Ilkogretim Online - Elementary Education Online, 2021; Vol 20 (Issue 2): pp. 2679-2690
http://ilkogretim-online.org
doi: 10.17051/ilkonline.2021.02.284

# Paralysis Agitans: An Assessment Of The Determinants And Therapeutic Tactics

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**ABSTRACT**

Paralysis agitans, often known as idiopathic parkinsonism, is a persistent neurological disease that affects 50 to 328 persons per lakh globally. Paralysis agitans affect more than 1% of the population over the age of 65, and the prevalence and incidence rates rise with age. Tremor, inflexibility, and difficulties in standing, walking, balancing, and synchronizing one's actions are all symptoms of paralysis agitans, a prevalent neurological disease. The primary cause of this condition is presumed to be the inexplicable breakdown of dopamine-secreting cells in the substantia nigra, which is located in the midbrain. Stationary tremor, cogwheel stiffness, and bradykinesia are three "cardinal indicators" of paralysis agitans. Spasticity is the fourth cardinal sign, and it is usually a late symptom of paralysis agitans. Symptoms that appear infrequently and symptomatic responses to L-dopa are also prevalent. The lack of a gold standard assays makes diagnosing paralysis agitans difficult. While the use of Levodopa is limited due to the occurrence of motor inconsistencies and drug-induced dyskinesias, it is still the basis of therapeutic intervention for paralysis agitans. Dopamine agonists (DAs) are also administered, either alone or in combination with Levodopa. Dopamine agonists stimulate the production of natural dopamine increasingly by acting directly on dopamine receptors. Another class of drugs known as Monoamine oxidase B (MAO-B) inhibitors increases dopamine levels in the basal ganglia by blocking dopamine catabolism. Catechol O-methyl transferase (COMT) inhibitors lengthen the half-life of L-dopa in the peripheral nervous system by reducing dopamine breakdown. Regardless of the several paralysis agitans therapies available, every sufferer needs L-dopa at some point throughout the therapy cycle. Individuals suffering from paralysis agitans who react to therapies, but experience uncontrolled side effects may choose to consider surgery. Among the surgical options are ablative methods (thalamotomy or pallidotomy), tissue transplantation, and deep brain stimulation (DBS). Although the exact cause of paralysis agitans is unknown, it is suspected that a potentiator is a combination of genetic, oxidative stress, and environmental factors.

**KEYWORDS:** Paralysis agitans, L-dopa, Movement disorder, Dopaminergic Medication, PINK1 gene

## INTRODUCTION

Paralysis agitans is the 2nd most frequent neurological disorder following the benign tremor, with an approximated frequency of roughly 1% among people over six. In 1817, James Parkinson was the first to identify and describe this disorder. There are two types of this ailment, inherited and spontaneous. Paralysis agitans having genetic predisposition follows Mendelian inheritance pattern. Desultory paralysis agitans, which account for at least 85-90% of all instances is a more convoluted class with unclear pathophysiological pathways [2]. The architecture of the basal ganglia (**Figure 1**) integrates messages from the brain, allowing voluntary actions to be executed correctly. The degeneration of dopaminergic neurons in the substantia nigra pars compacta causes a sequence of functional alterations across the basal ganglia circuitry in paralysis agitans [3]. Paralysis agitans manifests in various ways each with its unique set of causal factors, predisposing factors, pathophysiology, and therapeutic choices. This neurological ailment affects individuals between the ages of 50 and 65 and strikes 1%–2% of those over 60, increasing to 3.5 % by the age of 75–90. Inherited or linked to particular gene abnormalities, paralysis agitans is significantly connected to one's age [3, 4]. Both motor and non-motor symptom development has a significant influence on the victim's overall standard of life. As the condition progresses, those who are afflicted with paralysis agitans may have trouble standing, walking speaking, and balancing overall body movements. Additionally, throughout this condition, psychological and cognitive abnormalities are also documented with the most prevalent symptoms being sleep disruption, anxiety, sadness, concentration difficulties, and fatigue concerns. Equally men and women can be afflicted by paralysis agitans, however, the number of cases recorded in males is higher than in females [2, 5]. New therapeutic strategies and changes to existing ones are being explored extensively for paralysis agitans management. Physicians may now address not only the basic motor symptoms of paralysis agitans, but also patient-specific challenges, due to advancements in pharmacological sciences, and surgical, and therapeutic procedures for idiopathic parkinsonism.

