinson’s disease, deep diaphragmatic breathing exercises are beneficial in improving chest wall mobility and vital capacity. Exercise may improve constipation.

One of the most widely practiced treatments for speech disorders associated with Parkinson's disease is the Lee Silverman voice treatment (LSVT). Speech therapy and specifically LSVT may improve speech. Occupational therapy (OT) aims to promote health and quality of life by helping people with the disease to participate in as many of their daily living activities as possible. There have been few studies on the effectiveness of OT and their quality is poor, although there is some indication that it may improve motor skills and quality of life for the duration of the therapy.

9.3.2. Diet

Muscles and nerves that control the digestive process may be affected by PD, resulting in constipation and gastroparesis (food remaining in the stomach for a longer period of time than normal). A balanced diet, based on periodical nutritional assessments, is recommended and should be designed to avoid weight loss or gain and minimize consequences of gastrointestinal dysfunction. As the disease advances, swallowing difficulties (dysphagia) may appear. In such cases it may be helpful to use thickening agents for liquid intake and an upright posture when eating, both measures reducing the risk of choking. Gastrostomy to deliver food directly into the stomach is possible in severe cases. Levodopa and proteins use the same transportation system in the intestine and the blood-brain barrier, thereby competing for access. When they are taken together, this results in a reduced effectiveness of the drug. Therefore, when levodopa is introduced, excessive protein consumption is discouraged and well balanced Mediterranean diet is recommended. In advanced stages, additional intake of low-protein products such as bread or pasta is recommended for similar reasons. To minimize interaction with proteins, levodopa should be taken 30 minutes before meals. At the same time, regimens for PD restrict proteins during breakfast and lunch, allowing protein intake in the evening.

9.3.3. Palliative Care

Palliative care is often required in the final stages of the disease when all other treatment strategies have become ineffective. The aim of palliative care is to maximize the quality of life for the person with the disease and those surrounding him or her. Some
central issues of palliative care are: care in the community while adequate care can be given there, reducing or withdrawing drug intake to reduce drug side effects, preventing pressure ulcers by management of pressure areas of inactive patients, and facilitating end-of-life decisions for the patient as well as involved friends and relatives.

9.3.4. Other treatments

Repetitive transcranial magnetic stimulation temporarily improves levodopa-induced dyskinesias. Its usefulness in PD is an open research topic, although recent studies have shown no effect by rTMS. Several nutrients have been proposed as possible treatments; however there is no evidence that vitamins or food additives improve symptoms. There is no evidence to substantiate that acupuncture and practice of Qigong, or T'ai chi, have any effect on the course of the disease or symptoms. Further research on the viability of Tai chi for balance or motor skills are necessary. Fava beans and velvet beans are natural sources of levodopa and are eaten by many people with PD. While they have shown some effectiveness in clinical trials, their intake is not free of risks. Life-threatening adverse reactions have been described, such as the neuroleptic malignant syndrome.

9.4 NEWER DRUGS/ PATENT DRUGS FOR TREATMENT OF PARKINSON DISEASE

9.4.1. Fipamezole:
Fipamezole is a drug which, when taken with dopamine medication, appears to do two things: reduce the problem of dyskinesia and increase the time the dopamine medication works.[16]

9.4.2. BIIB014
The experimental drug BIIB014 is one of the first non-dopamine approaches to treating Parkinson’s. Preliminary studies shows that BIIB014 causes two things: One, alleviate Parkinson’s symptoms, when given on its own. Two, it appears that, when added to existing therapies, BIIB014 can improve the action of those therapies, decreasing the “off” time between the action of each pill.[16]

9.4.3. PYM50028 / Cogane
PYM50028, also known as Cogane. “Cogane has potential to restore the dopamine system in the brain, not just provide symptomatic benefit. “It could be disease-modifying, meaning it has the potential to change the course of the disease and maybe even reverse the disease progression.”

