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ALTERNATIVE TREATMENT OF PARKINSONS DISEASE: A REVIEW

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Abstract: Parkinson's disease typically develops between the ages of 55 and 65 years and occurs in 1 to 2% of persons over the age of 60 years. Approximately 0.3% of the general population is affected, and the prevalence is higher among men than women, with a ratio of 1.6 to 1.0. As the population ages, the incidence of PD is expected to increase dramatically in the coming decades. Current therapies are largely based on dopamine replacement strategies using the dopamine precursor levodopa. However, chronic treatment is accompanied by the development of motor complications and the disease progresses inexorably. Moreover, disease progression is associated with the emergence of symptoms such as freezing, falls, and dementia that cannot be adequately controlled with dopaminergic therapy. Indeed, these non-dopaminergic traits are now recognized to be common and a major cause of disability in patients with progressive disease. Many different treatments and therapeutic strategies have been evaluated, and many promising approaches are currently being tested in the laboratory and clinic. As a result, many new therapeutics and strategic approaches to treat different stages of Parkinson's disease have become available. Treatment for Parkinson's disease typically involves a combination of treatments. An important part of Parkinson's disease treatment is drug therapy supported by various combination therapies. Treatment is primarily aimed at relieving symptoms and side effects, as the disease itself cannot currently be cured. Each Parkinson's disease course is different, and the type and severity of symptoms vary widely. What is particularly worrying to one person may not be noticed by another. In addition to symptoms, medical history, age, and living environment also play an important role. Therefore, individualized treatment is necessary.

KEYWORDS: Parkinson's disease, neurodegenerative disorders, dopamine, levodopa, dopaminergic therapy, dementia, non-dopaminergic traits, medical history, combination therapies, etc.

INTRODUCTION:

The term alternative therapy is generally used to describe any medical treatment or intervention that complements conventional treatments, i.e. complementary medicine or CAM (complementary and alternative medicine). Parkinson's disease (PD) is a common neurodegenerative disorder that presents with a characteristic motor syndrome consisting of bradykinesia, rigidity, resting tremor, postural instability and falls as the disease progresses. These motor symptoms, a syndrome of parkinsonism, occur in PD due to relatively selective loss of dopaminergic neurons in the substantia nigra pars compacta and decreased striatal dopamine levels. Due to neurodegeneration, there are a number of additional non-motor symptoms that occur in other areas, including the cerebral cortex. Because the motor symptoms of Parkinson's disease result from the loss of specific neuronal populations, there has long been interest in whether the function of these neurons could be replaced with regenerative therapies that restore dopamine levels in the brains of Parkinson's disease patients. has been submitted.[(1)]

The annual incidence of PD is approximately 18/100,000, with a prevalence of approximately 180/100,000 in the UK. Age has a significant impact on incidence and prevalence, the latter increasing to 300-500/100,000 after he reaches 80 years of age. The median age of onset is approximately 60 years, and he is less than 5% of patients younger than 40 years. Genetic factors are increasingly being recognized and several individual genes responsible for Parkinson's disease have been identified, but overall they account for a very small proportion

of cases. Having a Parkinson's disease patient in your life doubles or triples your risk of developing Parkinson's disease. It is progressive and incurable. Variable prognosis. Motor symptoms are the most common feature, but as the disease progresses, non-motor symptoms (especially cognitive impairment, depression, and anxiety) become more prominent and significantly impact quality of life. [2]

About 1% of the population over the age of 50 and about 2.5% of the population over the age of 70 are affected. The lifetime risk of developing Parkinson's disease is 2.0% for men and 1.3% for women. The idiopathic form of PD, also known as sporadic PD, is the most common form of PD and primarily affects the elderly. In addition to motor symptoms, non-motor symptoms and complications such as neuropsychiatric or neurobehavioral problems, autonomic dysfunction and sensory problems are also considered important components of Parkinson's disease. Neuropsychiatric or neurobehavioral complications, such as depression, anxiety, rapid eye movement sleep behaviour disorder and dementia, are very common in Parkinson's disease and affect different neurotransmissions in different brain regions. It can occur due to neurodegenerative processes in the substance system. Other complications such as psychosis, delirium, and obsessive-compulsive/impulsive spectrum disorders such as impulse control disorders (ICD), dopamine dysregulation syndrome (DDS), and palpitations are also relatively common.[3]

Diagnosis of PD is primarily clinical, and it is important to recognize early features along with symptoms and signs suggestive of other causes of Parkinson's disease. Treatment options for both early- and late-stage disease are also expanding rapidly, as is awareness of non-motor complications. Guidelines for the diagnosis and treatment of patients with Parkinson's disease have been published by the National Institute for Health and Clinical Excellence (NICE) in the UK. [3]

Table 1: Comparison of impulsive control disorder(ICDs) versus Dopamine dysregulation syndrome (DDS) in Parkinson disease [4 - 5]

	ICDs	**DDS**
Description / presentation	Set of behavior(s) performed repetitively, excessively, and compulsively affection one's function 1) Pathologic gambling 2) Compulsive shopping (oniomania) 3) Compulsive eating (binge eating disorder) 4) Compulsive sexual behaviour (hypersexuality) - Nymphomania - Satyriasis	An excessive and compulsive use of dopaminergic medications well beyond the dose needed to control motor symptoms. It is characterized by the following: 1) Escalating daily dosages of medications 2) Aggressive or hypomanic behaviour during excessive use 3) withdrawal states characterized by dysphoria and anxiety
Primary medication cause(s)	Use of oral transdermal dopamine receptor agonists - Bromocriptine - Pergolide - Pramipexole - Ropinirole - Rotigotine	Long term dopaminergic treatment usually with - Levodopa, especially at greater dosages - Subcutaneous apomorphine (high potency, short acting dopamine receptor agonist)
Medication cause(s) with lesser extent	➢ Use of levodopa, especially at high doses ➢ Use of amantadine	

CAUSES:

Low dopamine levels: Parkinson's disease symptoms mainly result from low or falling levels of dopamine , a neurotransmitter. It happens when cells that produce dopamine die in the brain.[6]

Dopamine plays a role in sending messages to the part of the brain that controls movement and coordination. Therefore, low dopamine levels can make it harder for people to control their movement.[6]

Low norepinephrine levels: Low levels of norepinephrine in Parkinson's disease may increase the risk of both motor and nonmotor symptoms, such as:

- Stiffness and rigidity
- Postural instability
- Tremor
- Anxiety
- Difficulty focusing
- Dementia
- Depression
- Orthostatic hypotension.