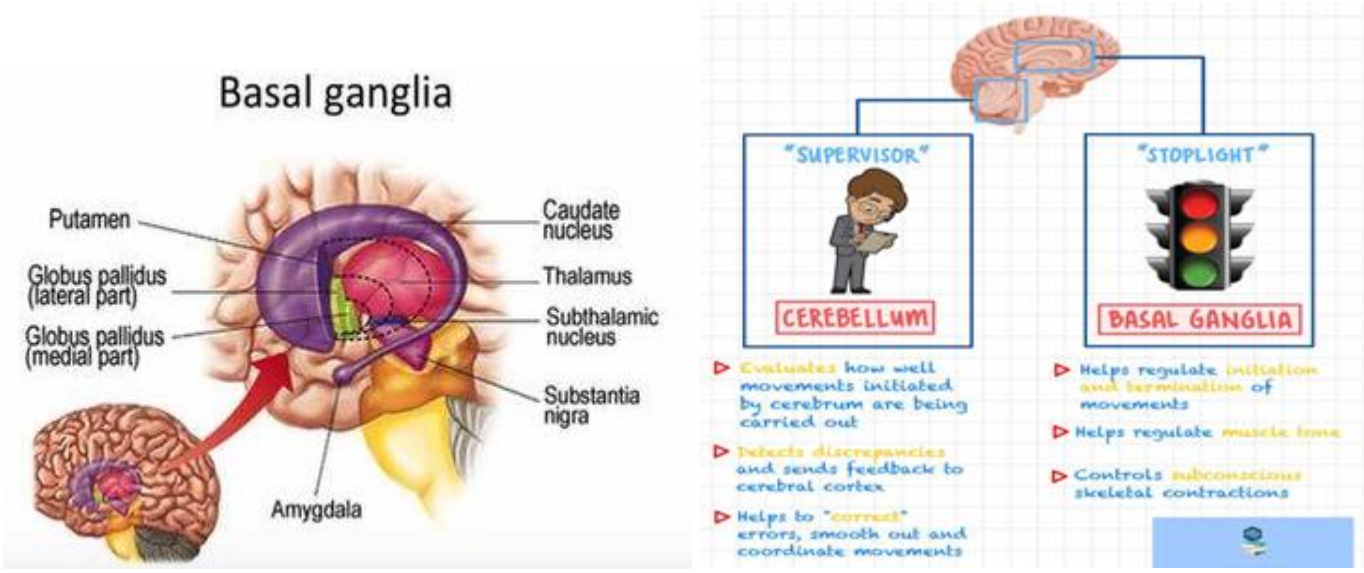


**Figure 1** | Basal Ganglia, the center for movement control

## GENERAL SYMPTOMS OF PARALYSIS AGITANS

Paralysis agitans show itself in a variety of forms, the most common of which is progressive neurodegeneration and finally movement abnormalities. The limbs and trunk are rigid, and the hands, arms, legs, jaw, or head tremor (shake) or are unable to move. Balance and coordination are reduced, which can lead to falls [5, 6]. Depression and other mood changes, difficulties eating, chewing, and speaking, bladder or constipation issues, skin problems, and sleep abnormalities are among symptoms that might occur. Paralysis agitans is a degenerative illness that becomes worse over time. Those who are impacted may suffer minor tremors or difficulty getting out of a chair. When paralysis agitans is in its initial phase, close associates of the victim may be the first to detect alterations in movement. They could note that the sufferer's face is devoid of expressions and pixilated, that arms or legs show an uncoordinated movement or there is pseudo balanced gait [6, 7]. A trembling on one side of the body (foot, arm, hand, or another body part) when the individual is at rest is one of three early indicators of paralysis agitans. Toughness, or reluctance to mobility, is the second symptom, which happens when a person tries to move a joint or transitions from a seated to a standing posture. The third symptom is bradykinesia, or sluggish movements [8]. Micrographia (cramped handwriting) and a paucity of facial expressions characterize Bradykinesia (In the majority of cases, the victim's expression is solemn). This is referred to as a "masked face" scenario [9]. (**Figure 2**.)