For the past decade, scientists have been exploring ways to increase the levels of glial cell-derived neurotrophic factor (GDNF) in the brain in Parkinson’s to help brain cells survive or even grow back. GDNF is a protein that is made in the brain and helps brain cells grow when the brain is developing or recovering from injury. Previous approaches have involved injecting GDNF into the brain through surgery or gene therapy. However, Cogane offers the possibility of delivering GDNF to the brain via a pill. The idea is that after you swallow the pill, the drug gets into the brain and then switches on the brain’s ability to make GDNF.[16]

Recent Treatment & Researches

10.1. DISCOVERY OD ADENOSINE A(2A) RECEPTOR ANTAGONIST FOR THE TREATMENT OF PARKINSON DISEASE.

The adenosine A2A receptor (AA2AR) has emerged as an attractive target for the treatment of Parkinson’s disease. The antagonists of the AA2AR may be neuroprotective and may help to alleviate the symptoms of Parkinson’s disease. During last decade, many efforts have been accomplished searching potent and selective AA2AR antagonists. In this field, various xanthines and non-xanthine heterocyclic compounds of monocyclic, bicyclic and tricyclic nucleus possessing very good affinity with a broad range of selectivity have been proposed.[17]

10.2. CIGARETTE SMOKING AND PARKINSON DISEASE.

Cigarette smoking is an established risk factor for various diseases such as lung cancer, COPD and heart disease. But recently several epidemiological studies have found a significant negative association between cigarette smoking and PD. Cigarette smoke is composed of more than 4700 chemical compounds including nicotine, the addictive substance of cigarettes, carbon monoxide, lead, cadmium and polycyclic aromatic hydrocarbons. The patients who smoke are 50% less likely to have PD when compared to their non-smoker counterparts. This suggests that cigarette smoking may have a “neuroprotective” effect on Parkinson Disease. Cigarette smoking protects from neurodegeneration thus prevent the Parkinson disease. Cigarette smoke has also inhibit monoamine oxidase (MAO) activity which is known to breakdown dopamine and also help in dopamine release in the body. cigarette smoke also contains several free radicals other than this is also contains carbon
monoxide (CO) which seems to be protective against hydrogen peroxide (H₂O₂)-induced membrane damage. CO also inhibits neural MAO-B-associated metabolism of dopamine to produce H₂O₂ and possibly creates a protective nigral “reducing environment”, therefore suppression of free radical generation in early life could possibly lead to reduced risk of PD by preserving dopamine producing cells.[18][19][20]

10.3. Continuous Dopamine Receptor Treatment of Parkinson’s Disease: Scientific Rationale & Clinical Implications.

Levodopa-induced motor complications are a common source of disability for patients with Parkinson’s disease. Evidence suggests that motor complications are associated with non-physiological, pulsatile stimulation of dopamine receptors. In healthy brains, dopamine neurons fire continuously, striatal dopamine concentrations are relatively constant, and there is continuous activation of dopamine receptors. In the dopamine-depleted state, standard levodopa therapy does not normalise the basal ganglia. Rather, levodopa or other short-acting dopaminergic drugs induce molecular changes and altered neuronal firing patterns in basal ganglia neurons leading to motor complications. The concept of continuous dopaminergic stimulation proposes that continuous delivery of a dopaminergic drug will prevent pulsatile stimulation and avoid motor complications. In monkeys treated with MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) and patients with Parkinson's disease, long-acting or continuous infusion of a dopaminergic drug reduces the risk of motor complications. The current challenge is to develop a long-acting oral formulation of levodopa that provides clinical benefits but avoids motor complications[21][22]

