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Review Article

A Holistic Approach to Parkinson's Disease: Integrating Advances in Pathophysiology, Diagnosis, and Therapy

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Abstract

Background: Parkinson's disease (PD) is a prevalent neurodegenerative disorder affecting millions worldwide, with an increasing burden projected in the coming years. It involves complex neurological decline primarily affecting the Substantia nigra and Locus coeruleus, leading to motor and non-motor symptoms.

Objective: This study aims to provide a comprehensive overview of Parkinson's disease, including its epidemiology, pathophysiology, diagnosis, and available therapies, encompassing both traditional pharmaceutical treatments and emerging technological advancements.

Methods: A thorough review of literature was conducted, synthesizing information from various studies and clinical trials to elucidate the current understanding of Parkinson's disease and its management strategies.

Results: Parkinson's disease is characterized by the gradual loss of dopamine-producing cells and the presence of Lewy bodies in the brain. Diagnosis relies on clinical evaluation, and treatment typically involves pharmaceutical interventions such as levodopa, COMT inhibitors, dopamine agonists, and deep brain stimulation. Additionally, advancements in technology offer promising avenues for objective symptom assessment and personalized treatment approaches.

Conclusion: The management of Parkinson's disease requires a multidisciplinary approach, integrating traditional pharmacological treatments with emerging technologies and complementary therapies like dance therapy, tai chi, and speech therapy. By combining these diverse modalities, healthcare professionals can provide more effective and personalized care, ultimately enhancing the quality of life for individuals living with Parkinson's disease.

Keywords: Parkinson's disease, medical therapy, device-aided therapy, alternative interventions, personalized treatment, neurodegenerative disorder.

1. Introduction:

Parkinson's disease is the second most common neurodegenerative disorder, just after Alzheimer's disease. The number of people with Parkinson's disease is expected to rise from 4.6 million in 2005 to 9.3 million in 2030[1].

Parkinson's disease is a continuous and severe neurological decline that primarily impacts the Substantia nigra (SN) and Locus coeruleus. It starts with early, subtle signs like a reduced sense of smell and advances to significant impairment in motor function[2–4]. Parkinson's disease is not just about movement problems; it also affects other parts of the nervous system, causing issues like dizziness, constipation, pain, memory loss, and feelings of anxiety or sadness. These additional symptoms make managing the disease even more challenging[5,6].

According to the World Health Organization's (WHO) recent report on Parkinson's disease (PD), the primary pharmacological treatment is Levodopa, which is most effective in managing PD symptoms in the early stages. However, it doesn't prevent motor complications, and higher doses can lead to more side effects and fluctuations in motor function for people with PD. As PD progresses, additional medications may be necessary to address new symptoms, but these can also result in side effects such as dry mouth and agitation. While medication initially helps with motor symptoms, its effectiveness may diminish over time, and it does not halt the progression of the disease[7].

The number of people with Parkinson's disease (PD) has risen significantly over the years, from 2.5 million in 1990 to 6.1 million in 2016. Predictions suggest this number could reach 14.2 million by 2040. Some experts even refer to PD as a non-infectious pandemic due to its rapid spread. PD becomes more common with age, with prevalence increasing from 41 per 100,000 people in their forties to over 1,900 per 100,000 in their eighties. Studies show lower rates of PD in Asian populations compared to non-Asian ones, such as in Taiwan and

Singapore where it's estimated at 113.1 and 61.9 per 100,000, respectively. In 2016, Malaysia had 1,856 registered PD patients, expected to rise fivefold by 2040[8].

2. Search methodology:

For our review on Parkinson's disease, we conducted a thorough search using multiple databases such as Research Scholar, Google Scholar, PubMed, NCBI, and ScienceDirect. This approach ensured we gathered a wide range of up-to-date research and expert opinions on the pathophysiology, diagnosis, and therapy of Parkinson's disease. By accessing diverse sources, we aimed to provide a comprehensive overview for our readers, facilitating informed decision-making in the management of this complex condition.