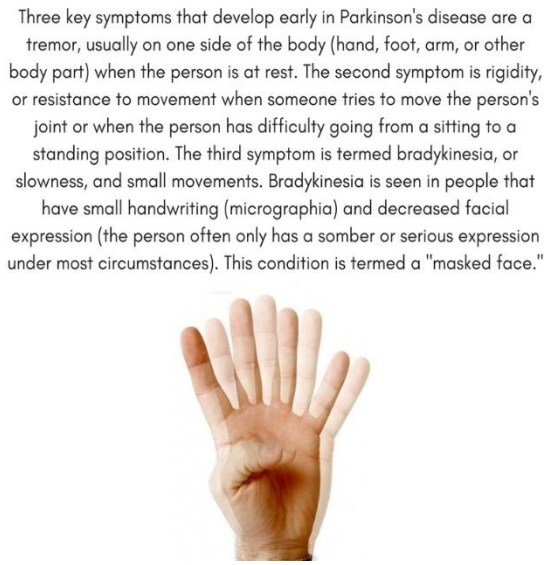


**Figure 2** |Three early signs of Paralysis agitans

Paralysis agitans affect people differently and progress at varying speeds. Early indications of paralysis agitans can be disseminated as part of the natural aging process. Because no medical tests have been done or published for this condition that can reliably detect it in the majority of cases, a correct diagnosis can be challenging. The five phases of paralysis agitans are as follows (**Figure 3**) [3, 7, 9].

**STAGE 1:**

The symptoms are minimal at this point and do not hamper regular activities.

- Tremors, rigidity, and bradykinesia are examples of movement symptoms that affect only one side of the body (unilateral).
- Issues with posture and balance that are not serious.
- Walking is a little challenging.
- Slightly changing facial expressions.

**STAGE 2:**

At this stage, the symptoms have worsened, making daily tasks more difficult. On the other hand, the individual is self-sufficient. Spasms, stiffness, and bradykinesia as movement disorder symptoms strike the body bilaterally.

- There is difficulty in Walking.
- It is difficult to balance or synchronise body movements.
- There is Poor posture and pseudo-gait.
- Face is masked or expressionless.

**STAGE 3:**

The symptoms are more severe at this level (middle stage) than in stage II. On the other hand, the individual is self-sufficient. A lack of balance with retardness in movement termed bradykinesia characterizes this stage. Daily routines such as eating, bathing, and clothing are all seriously disturbed.

**STAGE 4:**

Due to constraints in diurnal activities such as eating, dressing, bathing, resting, and getting up, independent life is almost unattainable at this stage. Although the patients may be capable of standing on their own, they will require assistance in moving around.

**STAGE 5:**

At this phase, the symptoms are so severe that trying to get up on one's own may be unfeasible. The individual becomes paraplegic and requires a wheelchair for transportation. Daily activities are impeded, necessitating a caregiver's supervision throughout the day. Some of the indications and symptoms are as follows:

- Imaginative disabilities
- Visual and auditory hallucinations (things that aren't there are seen, felt, or heard.).
- Olfactory disintegration.
- Constipation.
- Memory and concentration problems.
- Weight reduction.
- Sleep hypopnea.