10.4. COFFEE AS KEY INGREDIENT FOR NEW TREATMENT OF PARKINSON DISEASE.

Adenosine A2A receptors regulate the effects of neurotransmitters in the brain, cardiovascular and immune systems, and are of particular interest as a drug target for Parkinson’s disease. Although it was known that caffeine inhibits the action of the adenosine, the exact molecular mechanism involved was not fully understood. These co-structures of xanthines in complex with the adenosine A2A receptor advance our understanding of what is happening at the molecular level when the drug binds to its target and blocks the receptor’s response. The adenosine A2A receptor is a G-protein-coupled receptor (GPCR). GPCRs are responsible for transmitting chemical signals into a variety of different cell types. There are over 700 GPCRs encoded in the human genome and as many as 75 of these have clinical validation, presenting a wide range of opportunities as therapeutic targets in areas including cancer, diabetes, central nervous system disorders, obesity and pain. Caffeine is a methylxanthine, a stimulant derivative of xanthine, as is theophylline (in tea), and theobromine (in chocolate). Methylxanthines are among the most widely consumed substances in the world. Caffeine is present in many foods and drinks. The Journal of the American Medical Association (JAMA) published research showing a correlation between higher intake of caffeine and lower incidence of Parkinson’s disease, a devastating and incurable neurological disorder. While caffeine exerts a broad range of adverse effects, and is therefore poorly suited for use as a drug, pharmaceutical researchers have generated more potent and selective adenosine receptor modulators. A2A receptor antagonists, in particular, have shown clinical efficacy in the treatment of Parkinson’s disease. First generation A2A antagonists using older furan and xanthine type chemical structures have been associated with various safety, tolerability, and pharmacokinetic limitations. Heptares have used structural information to generate the next-generation of A2A antagonists[23]

10.5. AMANTADINE AS N-methyl-d-Aspartic acid receptor antagonist

The (NMDA) receptor is an intriguing target for the development of drugs with anti-Parkinsonian activity as well as with protective actions against degenerative processes induced by brain ischemia. Amantadine is used in the treatment of Parkinson's disease without a well established mechanism of action. We show here that amantadine inhibits, in a non-competitive way, the NMDA receptor-mediated stimulation of acetylcholine release from rat neostriatum in vitro in “therapeutic” (i.e., low micromolar) concentrations. This indicates that amantadine might exert its anti-Parkinsonian effect via blockade of NMDA receptors. Sustained stimulation of NMDA receptors induces so-called excitotoxicity. Recently, it was demonstrated that amantadine is able to inhibit NMDA induced cell death in a neuronal culture. On the basis of these findings it seems worth investigating if amantadine is also able to protect against neurodegenerative processes caused by brain ischemia in vivo.[24]
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### Illustrations

#### Illustration 1

Physiological Characterization Of Dopamine Receptor

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Illustration 2

Secondary Symptoms Of Parkinson Disease

<table>
<thead>
<tr>
<th>SECONDARY SYMPTOMS OF PARKINSON DISEASE</th>
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<tbody>
<tr>
<td>• Constipation</td>
<td>• Loss of intellectual capacity</td>
</tr>
<tr>
<td>• Difficulty swallowing</td>
<td>• Anxiety, depression, isolation</td>
</tr>
<tr>
<td>• Choking, coughing, or drooling</td>
<td>• Scaling, dry skin on the face or scalp</td>
</tr>
<tr>
<td>• Excessive salivation</td>
<td>• Slow response to questions</td>
</tr>
<tr>
<td>• Excessive sweating</td>
<td>• Small cramped handwriting</td>
</tr>
<tr>
<td>• Loss of bowel and/or bladder control</td>
<td>• Soft, whispery voice</td>
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Illustration 3

Target Area For Deep Brain Stimulation

<table>
<thead>
<tr>
<th>Target</th>
<th>Bradykinesia</th>
<th>Tremor</th>
<th>Dyskinesia</th>
<th>Comments</th>
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</thead>
<tbody>
<tr>
<td>Thalamus</td>
<td>-</td>
<td>+++</td>
<td>-</td>
<td>Bilateral thalamotomy is not recommended because of high incidence of bulbar dysfunction</td>
</tr>
<tr>
<td>Globus pallidus</td>
<td>++</td>
<td>++</td>
<td>+++</td>
<td>10-15% incidence of persistent adverse events with unilateral pallidotomy; no reliable data for bilateral procedures</td>
</tr>
<tr>
<td>Subthalamic nucleus</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
<td>Wait gain, contralateral dyskinesia, involuntary eyelid closure and speech disturbance.</td>
</tr>
</tbody>
</table>

+++ refers to the relative efficacy of the procedures for the clinical feature, - refers no benefit for the + to procedures for the clinical feature.
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