Lewy bodies: A person with Parkinson's disease may have clumps of protein known as alpha-synuclein, or Lewy bodies, in their brain. The accumulation of Lewy bodies can cause a loss of nerve cells, leading to changes in movement, thinking, behaviour, and mood. It can also lead to dementia.[6]

Genetic:

- Huntington's disease
- Fragile X tremor ataxia syndrome
- Dopa-responsive dystonia
- Spinocerebellar ataxias (particularly SCA 3)
- Wilson's disease

Autoimmune factors: In a 2017 study, scientists found a possible genetic link between Parkinson's disease and autoimmune conditions, such as rheumatoid arthritis.[6]

In 2018, researchers investigating health records in Taiwan found that people with autoimmune rheumatic diseases had a higher chance of also having Parkinson's disease.[6]

Environmental Factors : The interactions between genes and the environment can be quite complex. Some environmental exposures may lower the risk of PD, while others may increase it. Environmental risk factors associated with PD include head injury, area of residence, exposure to pesticides and more.[7]

Age: It usually starts in mid or late life and the risk increases with age. [8]

Heredity or family history: If a close relative or family member had this disease, then the chances to develop Parkinson's is very high. [8]

Sex: Men are more prone to the disease than women. [8]

Drugs and toxins:

- Antipsychotic drugs (older and 'atypical')

- Sodium valproate
- Metoclopramide prochlorperazine
- Lithium
- Tetrabenazine
- Manganese
- MPTP

SIGNS AND SYMPTOMS:

Table 2: Motor symptoms of Parkinson's Disease [9- 14]

Cardinal motor features ("Classical Triad")
Bradykinesia • Occurs in 80% to 90% of patients. • Slowness of movement • Decreased amplitude of movement Rigidity [1] Occurs in 80% to 90% of patients. [2] Resistance to passive movement in both flexor and extensor muscles with limb relaxed. [3] Often accompanied by "Cogwheel" phenomenon. Tremor at rest • Common initial symptoms (70% to 90% of patients) • Often resolves with action or during sleep • Primarily distal, involving hands • May also involve jaw, tongue, lips, chin, or legs.
Other
Postural instability • Predisposes patients to falls and injuries • Occurs in later stages of Parkinson's disease • Results from loss of postural reflexes Dysarthria and Dystonia

Table 3: Non-Motor symptoms of Parkinson's Disease [9- 14]

Autonomic dysfunction

Constipation (parasympathetic nervous system cholinergic)
Orthostatic hypotension (sympathetic nervous system noradrenergic)
Sexual dysfunction (parasympathetic nervous system cholinergic)
Sweating (sympathetic nervous system cholinergic)
Urinary retention (parasympathetic nervous system cholinergic)
Neuropsychiatric symptoms
Anxiety
Cognitive impairments (mild).
Dementia
Depression (e.g., dysphoria, suicidal ideation, apathy)
Impulse-control disorders (e.g., preoccupations, hypersexuality, compulsive shopping, binge eating)
Panic disorder
Psychosis (e.g., hallucinations, delusions)
Sensory symptoms
Olfactory dysfunction (hyposmia)
Paresthesia's
Pain
Sleep disorders
Daytime somnolence
Insomnia
Rapid eye movement disorder
Restless legs syndrome
Sleep attacks
Sleep apnea
Other
Fatigue , Sialorrhea and Weight loss

STAGES OF PARKINSON'S DISEASE:

Stage I:

- Symptoms at this stage are mild and do not interfere with daily activities.

- Movement symptoms that affect only one side of the body (unilateral), such as tremors, stiffness, and bradykinesia
- Slight problems with posture and balance
- Difficulty walking
- Slight changes in facial expressions [15]

Stage II:

- At this stage, symptoms worsen and daily activities become difficult. But he can take care of himself.
- Movement symptoms that affect both sides of the body (bilateral), such as tremors, stiffness, and bradykinesia
- Difficulty walking
- Hard to balance
- Poor posture
- Reduced facial expressions. [15]

Stage III:

- Symptoms in this stage (intermediate stage) are more severe than in stage II, but the person is still independent.
- Loss of balance and bradykinesia (sluggishness of movement) are characteristic symptoms of this stage. Daily activities such as eating, bathing, and dressing are severely impaired. [15]

Stage IV:

- At this stage, independent living is almost impossible as daily activities such as eating, bathing, dressing, sleeping and waking are restricted.
- May be able to stand alone but needs assistance to move around. A walker can help you move without falling. [15]

Stage V:

- The symptoms of this debilitating phase can become so severe that it is impossible to even stand on your own. The person becomes bedridden and requires a wheelchair.
- All daily activities are compromised and 24/7 monitoring is required. Symptoms include:
    - Delusions (false beliefs that persist despite conflicting evidence)
    - Hallucinations (seeing, feeling, or hearing things that are not there)
    - Loss of smell
    - Constipation
    - Poor thinking and memory
    - Weight loss
    - Sleep disturbance
    - Vision problems. [15]

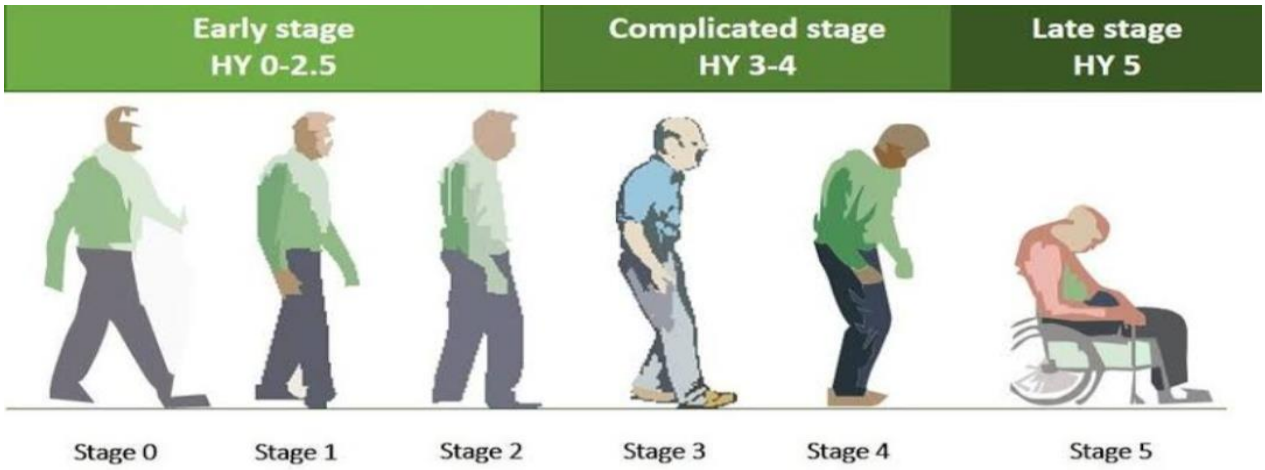


Fig. 1: Stages of Parkinson's disease

PATHOPHYSIOLOGY:

Parkinson's disease is increasingly recognized as a complex neurodegenerative disease with a continuum of progression. There is strong evidence that it first affects the dorsal motor nucleus and olfactory bulb and nucleus of the vagus nerve, then the locus coeruleus and finally the substantia nigra. In later stages, cortical regions of the brain are affected. Injuries to these different nervous systems cause complex pathophysiological changes, leading to impairments not only in the motor system but also in the cognitive and neuropsychological systems.[16]

Role of dopamine:

Dopamine, like other neurotransmitters, carries chemical messages from one neuron to another via synapses (the spaces between presynaptic cells and postsynaptic receptors). Dopamine is secreted into synapses from membrane storage vesicles in the presynaptic membrane. It crosses the synapse and binds to the post-synaptic membrane, where it activates dopamine receptors. Any unused dopamine remaining at the synapse is absorbed by the presynaptic cell. Upon returning to the presynaptic cell, excess dopamine is repackaged into storage vesicles and released into the synapse. As dopamine moves from one cell to another within the synapse, it can be broken down and inactivated by two enzymes: MAO (monoamine oxidase) and COMT (catechol-O-methyltransferase). One therapeutic strategy is to introduce her MAOI into the synapse, which interferes with the action of the MAO enzyme and prevents the breakdown of dopamine. This keeps more dopamine trapped in the synapse, making it more likely to bind to the post-synaptic membrane.[17]

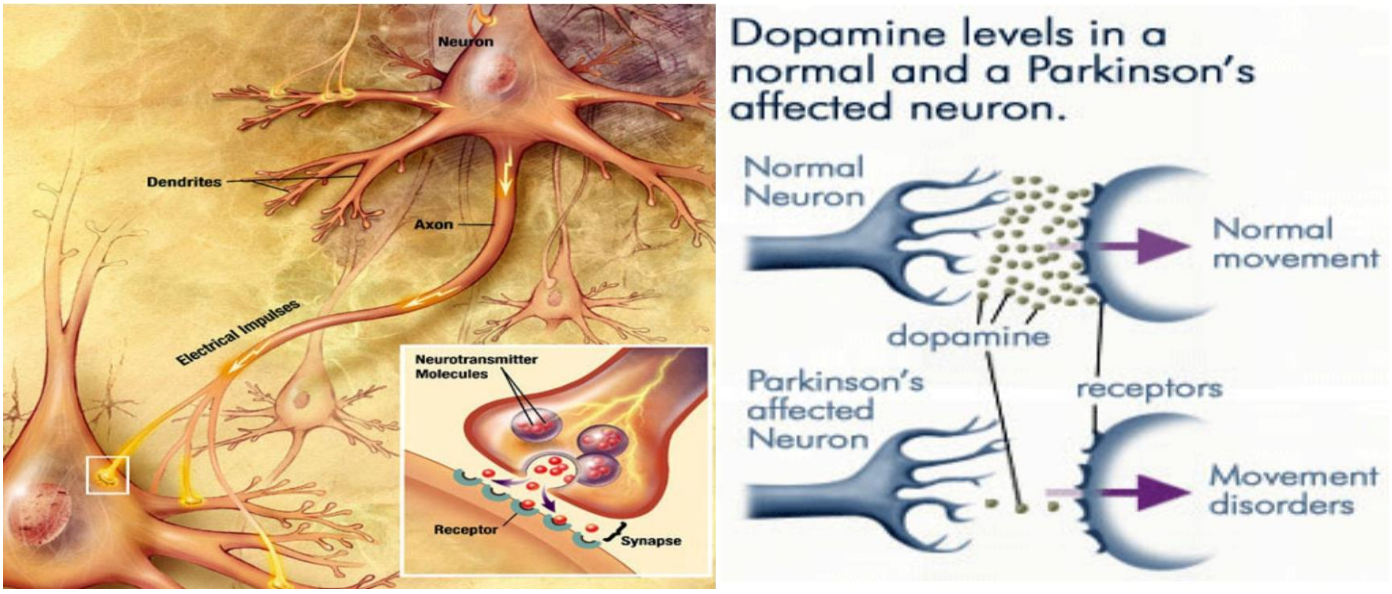
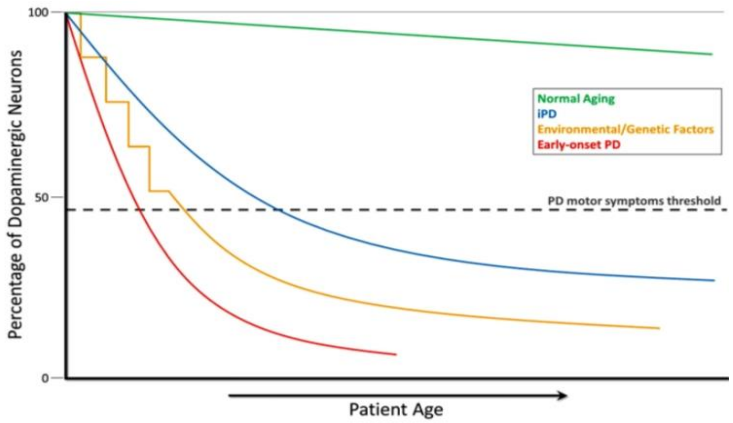


Fig. 2: Chemical Synaptic transmission and dopamine levels in a normal and a Parkinson's affected neuron

Progressive loss of dopamine:

Although dopamine cell loss cannot be measured directly, measurements in neurologically healthy humans and non-human primates show a slowly progressive loss of dopamine with age. Loss occurs much more rapidly in Parkinson's disease, and both biochemical measurements and imaging studies suggest that dopamine is greatly reduced by the time motor symptoms appear. is an accelerated version of cell death seen in normal aging. This is shown in the graph below, which shows the loss of dopaminergic neurons in normal aging, idiopathic PD, PD due to environmental or genetic factors, and early-onset PD.[18]



Evolution of dopamine depletion in Parkinson's disease

During normal aging (green line), small but slow dopaminergic degeneration occurs without any motor symptoms. Idiopathic PD (IPD, blue line) of unknown origin but is thought to develop gradually, with slow degeneration of dopaminergic neurons leading to the classic motor symptoms of Parkinson's disease later in life. life. Another model of dopamine neurodegeneration leading to motor symptoms of Parkinson's disease involves repeated exposure to environmental toxins over time combined with a genetic predisposition to loss of dopamine neurons. (yellow line). Early-onset PD (red line), caused by mutations in the PARKIN gene, is associated with rapid depletion of dopaminergic neurons and motor symptoms of PD can appear decades before the onset of symptoms. symptoms of idiopathic PD. Another scenario (not shown) for the development of motor symptoms of PD involves possible environmental toxins in utero or genetic factors predisposing to

neuronal counts abnormally low dopaminergic at birth and increased susceptibility to the development of PD.[19]

Degeneration of dopaminergic neurons is particularly evident in a part of the substantia nigra known as pars compacta. Significantly, the loss of dopamine in para compacta increases global excitability in the basal ganglia, disrupts voluntary motor control, and induces the hallmark symptoms of Parkinson's disease. Normalization of motor function was initially observed with levodopa treatment.[20]

As PD severity increases, dopamine depletion leads to further changes in basal ganglia pathways, including impaired function of other basal ganglia neurotransmitters such as glutamate, GABA, and serotonin. Although there is a relative weakness of dopamine-producing neurons in the substantia nigra, not all dopamine-secreting cells are affected in Parkinson's disease; In some parts of the brain, neurons that produce dopamine are relatively few.[18]

DIAGNOSTIC TEST:

- Blood tests (these can help rule out other forms of parkinsonism).
- Computerized tomography (CT) scan.
- Genetic testing.
- Magnetic resonance imaging (MRI).
- Positron emission tomography (PET) scan. [21]

Researchers have found possible ways to test for possible indicators or Parkinson’s disease.