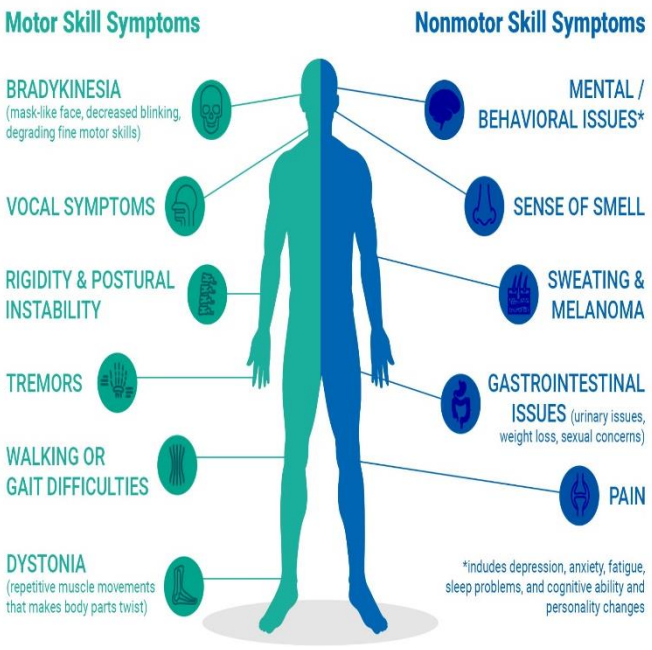


**Figure 3**| Stages and symptoms of the development of paralysis agitans

## CAUSES OF PARALYSIS AGITANS

Paralysis agitans is a type of dopamine-related neurological disintegration that affects an individual's bodily movements and produces neurological instability. This condition affects millions of people throughout the world. The exact etiology of this aliment is yet to be established. Around 1-2 % of adults over the age of 60 suffer from paralysis agitans. This affliction is developed by the unclear degeneration of dopamine-producing cells in the substantia nigra, located in the midbrain [6, 10]. While the majority of cases of paralysis agitans seem to be inherited, a tiny proportion is linked to specific genetic defects. In the majority of cases, the aliment appears to strike randomly. However, much study has been conducted in an attempt to determine the root cause of this problem. Many specialists believe that paralysis agitans is triggered by a mixture of inherited, oxidative stress, and environmental factors [11, 12].

## ENVIRONMENTAL FACTORS

Several research on the impact of the environment on paralysis agitans has been undertaken, and all of them have yielded mixed results. The impacts of acute toxicity due to exposure to pesticides and water-borne risk factors have received the most attention [13, 14]. Upon a gross pathological investigation, a large percentage of pesticides carrying manganese was detected in the brain tissue of patients, as per the location-specific research, which probed these relationships in five European states. Even a little quantity of acute poisoning of pesticides has been proven to greatly raise the risk of neurodegeneration [15]. Although this study was able to establish that pesticides alter paralysis agitan's development, it was hampered by its inability to identify the specific chemical in question. As shown in a meta-analysis that looked at environmental triggers for the initiation of paralysis agitans, people who live in rural areas and rely on wells for their water have a higher chance of developing paralysis agitans, according to the research, because toxins may have seeped into the soil and then into the groundwater. When risk variables were evaluated in rural and urban locations, the conclusions revealed no statistically significant variation. Since the findings of various studies fluctuate, new data gathering strategies are required to better understand the etiology of paralysis agitans [16].

## GENETIC FACTORS

Even though genetically caused paralysis agitans affects a relatively small number of people, it can provide a firm understanding of the underlying mechanisms. Paralysis agitans affect the majority of persons who have no clear family history of the condition. These occasional instances may or may not be transmitted, or they may have an unclear pattern of inheritance [3, 16]. The mode of inheritance for family instances of paralysis agitans varies depending on which gene is changed. Kurosinski et al. [17] employed knockout mice and fly experiment models to find the exact genetic changes linked to paralysis agitans development. Their data confirmed that SYN gene changes (A30P and A53T) cause paralysis agitans in animal models. Internal cellular -synuclein complexes arise due to the A30P and A53T gene alterations. Abramov et al. [18] explored the clinical disease model in another investigation. Because many biomolecules (proteins) are linked to paralysis agitans, the study's findings showed that the development of paralysis agitans may be related to a wide range of genes [19]. Abramov et al. studied PTEN-induced kinase 1, a gene that generates the important mitochondrial protein PINK1. Although the exact function of this protein is unknown, it has been discovered to deal with oxidative stress containment in mitochondria. Oxidative stress aids the course of paralysis agitans (discussed later). In fibroblasts from five separate paralysis agitans patient groups, the researchers detected a mutant PINK1 gene [19]. Since the etiology of paralysis agitans in these individuals can be linked back to a PINK1 gene mutation, a significant genetic involvement has been proposed. SYN and PINK1 gene mutations have been shown to cause paralysis agitans in their own right, based on these studies. The SYN mutation causes abnormal -synuclein folding, dopaminergic neuron loss, and other symptoms [19, 20]. The condition is autosomal-dominant form if the LRRK2 or SNCA genes are implicated, which implies that one copy of a mutated gene in each cell is enough to produce the condition. In the majority of instances, an afflicted person has one parent who has the disease [17, 21]. Paralysis agitans is passed in an autosomal recessive form if the PINK, PARK7, or PRKN gene is implicated. This kind of distribution involves the alteration of two sets of genes in each cell. The parents of a person with autosomal recessive paralysis agitans usually each have one copy of the mutated gene but do not display any indications of the disorder [18, 19, 22]. The mode of inheritance is largely unclear when genetic alterations influence the chance of acquiring paralysis agitans.