3. Brain Pathophysiology in Parkinson's Disease:

Parkinson's disease results from the gradual loss of dopamine-producing cells in the substantia nigra pars compacta (SNpc), leading to reduced dopamine availability. Dopamine is crucial for transmitting signals that regulate muscular coordination from SNpc to the corpus striatum. The presence of Lewy bodies, aggregates of abnormal proteins, characterizes PD at the cellular level. α-synuclein, the primary structural protein of Lewy bodies, regulates dopamine transporter activity, but in PD, its abnormal levels or mutations contribute to neuronal cell death, causing motor dysfunctions. Mutations in genes like PINK1, DJ-1, PRKN, and LRRK-2 confirm mitochondrial dysfunction's role in dopaminergic neurodegeneration in PD. The severity of symptoms correlates with the degeneration of the dopaminergic nigrostriatal pathway and dopamine depletion in the striatum. As people age, the loss of dopaminergic neurons increases, suggesting a link between age-related Parkinson's and the gradual decline in dopamine-producing cells[9].

4. Epidemiology:

Accurate epidemiological data on Parkinson's disease (PD) are crucial for understanding its impact and improving patient care. Studies suggest a prevalence of 41 to 100,000 cases in the fifth decade of life, rising to 1,900 cases per 100,000 in those aged 80 and above. PD is more common in men, occurring 1.5 times more frequently on average. Factors such as genetic predisposition and environmental toxins may contribute to this gender difference. The number of PD cases increases with age, with a peak prevalence around age 80. Global data indicate a rise in PD-related deaths and disability-adjusted life years (DALYs), particularly affecting women due to their longer lifespan. Disparities in PD prevalence exist between developed and underdeveloped countries, reflecting differences in healthcare access and treatment standards. Accurate epidemiological data, standardized diagnostic criteria, and uniform monitoring are essential for effective PD management and improving quality of life for patients, caregivers, and communities worldwide[10].

5. Diagnosis:

Diagnosing Parkinson's disease relies on clinical evaluation rather than a specific test. Doctors assess symptoms and rule out other conditions like essential tremor and multiple-system atrophy. The main symptoms of PD are resting tremor, cogwheel rigidity, and bradykinesia, which are known as the classical triad. Postural instability may develop later in the disease course. While PD typically affects older adults, it can also occur in younger individuals due to genetic factors, albeit with milder symptoms. Bradykinesia involves slow and small movements, while rigidity causes resistance to passive movement, often appearing as intermittent stiffness. Resting tremor, commonly seen in the hands, lips, chin, tongue, and legs, may diminish during sleep or with movement. In advanced stages, postural instability can lead to falls due to loss of reflexes. Traditionally, PD diagnosis focused mainly on motor symptoms, but attention to non-motor symptoms has increased. These symptoms, like constipation, REM behavior disorder, and hyposmia, may precede motor symptoms by years. Other non-motor symptoms, such as hallucinations, dementia, fatigue, shoulder pain, apathy, anxiety, and urinary dysfunction, can develop later in the disease course[11].

6. Advancements in Technology for Parkinson's Disease Management:

As Parkinson's disease (PD) progresses, both motor and non-motor symptoms evolve, becoming more complex and individualized, particularly in advanced stages. This complexity poses challenges for treatment, which now includes a range of options such as surgery, pumps, patches, and customized combinations of therapies. However, selecting the right treatment requires careful consideration of a patient's symptom patterns, which can vary widely and impact responsiveness to therapy. Standardized assessments struggle to capture this diversity, hindering easy translation of research findings to clinical practice. In response, emerging healthcare technologies focus on objective assessment of PD symptoms, leveraging wearable devices and novel monitoring systems. These technologies aim to provide personalized insights into symptom patterns and quality of life, although challenges remain in validating their effectiveness and ensuring patient privacy. Despite these hurdles, advancements in technology offer promising opportunities to improve PD care by providing tailored treatment strategies and facilitating more targeted clinical studies. The ongoing validation and refinement of these technologies will be crucial in realizing their potential benefits for patients with PD[12].

7. Medical therapies for motor symptoms:

a. Levodopa:

The latest medication for Parkinson's disease, called Rytary, offers improved symptom control compared to previous options. Rytary comes in extended-release capsules containing levodopa and carbidopa beads that are absorbed at different rates, reducing the need for frequent dosing. It's approved by the FDA for both new patients and those experiencing motor complications, helping increase "on" times without worsening troublesome movements. Rytary's side effects and how well it's tolerated are similar to other levodopa treatments[13,14].