Spinal tap: One of these tests looks for misfolded alpha-synuclein proteins in cerebrospinal fluid, which is the fluid that surrounds your brain and spinal cord. This test involves a spinal tap (lumbar puncture), where a healthcare provider inserts a needle into your spinal canal to collect some cerebrospinal fluid for testing.[22]

Skin biopsy: Another possible test involves a biopsy of surface nerve tissue. A biopsy includes collecting a small sample of your skin, including the nerves in the skin. The samples come from a spot on your back and two spots on your leg. Analysing the samples can help determine if your alpha-synuclein has a certain kind of malfunction that could increase the risk of developing Parkinson’s disease.[22]

TREATMENT:

Drug Therapy:

1. Levodopa and Carbidopa (Sinemet): [23]

Carbidopa-levodopa remains a first-line treatment for Parkinson’s disease.

Administration:

Sinemet: 10mg/100mg, 25mg/100 mg, 25mg/250mg oral tablet

Parcopa: 10mg/100mg, 25mg/100mg, 25mg/250mg oral tablet

Sinemet controlled release (CR): 25mg/100mg, 50mg/200mg oral tablet

Rytary extended release (ER): 23.75mg/95mg, 36.25mg/145mg, 48.75mg/195mg, 61.25mg/245mg oral tablet

Duopa extended release (ER): 4.63mg/20mg liquid suspension

These medications are taken several times per day depending on the formulation. Traditional Sinemet is taken every 6 to 8 hours.

Benefits: Carbidopa-levodopa medications help replace depleted dopamine levels to control Parkinson's symptoms. This medication can help lessen symptoms like slowness, tremors, and movement problems, but it is not likely to cure them completely.

Onset of action: Traditional Sinemet takes about 30 minutes to reach its peak effect, while extended- or controlled-release formulas take about 2 hours.

Side effects: Abnormal, uncoordinated movements (dyskinesia), nausea, abdominal pain, confusion, dizziness, heart rate or blood pressure changes.

Efficacy: Levodopa is not effective on some symptoms of Parkinson's that affect balance, speech, or swallowing. Dosages usually need to be increased over time as the disease progresses.

2. DOPAMINE AGONISTS: [23]

Dopamine agonists are another medication group that helps make up for the lack of dopamine in people with Parkinson's disease.

Administration:

Pramipexole (Mirapex): 0.125-mg, 0.25-mg, 0.5-mg, 0.75-mg, 1-mg, or 1.5-mg oral tablets three times per day, or 0.375-mg, 0.75-mg., 1.5-mg, 2.25-mg, 3-mg, 3.75-mg, or 4.5-mg oral extended-release tablets once per day

Ropinirole (Requip): 0.25-mg, 0.5-mg, 1-mg, 2-mg, 3-mg, 4-mg, or 5-mg oral tablets three times per day, or 2-mg, 4-mg, 6-mg, 8-mg, or 12-mg extended-release tablets once per day

Apomorphine (Apokyn): 30-mg/3-ml vial for injection, 0.2 mg per dose

Apomorphine (Kynmobi): sublingual film, 10 mg, 15 mg, 20 mg, 25 mg, and 30 mg

Rotigotine (Neupro): 1-mg, 2-mg, 3-mg, 4-mg, 6-mg, or 8-mg transdermal patches, 4 mg–8 mg max per day

Benefits: Dopamine agonists can improve the motor symptoms that come with Parkinson's disease but are not as effective as levodopa. Typically used early in the disease process, dopamine agonists may be combined with carbidopa-levodopa as the disease progresses. These medications help most with stiffness and tremors

Onset of action: Injectable dopamine agonists like apomorphine work as quickly as 10 minutes.

Oral medications reach their peak effectiveness in about 2 hours.

Side effects: Drowsiness, hallucinations, leg swelling or discoloration, compulsive behaviours, dyskinesia.

Efficacy: These are the most frequently used medications to treat Parkinson's disease after carbidopa-levodopa. They can also be combined with carbidopa-levodopa in later stages of the disease to aid in movement and tremor control.

3. MAO-B INHIBITORS: [23]

Monoamine oxidase Type B (MAO-B) is an enzyme that breaks down dopamine in the brain. By blocking this enzyme, MAO-B inhibitors leave more dopamine for the body to use.

Administration:

Selegiline (I-deprenyl, Eldepryl): 5-mg oral tablet taken twice per day

Selegiline HCL (Zelapar): 1.25-mg and 2.5-mg orally disintegrating tablet taken once daily

Rasagiline (Azilect): 0.5-mg and 1-mg oral tablet taken once per day

Safinamide (Xadago): 500-mg and 100-mg oral tablet taken once per day

Benefits: This medication reduces the amount of dopamine that is broken down in the brain and can also help with some motor symptoms.

Onset of action: These medications take time to build up in your system before they begin to have the full effect.

Side effects: nausea, dry mouth, constipation, dizziness, confusion, hallucinations

Efficacy: While MAO-B inhibitors can help Parkinson's symptoms, they are not usually used as a primary treatment.

Instead, they are an adjunctive (or add-on) therapy used alongside other medications.

4. COMT INHIBITORS: [23]

COMT inhibitors help prevent an enzyme called catechol-O-methyl transferase (COMT) from deactivating levodopa before it has a chance to be absorbed into the bloodstream.

Administration:

Entacapone (Comtan): 200-mg oral tablet taken four to eight times per day with levodopa doses

Tolcapone (Tasmar): 100-mg or 200-mg oral tablets taken one to three times per day

Carbidopa/levodopa/entacapone tablets (Stalevo): 12.5/50/200-mg, 18.75/75/200-mg, 25/100/200-mg, 31.25/125/200-mg, 37.5/150/200-mg, or 50/200/200-mg oral tablets taken multiple times daily

Opicapone (Ongentys): 25-mg and 50-mg oral capsules taken once daily

Benefits: This medication is used alongside levodopa to treat motor fluctuations and "off" time.

Onset of action: This medication reaches its peak in about 1 hour.

Side effects: Dyskinesia, confusion, hallucinations, urine discoloration, diarrhea

Efficacy: This medication is only effective when taken alongside levodopa

5. AMANTADINE: [23]

Originally developed as an antiviral treatment, amantadine was accidentally discovered to reduce tremors.

Administration:

Amantadine (Symmetrel): 100-mg capsules, 100-mg tablets, 50-mg/5-ml syrup taken two to three times per day

Amantadine ER capsules (Gocovri): 68.5-mg and 137-mg capsules taken once per day at bedtime

Amantadine ER tablets (Osmolex ER): 129-mg, 193-mg, and 258-mg tablets taken once per day in the morning

Benefits: Amantadine can reduce tremors and other movement problems.

Onset of action: Amantadine takes about 48 hours to begin taking full effect from the time the medication is started.