## OXIDATIVE STRESS-RELATED FACTORS

One theory for the pathophysiology of paralysis agitans that is grabbing prominence is that reactive free radicals (ROS) contribute to nerve cell demise that is liable for the secretion of dopamine in the nigrostriatal system [22, 23]. The body's normal metabolic activities generate free radicals as by-products of chemical reactions mostly in mitochondria which in turn create oxidative stress. A free radical is an atom, molecule, or compound that is highly reactive due to its atomic or molecular makeup of having free unpaired electrons. Free radicals, also known as reactive oxidative species (ROS), created under some conditions may exceed the capacity of the clean-up systems of enzymes and antioxidants. This situation is referred to as oxidative stress [19, 23]. Genetic material has been identified as one of the key targets of this mechanism in several studies. Dopamine catabolism gives rise to an endogenous bioactive chemical called Norsalsolinol. It has been demonstrated to be a selective dopaminergic neurotoxin and has been hypothesized as a probable cause of neurological disorders including paralysis agitans. According to Tatton et al., [24], norsalsolinol neurotoxin is present in dopamine-rich areas and have revealed to alter cytochrome c release and caspase 3 activation in a manner that generated ROS and caused apoptosis. In cell cultures and animal models, Nakabeppu et al. [25] observed that the inactivation of MTH1, an oxidised purine nucleoside triphosphatase, is linked to the build-up of 2-

deoxy-8-oxoguanosine triphosphate in both nuclear and mitochondrial DNA, resulting in an increase in reactive oxygen species and hence oxidative stress. As per research, MTH1 effectively protects human paralysis agitans patients against oxidative stress-prompted apoptosis.

**THE MPTP TOXIN: ACTION AND MECHANISM**

MPTP damages dopaminergic (DA) neurons in the substantia nigra pars compacta (SNpc), as documented in paralysis agitans. MPP +, the active ingredient of MPTP, aggregates inside SNpc DA neurons after systemic treatment, at which it suppresses ATP synthesis and induces superoxide radical generation. The generated superoxide radicals combine with nitric oxide (NO) to form peroxynitrite, a strong oxidizing tissue-damaging molecule that oxidises and nitrates proteins. Merely a few proteins get nitrated, and one of them is tyrosine hydroxylase (TH), the rate-limiting enzyme in DA production. The nitration process disables TH and, as a result, dopamine release. Peroxynitrite also trims DNA, activating poly (ADP-ribose) polymerase (PARP). PARP expression utilizes ATP, depleting cell energy stores quickly. This latter event exacerbates the pre-existing energy failure caused by MPP +-induced mitochondrial respiration blockage and causes apoptosis. Overall, an ample number of studies reinforce the hypothesis that MPTP causes a negative cascade of events that includes mitochondrial respiration shortfall, reactive oxygen species, and energy depletion. Due to the similarities between the MPTP mouse model and Parkinson's disease, it is tempting to hypothesize that a similar episode pertains to the development of paralysis agitans in humans [26, 14].