There isn't enough long-term data to recommend starting patients directly on Rytary instead of immediate-release (IR) levodopa. The main reason to consider switching from IR to Rytary is if the patient is experiencing wearing off, especially when taking IR more than four times a day. The conversion ratio is roughly 2:1 (Rytary to IR levodopa), and it can be done overnight. As Rytary contains IR granules, patients should be advised to take it without food (with at least a 30-minute gap). It may take up to 8 weeks to see the full benefits after switching, and dose adjustments are often necessary[15].

b. Catechol-o-methyltransferase (COMT) inhibitors:

COMT inhibitors help levodopa work better by slowing down its breakdown in both the body and the brain. Entacapone is one such inhibitor, typically taken as a 200 mg dose alongside each levodopa dose. It's also found in combined formulations with carbidopa-levodopa, which can reduce the number of pills needed, though the overall treatment results are similar. However, findings from the STRIDE PD study revealed that using entacapone in early PD might lead to quicker onset and more frequent dyskinesias compared to using carbidopa-

levodopa alone[16]. Opicapone is a newer COMT inhibitor taken just once a day (at a dose of 50 mg). In Phase III studies, it showed better results than a placebo and was equally as effective as entacapone. Unlike tolcapone, opicapone has less risk of causing liver damage, which has restricted the use of tolcapone in clinical practice[17,18].

c. Amantadine:

Amantadine, originally used for type A influenza, now helps control dyskinesia by targeting the NMDA receptor. In 2017, the FDA approved a sustained-release version (274 mg capsule) after it showed effectiveness in the EASE LID study[19]. The slow-release form of amantadine also helps improve motor symptoms when Parkinson's patients experience off periods despite being treated with levodopa[20].

d. Adenosine A2 receptor antagonists:

Istradefylline, approved by the FDA for addressing motor fluctuations, works by adjusting GABAergic transmission to decrease the excitability of the indirect pathway[21]. Istradefylline is offered in 20 mg and 40 mg forms, taken once daily. Studies indicate it can decrease "off" time by approximately 0.7 hours compared to a placebo[22].

e. Dopamine agonists:

Dopamine agonists (DAs) attach to dopamine receptors after synaptic transmission. They can be used alone in early stages of the disease or along with other treatments in later stages. Common side effects include nausea, vomiting, swelling, low blood pressure, sleepiness, impulse control problems, and hallucinations, especially in older patients. Popular options include pramipexole, ropinirole, and rotigotine. Apomorphine, another agonist, acts strongly on D1 and D2 receptors. It's available as an occasional injection or continuous infusion in some countries due to poor oral absorption. Ideal candidates are those managing a stable medication routine, recognizing their "off" periods, and capable of self-injecting or having assistance. It's used for quick relief from symptoms like early morning "off" periods or delayed responses. Subcutaneous injection yields fast results within 10 to 20 minutes, lasting up to an hour. Initial doses should be closely monitored for low blood pressure and nausea. Side effects may include nausea, injection site reactions, low blood pressure, confusion, impulse control issues, and rarely, anemia or eosinophilic syndrome[23].

f. Monoamine oxidase-B (MAO-B) inhibitors:

Monoamine oxidase (MAO) is an enzyme found in mitochondria that breaks down various monoamine neurotransmitters. There are two types: MAO-A and MAO-B. MAO-A prefers noradrenaline and serotonin, while MAO-B targets beta-phenylethylamine. Both enzymes metabolize tyramine and dopamine. Selegiline and rasagiline are medications that selectively inhibit MAO-B, used in early Parkinson's disease and for those with motor fluctuations. However, they are generally considered to be relatively weak treatments. These drugs work by reducing dopamine breakdown, thereby increasing its levels in the central nervous system. Selegiline is typically taken in the morning and afternoon due to its potential to produce amphetamine-like byproducts that can lead to insomnia. Research suggests that selegiline may have neuroprotective effects, as patients treated with it required levodopa treatment later than those in a control group, hinting at possible disease-modifying properties[24].

8. Therapies for non-motor symptoms:

Non motor symptoms like depression, constipation, and REM sleep behavior disorder are increasingly acknowledged and can appear years before a PD diagnosis. Non-motor fluctuations are also known, and some may get better with improved dopaminergic therapy to alleviate wearing off[25].

a. Psychosis:

The process typically begins with discontinuing medications like anti-cholinergics, selegiline, amantadine, and dopamine agonists. If needed, the next step involves reducing the dosage of levodopa therapy. It's crucial to withdraw these medications gradually to avoid triggering Parkinsonism-hyperpyrexia syndrome, which presents with symptoms like high fever, autonomic dysfunction, mental status changes, muscle breakdown, and kidney failure[26].