Side effects: Dizziness, hallucinations, low blood pressure, nausea, insomnia, confusion, paranoia, leg discoloration

Efficacy: This medication can be helpful alone or taken with other medications like levodopa to decrease muscle problems and tremors from Parkinson's.

6. ANTICHOLINERGIC: [23]

Anticholinergics decrease the power of acetylcholine, a neurotransmitter that helps regulate movement.

Administration:

Benztropine (Cogentin): 0.5-mg, 1-mg, 2-mg oral tablets taken two to three times daily

Trihexyphenidyl HCL: 2-mg or 5-mg tablets, or a 2-mg/5-ml liquid taken two to three times daily

Benefits: Anticholinergics can help reduce involuntary muscle contractions and tremors.

Onset of action:: These medications begin working immediately.

Side effects: Confusion, hallucinations, decreased memory, dry mouth, blurry vision, urinary retention

Efficacy: Anticholinergics have the greatest benefit in younger patients whose primary symptom is tremors.

7. ADENOSINE A2a ANTAGONISTS: [23]

Adenosine A2a antagonists manipulate the receptor in the brain that is responsible for slowed movement in Parkinson's disease. While the exact way the adenosine A2a antagonists work is unknown, when combined with Levodopa they can improve motor function.

This medication can also increase the sensitivity of dopamine receptors to help reduce motor symptoms in Parkinson's.

Administration:

Istradefylline (Nourianz): 20-mg or 40-mg oral tablets taken once per day

Benefits: This medication reduces motor symptoms of Parkinson's when used with other medications.

Onset of action: This medication reaches its peak time in about 4 hours, but it requires several weeks to achieve lasting effects.

Side effects: Dyskinesia, insomnia, dizziness, hallucinations

Efficacy: These medications work well in combination with other Parkinson's treatments, but people who smoke 20 cigarettes or more per day will require larger doses.

PHYSICAL THERAPY:

Physical therapy can help you offset the changes caused by the disease. These "compensatory treatments," as they are called, involve learning new movement techniques, strategies, and devices. A physical therapist can teach you exercises to strengthen and relax your muscles. The goal of physical therapy is to improve your independence and quality of life by improving motion and function as well as reducing pain. Physical therapy can help with balance problems, lack of coordination, fatigue, pain, gait, immobility, and weakness. [24, 25, 26]

OCCUPATIONAL THERAPY:

Occupational therapy can help people with Parkinson's disease stay active in their daily lives. By improving your skills, showing you different ways to complete a task, or introducing you to equipment for practice, an occupational therapist can help you perform everyday activities with ease. easier and more satisfying. Occupational therapists typically provide assessment, treatment, and recommendations in the following areas: Arm and hand therapy, handwriting assistance, ome revision information, driver assessment and vehicle modification information, adjustments for cooking and household chores, adjustments for eating and dishes, how to get the most out of your energy, adjust your computer, adjust your workplace or work equipment, develop recreational skills, use a manual or electric wheelchair, use a use bath equipment and grooming, dressing and grooming tools. [26, 27, 28]

SPEECH THERAPY:

Dysarthria (difficulty speaking) and dysphagia (difficulty swallowing) can significantly limit the symptoms of Parkinson's disease. Both can be helped by consulting a speech therapist or speech therapist. Examples of devices available to help people with Parkinson's disease communicate more clearly.

Elevation of the palate: Dental appliances are like braces. It lifts the soft palate and prevents air from escaping from the nose during speech.

Amplification: Personal amplifiers can be used to increase voice volume. The amplifier also reduces voice fatigue.

TTY phone relay system: The phone is equipped with a keypad so that the relay operator can input and read speech to the listener. You can enter the entire message or just the words you don't understand.

Low-tech equipment: Handbooks and language tables can be used as alternative communication techniques. High-tech electronic voice amplifier, communication equipment. Computers equipped with speech synthesizers and dedicated communication equipment are available.[29, 30, 31, 32]

SURGERY:

Deep Brain Stimulation: Deep brain stimulation was approved by the Food and Drug Administration (FDA) in 2002 "as an adjuvant therapy for the relief of certain symptoms of progressive, uncontrolled Parkinson's disease responsive to levodopa that is uncontrolled full of drugs".

Deep brain stimulation is a surgical technique in which one or more electrodes attached to wires are implanted into specific regions of the brain. The electrodes are connected to a device called a pulse generator, which transmits electrical stimuli to brain tissue to modulate or disrupt nerve signal patterns in a targeted area. Two specific brain sites have been most commonly targeted for deep brain stimulation in Parkinson's disease: hypothalamic nucleus and medial segment of the glomerulus. Both are nuclei in the basal ganglia, where many of the degenerative changes in Parkinson's disease occur. Deep brain stimulation acts on the cells and fibers closest to the implanted electrode, in most cases by inhibiting the cells and stimulating the fibers [33, 34](Figure 3). This therapy affects several hippocampal circuits, downstream pathways, and other brain structures. Deep brain stimulation changes the firing rate and firing pattern of individual neurons in the basal ganglia.[35] The current also acts on synapses and prompts nearby astrocytes to release a burst calcium waves and promote the release of local neurotransmitters (e.g., adenosine and glutamate).[36 - 38] Finally, the therapy increases blood flow and stimulates neurogenesis. [39] All of these effects occur cumulatively through an extensive neural network, extending beyond the local neurons and axons located around the electric field (Figure 4). Thus, deep brain stimulation has electrical, chemical, and other neural network effects on brain tissue. However, it remains unclear exactly how these effects lead to changes in Parkinson's disease symptoms; therefore, the benefits of this therapeutic modality are more or less established empirically.[40]