Whatever the reason for its emergence, paralysis agitans manifests when nerve cells in the brain die or a section or fragment of the brain that governs movement is harmed or compromised. The production of dopamine, a vital neurotransmitter in the brain, is dependent on these neurons. The depletion in the quantity of neurotransmitter dopamine due to the disintegration of cells that are responsible for its production is the fundamental cause that gives rise to this condition [12, 18, 26]. Scientists are still baffled as to why dopamine-producing cells die. The release of norepinephrine which is the most important neurotransmitter of the sympathetic nervous system regulating most physiological activities like heart rate is also disintegrated in the individuals afflicted with paralysis agitans. Some of the non-movement complications of this disorder, like fatigue, fluctuating cardiac output, distressed peristalsis, and acute hypotension when a person gets up from a sitting position, can be justified by a sudden loss or disintegration of norepinephrine [27]. Lewy bodies, bizarre collections of the protein alpha-synuclein, are seen in many brain cells in persons with paralysis agitans. Scientists are looking at alpha-normal synuclein's neuropathological functions, as well as its link to genetic defects that underlie paralysis agitans and Lewy body dementia [22, 28].

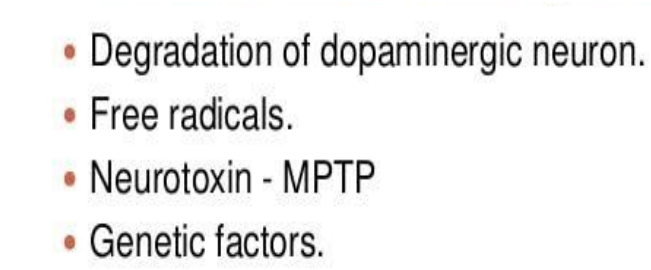


Figure 4 | Major causes of paralysis agitans

**TREATMENT**

Levodopa, sometimes known as L-dopa, which is utilized as a dopamine substitution for this neurological condition, is still the most widely employed therapy for paralysis agitans [20, 29]. To refill the brain's decreased supply of dopamine, nerve cells require levodopa. While other dopamine agonists are useful in managing indications of paralysis agitans initially on in the illness's progression, Levodopa is the most effective pharmacological agent for improving quality of life, particularly when symptoms become unbearable with other anti-parkinsonian treatments [30]. Carbidopa is frequently used with levodopa in the management of paralysis agitans. It reduces the quantity of levodopa needed to treat symptoms while also avoiding or minimising side effects such as vomiting, nausea, dizziness, hypotension, and agitation [31]. Patients with paralysis agitans should never quit taking levodopa without first visiting their physician. Stopping the drug suddenly might have serious implications, including incapacity to move or respiratory problems [32]. Although there is no curative therapy for paralysis agitans, there are a variety of medications, surgical procedures, and behavioural treatment options available, and innovative drugs are being developed to help lessen the illness's severe symptoms and manifestations. Surgical treatments including ablative surgery, deep brain stimulation, gene therapy and transplantation, occupational therapy, speech therapy, and cognitive behavioural therapy are non-drug options that can be utilised in conjunction with pharmaceuticals or on their own for people who want a more systematic strategy [33]. Following is an overview of current pharmacological interventions incorporated in the management of

1. **Drug Treatments**. When medications are used, there is little to no invasive therapy necessary. However, the biggest disadvantage of their use is that they may lose their potency with time [35].
2. **Dopaminergic Medication**: These are dopamine agonists that are given orally or intravenously. These are currently regarded as the "gold standard for therapy" due to their high response (80%) in idiopathic parkinsonism. It is the preferred therapy for late-onset paralysis agitans. The disadvantages of its use include that it is less preferred for early-onset paralysis agitans therapy owing to levodopa-related dyskinesia and that most patients eventually require dopamine agonists as the illness develops and other therapies fail. With oral treatment, levodopa necessitates increased dosage over time due to "on-off" swings [10, 36].
3. **Anticholinergics**: These medicines inhibit acetylcholine activity at choline receptors by quick permeation and can be used as monotherapy in the initial phases of tremor-predominant paralysis agitans. In senior people, these drugs have a low propensity. The new study suggests that cholinergic agents, instead of anticholinergics, may help with paralysis agitans symptoms. Dopamine agonists have mainly supplanted these medications in contemporary treatment regimens [19, 37].
4. **MAOIs inhibitors and antagonists**: These medicines impede the dissolution of levodopa and sustain dopamine levels and are benign in that their dosage does not need to be raised over time. These drugs may help with cognitive decline in later stages of paralysis agitans and have milder side effects than dopaminergic drugs. These medicines may be used in the management of L-DOPA-related dyskinesia. These agents may lack extensive effects on symptoms for late-stage paralysis agitans and must be supplemented with a group of drugs such as COMT inhibitors [38].
5. **Glial cell line-derived neurotrophic factors:** These are small endogenous peptides that are supplied to the brain via implantation. They work by increasing dopamine levels in the striatum. One issue with their use is the difficulty in getting them to brain cells across the blood-brain barrier. Studies on the usefulness of GDNF for symptomatic alleviation have yielded mixed results, indicating that additional study is needed [22, 39].