The most effective treatment for psychosis, which includes visual or auditory hallucinations and delusions, is clozapine (Clozaril). However, it requires weekly monitoring due to the risk of agranulocytosis. If regular monitoring is not feasible, quetiapine (Seroquel) is a moderately effective alternative. Olanzapine (Zyprexa) exacerbates motor symptoms and is ineffective for psychosis in Parkinson's disease patients. Typical antipsychotics like haloperidol should be avoided because they worsen motor symptoms[27].

Pimavanserin compound selectively blocks the 5-HT2A receptor in the brain while showing less affinity for 5-HT2C and sigma-1 receptors. It doesn't affect dopamine, muscarinic, adrenergic, or histaminergic activity. Pimavanserin is the only FDA-approved drug for treating hallucinations and delusions linked to psychosis in Parkinson's disease[28]. The data indicates a favourable balance between benefits and risks, with a low Number Needed to Treat (NNT) of less than 10, suggesting a significant likelihood of improvement. The Number Needed to Harm (NNH) was greater than or equal to 10, although not significantly different from placebo. Overall, the chances of benefiting from the medication were consistently higher than not[29].

b. Orthostatic Hypotension:

Orthostatic hypotension can be managed through simple lifestyle adjustments like increasing water and salt intake, wearing compression stockings, and changing positions slowly. Eating smaller, more frequent meals and reducing carbohydrates can help with postprandial hypotension. Patients should be cautious of diuretic effects from caffeine and alcohol. Certain medications like diuretics, vasodilators, levodopa, and dopamine agonists can worsen orthostatic hypotension. Medication options include fludrocortisone, midodrine, and droxidopa, but they can cause supine hypertension, so patients should avoid lying flat and sleep with their head elevated. Pressors like droxidopa and midodrine should be avoided close to bedtime. For constipation, probiotics, fibers, stool softeners, and laxatives like lubiprostone and linaclotide can be helpful[30].

c. Rapid-Eye-Movement Sleep Behaviour Disorder:

Tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) can worsen symptoms of rapid eye movement sleep behavior disorder (RBD) and should be stopped if RBD leads to injuries. The preferred initial treatment is clonazepam, taken at a dose of 0.5–1.0 mg two hours before bedtime. Clonazepam is generally well tolerated, effective in about 90% of cases, and can reduce abnormal movements and harmful behaviours within a few days[31–33]. If clonazepam is not effective or not well tolerated, melatonin (3–6 mg at night) is suggested as a second-choice treatment[34].

d. Depression:

The most common medications for treating depression in Parkinson's disease are selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants. While SSRIs are more

frequently prescribed, recent small-scale studies comparing the two suggest that tricyclic antidepressants, such as desipramine, may be more effective[35].

e. Pain and other sensory symptoms:

Annoying sensory issues are common in Parkinson's disease. These can include loss of smell (anosmia) and taste (ageusia), as well as pain, especially in the shoulder, tingling sensations (paresthesias), restlessness (akathisia), and discomfort in the mouth and genitals[36]. Some patients find relief from these symptoms with tricyclic antidepressants, carbamazepine, pregabalin, and gabapentin[37].

9. Device-Aided Therapies:

Device-aided therapies are intended for individuals with severe Parkinson's symptoms. They are initiated based on motor symptoms, especially when managing fluctuations becomes challenging[38–40].

a. Deep brain stimulation (DBS):

DBS placement commonly targets two main areas: the subthalamic nucleus (STN) and the globus pallidus (GPi). STN-DBS enhances off-drug scores, reduces off-time throughout the day, enhances quality of life, and permits a decrease in the daily levodopa equivalent dose, leading to a reduction in levodopa-induced dyskinesia[41]. Subthalamic nucleus deep brain stimulation (STN-DBS) is a highly effective surgical treatment for the main motor symptoms in advanced Parkinson's disease (PD) patients[42]. However, GPi-DBS might offer improved suppression of dyskinesia[43].

b. Levodopa–carbidopa intestinal gel (LCIG):