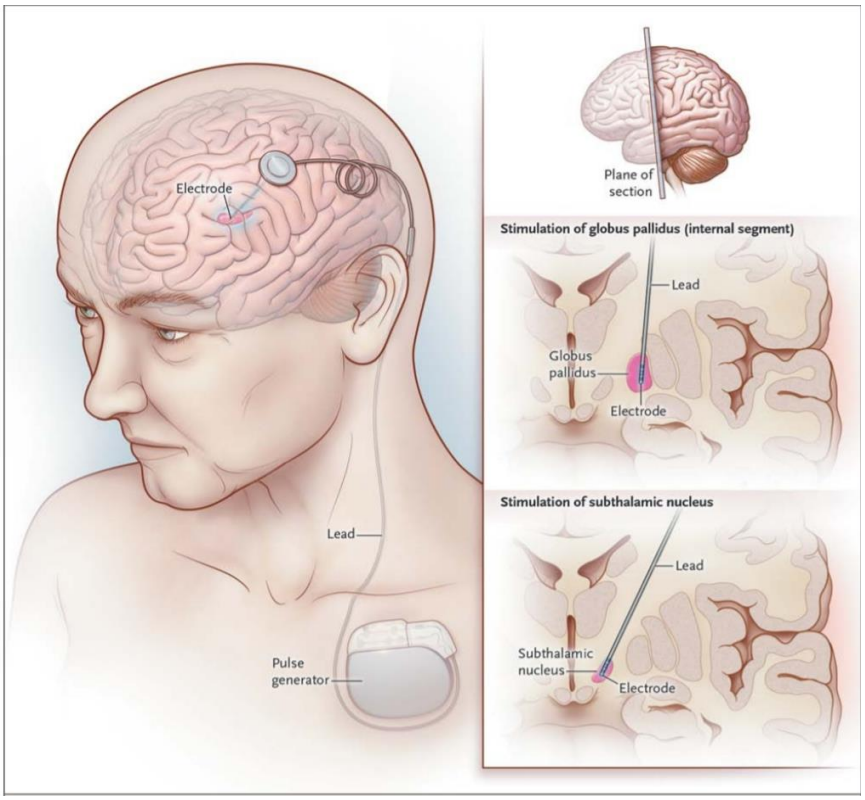


Fig 3: Electrode implantation for deep brain stimulation

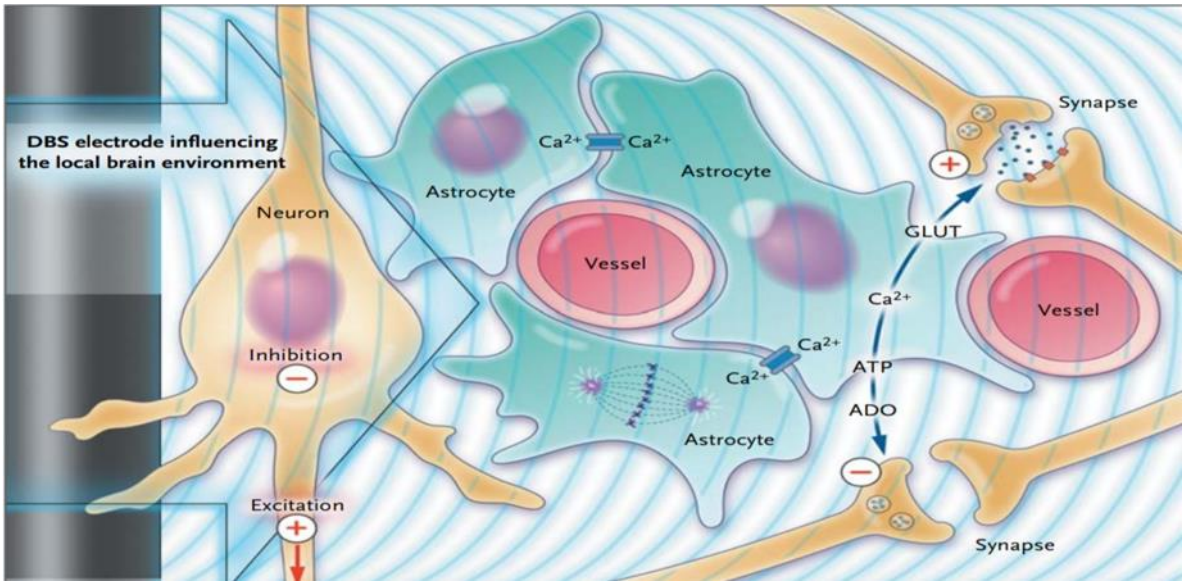


Fig 4: Local Effects of Deep-Brain Stimulation (DBS)

PALLIDOTOMY:

Pallidotomy surgery is an alternative to deep brain stimulation to treat involuntary movements called dyskinesia, which can become a problem in people with Parkinson's disease after long-term treatment. levodopa - a condition known as levodopa-induced dyskinesia.[41] Once used as the mainstay of treatment for Parkinson's disease, it has been largely replaced by levodopa. Pallidotomy surgery can sometimes be used to treat difficult essential tremors as an alternative to deep brain stimulation.[43] It can also be used for dystonia and hemiplegia.[42]

THALAMOTOMY:

Thalamotomy also known as hippocampal surgery, is a surgical procedure used to destroy part of the thalamus, a small part of the brain that controls involuntary muscle movements, so patient experience bias is limited. Because of its ability to control involuntary tremors and muscle spasms, this procedure is used in the treatment of Parkinson's disease and management of its symptoms. However, it is less commonly used, with many doctors recommending pallidotomy, which is similar in concept to thalamic surgery but can control more symptoms, or deep brain stimulation, which is associated with less risk.[44]

FOCUSED ULTRASOUND:

Focused ultrasound is an early-stage, non-invasive treatment technology that has the potential to improve quality of life and reduce the cost of care for patients with Parkinson's disease. This new technology precisely focuses ultrasonic energy beams on targets deep in the brain without damaging surrounding normal tissues. When the beams are focused, the ultrasound waves can produce a variety of therapeutic effects that allow the treatment of Parkinson's disease without the need for skin incisions or radiation. In December 2018, the FDA approved the use of focused ultrasound to treat patients with Parkinson's disease.[45]

GAMMA KNIFE TREATMENT:

Gamma knife stereotactic radiosurgery is a minimally invasive brain procedure called gamma knife thalamotomy that can help reduce tremors in people with Parkinson's disease. "Shows sustained efficacy and safety for intractable ET and PD-associated tremor, even in patients who are elderly, on anticoagulants, or with a history of stroke, which are contraindications." determined at DBS."[46]

NEURAL ALCHEMY:

There are two types of adult stem cells. One type can be found in fully developed tissues such as bone marrow, liver, and skin. These stem cells are few in number and often develop into the type of cell that belongs to the tissue from which they originate. The second type of adult stem cells (and the focus of this study) are called induced pluripotent stem cells (iPSCs). The iPSC manufacturing technique used in the study took place in two phases. In a way, cells are made to move in time, first in the opposite direction and then in the opposite direction. First, the adult blood cells are treated with specific reprogramming factors to turn them back into embryonic stem cells. The second stage treats these embryonic stem cells with additional factors, causing them to differentiate into the desired target cells, dopamine-producing neurons. Research demonstrates that the outcome of this nerve transplant is an effective reversal of motor symptoms caused by Parkinson's disease.[47]

When a small number of iPSCs were grafted into the animal brain, recovery was negligible, but a large complement of cells produced more profuse neural branching, and complete reversal of Parkinson’s symptoms. The initial clinical trial will apply iPSC therapy to a group of Parkinson’s patients bearing a particular genetic mutation, known as a Parkin mutation. Such patients suffer from the typical symptoms of motor dysfunction found in general or idiopathic Parkinson’s, but do not suffer from cognitive decline or dementia. The treatment could potentially be combined with existing therapies to treat Parkinson’s disease. Once the brain has been seeded with dopamine-producing replacement cells, lower doses of drugs like L-DOPA could be used, mitigating side effects, and enhancing beneficial results.[47]

FETAL TISSUE TRANSPLANTATION:

Cell transplants are being developed for patients with Parkinson's disease (PD) who do not receive standard medical treatment. Clinical features of five patients with persistent dyskinesia after fetal dopaminergic tissue transplantation. All had levodopa-induced dyskinesia before surgery. Fetal midbrain dopaminergic tissue was implanted in bilateral putamina in 34 patients with advanced PD. They are not immunocompromised. Patients with unilateral pallidal pacemakers had significant reductions in dyskinesia, but efforts to treat residual "off" symptoms with levodopa were limited by worsening dyskinesia. Although the number of patients who develop this persistent movement disorder is small, these five patients showed significant improvement after transplantation. As a group, they had milder Parkinson's disease symptoms at baseline and improved to minimal Parkinson's disease, with the reduction or elimination of levodopa therapy prior to development of the dyskinesia. persistent. These involuntary movements establish the principle that fetal dopaminergic tissue grafts can mimic the effects of levodopa, not only reducing bradykinesia but also causing dyskinesia.[48]

STEM CELL REPLACEMENT THERAPY:

Stem cell replacement therapy represents an entirely new strategy for the treatment of Parkinson's disease and other neurodegenerative diseases. The future method will soon be put to the test in the first clinical trial of its kind, in a specific group of people with Parkinson's disease who carry mutations in the Parkinson gene. New research details the experimental preparation of stem cells suitable for transplantation to reverse the effects of Parkinson's disease. Adult cells can be reprogrammed, making them 'pluripotent' - or able to differentiate into any cell type in the body. These pluripotent stem cells are functionally equivalent to fetal stem cells, they thrive during embryonic development, migrate to residence, and develop into heart, nerve, and lung cells. and other cells, in one of nature's most remarkable transformations. [47]

ALTERNATIVE THERAPIES:

Supportive therapies can help relieve some of the symptoms and complications of Parkinson's disease, such as pain, fatigue, and depression. When taken in conjunction with your treatments, these therapies can improve your quality of life:

Massage: Massage therapy can relieve muscle tension and promote relaxation. However, this therapy is rarely covered by health insurance.

TAI CHI: An ancient Chinese form of exercise, tai chi uses slow, fluid movements that can improve flexibility, balance, and muscle strength. Tai chi can also help prevent falls. Some forms of tai chi are appropriate for people of any age or physical condition. One study has shown that tai chi can improve balance in people with mild to moderate Parkinson's disease more than endurance training and stretching.

Yoga: In yoga, gentle stretches and movements can increase your flexibility and balance. You can modify most poses according to your physical ability.

Alexander technical: This technique mainly focusing on muscle posture, balance, and thinking about how you use your muscles which can reduce muscle tension and pain.

Meditation: In meditation, you think quietly and focus your mind on an idea or image. Meditation can reduce stress and pain and improve your sense of well-being.[49]

CONCLUSION:

Treatment for Parkinson's disease typically involves a combination of treatments. An important part of Parkinson's disease treatment is drug therapy supported by various combination therapies.

Treatment is primarily aimed at relieving symptoms and side effects, as the disease itself cannot currently be cured. Each Parkinson's disease course is different, and the type and severity of symptoms vary widely. What is particularly worrying to one person may not be noticed by another. In addition to symptoms, medical history, age, and living environment also play an important role. Therefore, individualized treatment is necessary.

Alternative therapies that have been shown to be beneficial in treating Parkinson's disease include acupuncture, guided imagery, chiropractic, yoga, hypnosis, biofeedback, aromatherapy, relaxation, herbal remedies, and massage. There are many fields. Music and art therapy are also used as complementary and alternative medicine.

Currently, the most common treatment uses the drug levodopa to stimulate dopamine production in specific neurons associated with exercise performance. These dopaminergic neurons are found in the nigrostriatal pathway, a brain circuit that connects neurons in the substantia nigra pars compacta to the dorsal striatum. However, levodopa has a variety of side effects, ranging from physiological to psychological. Even in the long term, the benefits of such dopamine-modulating drugs are limited. Scientists therefore need to develop more effective strategies to repair brain damage caused by Parkinson's disease.

Stem cells offer the potential for a virtually limitless supply of optimized dopaminergic neurons and may have enhanced advantages compared to fetal midbrain transplantation. Stem cells have now been shown to be able to differentiate into beneficial dopamine neurons after transplantation into animal models of Parkinson's disease. Although the exact mechanism by which Mesenchymal Stem Cell Therapies (MSCs) can exert their beneficial effects in neurological diseases remains to be elucidated, several different mechanisms appear to contribute. First, MSCs have been shown to secrete neurotrophic growth factors (such as glial-derived neurotrophic factor (GDNF)), vascular endothelial growth factor, and brain-derived neurotrophic factor (BDNF), which under certain culture conditions can be further enhanced with Neurotrophic growth factors have been shown to promote neuronal cell survival in various preclinical models of neuronal injury, including Amyotrophic lateral sclerosis (ALS) , Parkinson's disease (PD), and Multiple system atrophy (MSA) transgenic animals and neuro injury models.

REFERENCE:

1. Stoker TB. Stem Cell Treatments for Parkinson’s Disease. In: Stoker TB, Greenland JC, editors. Parkinson’s Disease: Pathogenesis and Clinical Aspects [Internet]. Brisbane (AU): Codon Publications; 2018 Dec 21. Chapter 9.
2. Stuart H. Ralston, lan D. Penman, Mark W. J. Strachan, Richard P. Hobson; Textbook of Davidson's principles and practice of Medicine, 23rd Edition, Elseiver.
3. Marvanova M. Introduction to Parkinson disease (PD) and its complication. Ment Health Clin Internet). 2016;5(5):229-35. DO 10097402006.05.229

4. Wolters EC, van der Werf YD, van den Heuvel OA. . Parkinson's disease-related disorders in the impulsive-compulsive spectrum. J Neurol. 2008; 255 Suppl 5: 48- 56. DOI: 10.1007/s00415-008-5010-5. PubMed PMID: 18787882. [PubMed]
5. Walsh RA, Lang AE. . Multiple impulse control disorders developing in Parkinson's disease after initiation of amantadine. Mov Disord. 2012; 27 2: 326 DOI: 10.1002/mds.23964. PubMed PMID: 21954056. [PubMed].
6. Seunggu Han, M.D., Yvette Brazier. Parkinson's disease early signs and causes. Updated on April 13, 2021.
7. Causes of Parkinson's disease .The Parkinson's Foundation is a 501(c)3 non-profit organization. EIN: 13-1866796
8. Parkinson's disease meaning, causes and symptoms. Retrieved form: https://www.credihealth.com/blog/parkinsons-disease-meaning-causes-symptoms/
9. Baumann CR. Epidemiology, diagnosis and differential diagnosis in Parkinson's disease tremor. Parkinsonism Relat Disord. 2012;18(suppl 1):S90–S92.
10. Hughes AJ, Daniel SE, Lees AJ. Improved accuracy of clinical diagnosis of Lewy body Parkinson's disease. Neurology. 2001;57:1497–1499
11. Postuma RB, Aarsland D, Barone P, et al. Identifying prodromal Parkinson's disease: pre-motor disorders in Parkinson's disease. Mov Disord. 2012;27:617–626
12. Huot P, Fox SH, Brotchie JM. The serotonergic system in Parkinson's disease. Prog Neurobiol. 2011;95:163–212.
13. Doherty KM, van de Warrenburg BP, Peralta MC, et al. Postural deformities in Parkinson's disease. Lancet Neurol. 2011;10:538–549.
14. The Unified Parkinson's Disease Rating Scale (UPDRS): status and recommendations. Mov Disord. 2003;18:738–750
15. Shaziya Allarakha, MD, Pallavi Suyog Uttekar, MD. What Are the 5 Stages of Parkinson's Disease? Reviewed on 9/30/2021. Medicinet.com.
16. Kwan LC, Whitehill TL. Perception of speech by individuals with Parkinson's disease: a review. Parkinsons Dis. 2011;2011:389767. doi: 10.4061/2011/389767. Epub 2011 Sep 22. PMID: 21961077; PMCID: PMC3179876
17. Parkinson's Disease: Moving Forward. 2. Pathophysiology of Parkinson's Disease. A train education - continuing education for health care professionals
18. Cookson, M.R. α-Synuclein and neuronal cell death. Mol Neurodegeneration 4, 9 (2009). https://doi.org/10.1186/1750-1326-4-9
19. Brian R Haas, Tessandra H Stewart, Jing Zhang. PREMOTOR BIOMARKERS FOR PARKINSON'S DISEASE - A PROMISING DIRECTION OF RESEARCH. Academic research paper on "Clinical medicine". Translational neurodegeneration 2012, 1:11. DOI: 10.1186/2047-9158-1-11