6. **Nanomedicine.** Nanotechnology aims to enhance the delivery, absorption, and avoidance of negative effects of already available medications. Nanocarriers improve medication transport across the blood-brain barrier and reduce drug loss in peripheral tissue, resulting in increased bioavailability and efficacy. Because nanomedicine is a relatively new subject, additional testing is required before administering bioactive molecules to treat paralysis agitans [40].

| | Class | Agent | Usage | Adverse effects[17] |
|---|---|---|---|---|
| First line | Dopamine precursor | Carbidopa/levodopa | Monotherapy to treat bradykinesia, postural instability, and rigidity | Orthostatic hypotension, dizziness, headache, depression, dyskinesia |
| Second line | Dopamine agonist | Pramipexole, ropinirole | Monotherapy or adjunct to levodopa to treat bradykinesia, postural instability, and rigidity | Orthostatic hypotension, drowsiness, dizziness, insomnia, abnormal dreams, nausea, constipation |
| | | Bromocriptine | Due to adverse effects and monitoring (baseline and annual ESR, renal function, and chest x-ray[16]) required, this drug is indicated only if the patient has failed all other pharmacologic therapy | *Contraindications*: uncontrolled HTN, syncopal migraines<br>*Adverse effects*: dizziness, nausea, hypoglycemia, pulmonary fibrosis, somnolence, hallucinations, rhinitis |
| | Monoamine oxidase B inhibitors | Selegiline | Off-label use as monotherapy. Adjunctive therapy in patients with decreasing response to carbidopa/levodopa | Headache, dizziness, insomnia, nausea, hypotension |
| | | Rasagiline | Monotherapy or adjunct to carbidopa/levodopa to treat bradykinesia, postural instability, and rigidity | Orthostatic hypotension, headache, dizziness, rash, nausea |
| | | Safinamide | Approved March 2017 as adjunctive therapy to reduce off time | Orthostatic hypotension, hypertension, falls, increased ALT and AST, nausea |
| Third line | Antiviral | Amantadine | Monotherapy or adjunctive therapy to treat dyskinesia. Should not be drug of first choice, according to NICE recommendations[16] | Orthostatic hypotension, syncope, peripheral edema. Avoid use 2 weeks before and 2 weeks after live influenza vaccine |

ALT, alanine aminotransferase; AST, aspartate aminotransferase; ESR, erythrocyte sedimentation rate; HTN, hypertension; NICE, The National Institute for Health and Care Excellence.

**Figure 5** | Pharmacologic options for managing the symptoms of Paralysis agitans

## CONCLUSION

Paralysis agitans is a nervous system disorder characterized by mobility problems. The fundamental cause of paralysis agitans symptoms is low or diminishing levels of dopamine, a neurotransmitter. It happens after dopamine-producing cells in the brain die. Dopamine aids in the transmission of signals to the brain region responsible for balance and coordination. As a result, persons with low dopamine levels may struggle to retain control over their movements. As dopamine levels fall, symptoms become more severe. Though there is no cure for paralysis agitans, there are various medicines, surgical techniques, and psychodynamic psychotherapy alternatives available, and innovative therapies are being researched to help reduce the disease's symptoms and negative consequences. Non-drug treatments such as occupational, physical, and speech therapy can be used in conjunction with

pharmaceuticals or as a stand-alone treatment for people seeking a more natural approach. When specific symptoms appear, they may help with symptom management. Other treatments need to be investigated more, and there is a need for more study on under-researched paralysis agitans medicines. Patient-specific therapy, which is more effective and has fewer adverse effects, appears to have a promising future in alleviating paralysis agitans symptoms.

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