LCIG is a gel solution made of carboxymethylcellulose, containing 20mg/mL of levodopa and 5mg/mL of carbidopa. It comes in cassettes with 100mL of gel each, providing an adequate daily dose for the majority of patients[44–46]. The gel is given using a portable pump (CADD-Legacy Duodopa, Smiths Medical, MN, USA) connected to the cassette. A small tube extends from the cassette and links to a percutaneous endoscopic gastrostomy (PEG) tube inserted into the duodenum or proximal jejunum for long-term use[44,47]. By directly entering the bloodstream, levodopa avoids fluctuations, reducing motor issues like dyskinesia and fluctuations. Dosage is adjusted for each person, with a morning dose followed by continuous infusion for 16 hours, and additional doses if needed. LCIG can be used alone or with other treatments, and can be continued as long as it remains effective. Adverse events related to the procedure or device are common, with about 76% of subjects experiencing them; however, only 17% are considered serious. Common non-procedure/device adverse events include dyskinesias, chronic polyneuropathy, stoma infection, and weight loss[48,49].

10. Medications to Avoid in Parkinson's:

Some medications that block dopamine receptors can cause parkinsonism or make motor symptoms worse in people with Parkinson's disease. These medications include certain neuroleptics like haloperidol, thioridazine, chlorpromazine, promethazine, fluphenazine, risperidone, and olanzapine. Additionally, antiemetics like prochlorperazine and metoclopramide, tetrabenazine, and antihypertensives like methyldopa can also have similar effects[50,51]. Don't take meperidine if you're using monoamine oxidase B inhibitors[52].

11. Prevention of Parkinson's Disease:

a. Dance therapy:

Dancing can help boost movement speed, balance, overall well-being, and quality of life in Parkinson's disease patients[53,54]. A review of 38 articles exploring various dancing interventions for Parkinson's disease (PD) found positive effects. Different dance styles like tango, waltz, Sardinian folk dancing, and others, done once a week to daily for 30 minutes to 2 hours, showed improvements in balance, mobility, gait freezing, and depression in mild-to-moderate PD cases[55].

b. Tai Chi and Qigong:

Tai chi and qigong are gentle exercises involving flowing movements and focused breathing. They're popular for their low impact on joints and ability to promote a calm state of mind by releasing life energy (chi). Studies have shown that both tai chi and qigong can improve symptoms in people with PD[56].

c. Music Therapy:

Music therapy is a low-cost and non-invasive treatment option, with the main benefit being the lack of side effects associated with medication[57]. This treatment has proven effective for various neurodegenerative conditions like Alzheimer's disease, Huntington's disease, and Parkinson's disease[58]. Music therapy enhances rehabilitation by activating brain regions linked to emotions, releasing substances that alleviate pain and improve mental symptoms. Rhythmic auditory stimulation (RAS), a technique using metronome pulses or rhythmic music cues, improves motor symptoms in Parkinson's disease by enhancing movement coordination and reducing muscle activation time. Combining music or RAS with exercise therapy has been effective in rehabilitating various conditions, including Parkinson's disease. While studies suggest benefits for motor function, cognition, and mental state, more research is needed due to limited sample sizes and inconsistent results. This meta-analysis aims to thoroughly explore the effects of rhythmically cued exercise interventions on Parkinson's patients' motor function, cognition, and mental state[59].

d. Yoga Therapy:

Yoga offers significant benefits beyond medication in managing Parkinson's disease, improving quality of life for patients. These aspects are often overlooked in standard treatment, highlighting the need for alternative therapies to enhance neural function and overall well-being in Parkinson's patients. Yoga improves muscle strength, endurance, flexibility, and balance, enhancing overall health and coordination. It combines physical postures (Asanas), breathing techniques (Pranayama), meditation, and relaxation. Regular practice of yoga reduces stress, anxiety, and depression while boosting memory and general well-being, attributed to increased cortisol levels.[60].

e. Phytotherapy:

Phytotherapy involves using natural compounds found in different plants for medicinal purposes[61]. For Parkinson's disease (PD), certain natural compounds have shown potential benefits. Evidence suggests that herbs used in traditional Chinese and Indian medicine may have antioxidant and anti-inflammatory properties, offering neuroprotective effects against PD[62]. Similar effects extend to other types of molecules found in various nutritional products, such as phenolic compounds. These include substances like secoiridoids, phenolic alcohols, phenolic acids, flavonoids, and lignans. Studies in living organisms have shown that these compounds can reduce neuroinflammation, regulate cellular iron levels, control signaling pathways, and alleviate protein-related issues. Additionally, they have been linked to improvements in behavior, including enhanced locomotor activity, reduced turning time, improved motor balance, and less bradykinesia[63].

f. Speech and language pathology/therapy:

Speech therapists specialize in treating communication issues, including speech sounds, volume, language, swallowing, and

cognitive aspects. For people with Parkinson's disease (PD), they help optimize speech, voice, swallowing, language, and cognition. They often collaborate with other healthcare professionals such as dieticians, otolaryngologists, and occupational therapists. Speech therapy for PD focuses on strategies to improve voice, speech, and swallowing safety. Techniques may include breathing control, vocal training, and exercises to strengthen swallowing muscles. Regular monitoring of vocal loudness, pitch range, and swallowing function is important. Intensive speech programs like Lee Silverman Voice Treatment (LSVT) are commonly used. Singing and technology-based tools can also aid in therapy. Dysphagia, a common issue in PD, requires regular assessment and may involve modifications in diet texture, posture, and specific exercises. Speech therapists also address drooling and facial expression issues in PD patients[64].

12. Conclusion:

In conclusion, Parkinson's disease presents a multifaceted challenge, characterized by both motor and non-motor symptoms, which evolve and worsen over time. While traditional treatments like levodopa have been effective in managing motor symptoms, advancements in technology are paving the way for more personalized and targeted approaches to treatment. Wearable devices and monitoring systems offer the potential for objective assessment and tailored interventions, which could significantly improve patient outcomes.

Moreover, the development of new medications and therapeutic approaches, such as levodopa-carbidopa intestinal gel (LCIG) and deep brain stimulation (DBS), provides additional options for individuals with severe symptoms. These interventions aim to alleviate motor complications and improve overall quality of life.

Furthermore, complementary therapies like dance therapy, tai chi, music therapy, yoga, phytotherapy, and speech therapy offer holistic approaches to symptom management, addressing not only physical but also emotional and cognitive aspects of the disease. These therapies contribute to enhancing neural function, reducing stress, and improving overall well-being.

Overall, the comprehensive management of Parkinson's disease requires a multidisciplinary approach, integrating medical treatments, technological advancements, and complementary therapies to address the diverse needs of individuals living with the condition. By combining these various approaches, healthcare professionals can offer more effective and personalized care, ultimately enhancing the quality of life for patients with Parkinson's disease.

13. Future perspectives:

Future research and management of Parkinson's disease focus on early detection using biomarkers and advanced imaging, understanding disease progression through genetics and neuroscience, and personalized treatments. Device-aided therapies like deep brain stimulation and drug delivery systems offer hope for advanced cases. Holistic approaches such as dance therapy and yoga are recognized for addressing non-motor symptoms. Patient care must adapt with interdisciplinary models and telehealth services to improve outcomes and quality of life.

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Conflicts Of Interests:

No conflicts of interest

Abbreviation:

5-HT2A receptor: 5-Hydroxytryptamine 2A receptor.

5-HT2C receptor: 5-Hydroxytryptamine 2C receptor

COMT inhibitors: Catechol-O-Methyltransferase inhibitors

DAs: Dopamine agonists

DBS: Deep Brain Stimulation

FDA: Food and Drug Administration

GPi: Globus pallidus

IR: Immediate-release

LCIG: Levodopa–carbidopa intestinal gel

LSVT: Lee Silverman Voice Treatment

MAO-A: Monoamine oxidase A

MAO-B: Monoamine oxidase-B inhibitors

NMDA receptor: N-Methyl-D-Aspartate receptor

NNT: Number Needed to Treat

NNH: Number Needed to Harm

PD: Parkinson's disease

PEG: Percutaneous endoscopic gastrostomy

RAS: Rhythmic auditory stimulation

REM: Rapid Eye Movement

SN: Substantia nigra

SNpc: Substantia nigra pars compacta

SSRIs: Selective serotonin reuptake inhibitors

STN: Subthalamic nucleus

TCAs: Tricyclic antidepressants

WHO: World Health Organization

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