20. Gasparini F, Di Paolo T, Gomez-Mancilla B. Metabotropic glutamate receptors for Parkinson's disease therapy. Parkinsons Dis. 2013;2013:196028. doi: 10.1155/2013/196028. Epub 2013 Jun 19. PMID: 23853735; PMCID: PMC3703788.
21. Tom Mihaljevic, Parkinson's disease, Cleveland Clinic, reviewed on 04/15/2022.
22. Gilbert DR. New Laboratory Tests for Parkinson's Disease. (https://www.apdaparkinson.org/article/new-laboratory-tests-for-parkinsons-disease/) APDA. Published Dec. 14, 2021.
23. Alan Carter, Pharm.D., Rachael Zimlich, RN, BSN. What Should I Know about Parkinson's Medications? Reviewed on June 24, 2021.https://www.healthline.com/health/parkinsons/parkinson-medication
24. National Parkinson Foundation: "Managing Advanced Parkinson's Disease."
25. Parkinson's Disease Foundation: "Physical Therapy in PD."
26. Ohio State University Wexner Medical Centre: "Physical Therapy and Occupational Therapy for Parkinson's Disease."
27. Parkinson's Disease Foundation: "Frequently Asked Questions: Occupational Therapy."
28. National Parkinson Foundation: "Guidelines for Occupational Therapy in Parkinson's Disease."
29. Parkinson's Disease Foundation: "Speech Therapy in PD."
30. Parkinson's Disease Foundation: "Coping with Symptoms."
31. National Parkinson Foundation: "Speech & Swallowing."
32. National Institute of Neurological Disorders and Stroke: "Parkinson's Disease: Hope Through Research."
33. McIntyre CC, Hahn PJ. Network perspectives on the mechanisms of deep brain stimulation. Neurobiol Dis 2010;38: 329-37.
34. Vitek JL. Mechanisms of deep brain stimulation: excitation or inhibition. Mov Disord 2002;17:Suppl 3:S69-S72.
35. Wichmann T, DeLong MR, Guridi J, Obeso JA. Milestones in research on the pathophysiology of Parkinson's disease. Mov Disord 2011;26:1032-41.
36. Tawfik VL, Chang SY, Hitti FL, et al. Deep brain stimulation results in local glutamate and adenosine release: investigation into the role of astrocytes. Neurosurgery 2010;67:367-75.
37. Lee KH, Hitti FL, Chang SY, et al. High frequency stimulation abolishes thalamic network oscillations: an electrophysiological and computational analysis. J Neural Eng 2011;8(4):046001.
38. Lee KH, Chang SY, Roberts DW, Kim U. Neurotransmitter release from high-frequency stimulation of the subthalamic nucleus. J Neurosurg 2004;101:511-7.
39. Vedam-Mai V, van Battum EY, Kamphuis W, et al. Deep brain stimulation and the role of astrocytes. Mol Psychiatry 2012;17:124-31.
40. Michael S. Okun, M.D. Deep-Brain Stimulation for Parkinson's Disease, The New England Journal of Medicine, N Engl J Med 2012;367:1529-38.DOI: 10.1056/NEJMct1208070, Copyright © 2012 Massachusetts Medical Society.
41. Oertel, W.H.; Berardelli, A.; Bloem, B.R.; Bonuccelli, U.; Burn, D.; Deuschl, G.; et al. (2011). "Late (complicated) Parkinson's disease" (PDF). In Gilhus, Nils Erik; Barnes, Michael R.; Brainin, Michael

(eds.). European Handbook of Neurological Management. Vol. I (2nd ed.). Blackwell. pp. 240–1. ISBN 978-1-405-18533-2. Retrieved 31 October 2012.

42. Smith, K. A.; Javedan, S. P.; Shetter, A. G. (2014). "Pallidotomy". Encyclopedia of the Neurological Sciences - Reference Module in Neuroscience and Biobehavioral Psychology (2nd ed.). Academic Press. pp. 778–780. doi:10.1016/B978-0-12-385157-4.00773-9. ISBN 978-0-12-385158-1.
43. Hooper, Amanda K.; Okun, Michael S.; Foote, Kelly D.; Fernandez, Hubert H.; Jacobson, Charles; Zeilman, Pamela; Romrell, Janet; Rodriguez, Ramon L. (2008). "Clinical Cases where Lesion Therapy Was Chosen over Deep Brain Stimulation". Stereotactic and Functional Neurosurgery. 86 (3): 147–52. doi:10.1159/000120426. PMID 18334856
44. Clarke CE, Moore AP (2007). Parkinson's disease, search date November 2006. BMJ Clinical Evidence. Available online: http://www.clinicalevidence.com
45. Parkinson's Disease, https://www.fusfoundation.org/diseases-and-conditions/neurological/parkinsons-disease, Last Updated: 11 April 2022
46. Marisa Wexler, MS, Gamma Knife Brain Procedure May Ease Tremor, March 25, 2022, Parkinson's News Today, https://parkinsonsnewstoday.com/2022/03/25/thalamotomy-gamma-knife-eases-parkinsons-tremor-study/
47. Jeffrey Kordower, Arizona State University, Designer Neurons Offer New Hope for Treatment of Parkinson's Disease, May 11, 2022, neuroscience news.com.
48. Greene, P.E., Fahn, S., Eidelberg, D. et al. Persistent dyskinesias in patients with fetal tissue transplantation for Parkinson disease. npj Parkinsons Dis. 7, 38 (2021). https://doi.org/10.1038/s41531-021-00183-w
49. Parkinson's disease. Mayo clinic. Patient care and health information, https://www.mayoclinic.org/diseasesconditions/parkinsons-disease/diagnosis-treatment/drc-20376062