

REVIEW ARTICLE

Parkinson's disease – a review of pathogenesis, recent advances in management, and challenges of care in sub-Saharan Africa

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Abstract

Parkinson's disease (PD) remains a common neurodegenerative movement disorder with significant morbidity, which is expected to increase worldwide in the coming decades. Since its initial description, much has been elucidated about its etiology, pathogenesis, and the role of genetic and environmental risk factors. Effective treatments, including surgical therapies, have been discovered. Despite these strides, many questions remain unanswered; PD remains an active research area with ongoing efforts to discover newer treatment modalities and identify neuroprotective strategies. As with many neurological conditions, there is an unequal distribution of health resources, resulting in some management challenges in low resource settings, especially sub-Saharan Africa (SSA). In this communication, we provide an overview of PD etiopathogenesis, including genetics and management strategies, including some recent advances with respect to treatment options and disease modification approaches. Finally, we discuss some challenges of PD management in low-resource settings and highlight efforts to turn the tide.

Keywords: Parkinson's disease, Management, Dopamine replacement, Neurodegeneration, low-resource setting

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Parkinson's disease (PD) is the second most common neurodegenerative disease after Alzheimer's disease. The description of the disease was provided by James Parkinson in 1817 in his classic monograph 'An Essay on the Shaking Palsy'. He named the condition as *paralysis agitans*, noting that sufferers had 'involuntary tremulous motion, with lessened muscular power, in parts not in action, and even when supported; with a propensity to bend the trunk forwards, and to pass from a walking to a running pace: the senses and intellects being uninjured' [1]. Some of the cardinal motor manifestations of PD are discernible in Parkinson's apt description, viz, rest tremors, bradykinesia, and postural/gait problems. Parkinson also noted the slowly progressive nature of the disease and highlighted a few non-motor symptoms, including sleep disturbance and drooling in the latter stages [1]. The use of the nomenclature 'Parkinson's Disease' was popularized by Charcot in France in the latter parts of the 19th century and has remained so since.

In the over two centuries since that seminal publication, there has been remarkable progress in the understanding of

the etiology, including genetics, pathophysiology, and treatment options, including surgical and device therapies of PD. This article has three objectives: 1) to provide an overview of PD including pathogenesis, clinical presentation, and management, 2) to highlight recent developments in PD treatment and research, and 3) to discuss some challenges of PD management in low resource settings.

Epidemiology

According to a Global Burden of Disease analysis, PD affected 6.1 million people globally in 2016, indicating a 2.4-fold increase in global prevalence of PD from 1990 [2]. PD prevalence increases with advancing age and peaked in the 84–89 age group in 2016. It also affects slightly more men than women, with an estimated male-to-female ratio of 1.4:1 [2].

The prevalence of PD appears to be lower in Africa – especially in sub-Saharan Africa (SSA) – relative to more affluent regions of the world. Population studies of PD in Africa have revealed prevalence rates ranging from seven per 100,000 in Ethiopia [3] to 40 per 100,000

in rural Tanzania [4], and 67 per 100,000 in rural southwestern Nigeria [5, 6]. This compares to a PD prevalence of 572 per 100,000 reported in North America [7]. In a comparative study by Schoenberg et al., the PD prevalence in southwestern Nigeria was fivefold less than that recorded among White and Black Americans in Copiah County, MS, USA [5]. These figures indicated lower PD prevalence in Africa; potential reasons for the lower numbers have been suggested, including differences in study methodologies and difficulties with case ascertainment (for instance, differentiating PD from other causes of parkinsonism) among others. The lower prevalence of PD in Africa could also be reflective of the relative differences in population structure, with African populations generally being younger, and having lower proportions of individuals older than 65 years at the time some of the studies were conducted [8, 9]. Furthermore, some authors contend that PD underdiagnosis, inadequate access to multidisciplinary specialist care, and effective drug treatment may contribute to reduced survival [10], which may, in turn, partially explain the relatively low prevalence of PD in SSA.

Etiology, pathology, and pathogenesis

Etiology

About 90% of PD cases are considered to be sporadic. Age is perhaps the single most important risk factor for PD with incidence being low below the age of 50 years, and increasing 5–10-fold from the 6th to 9th decades of life [11, 12]. Epidemiological studies have identified certain environmental risk factors that increase the probability of developing PD. These include exposure to pesticides, especially those who cause oxidative stress or inhibit mitochondrial complexes, traumatic brain injury, well-water drinking, and high consumption of dairy products [11]. Identified protective factors include cigarette smoking, caffeine consumption, physical activity, and regular ibuprofen use [11].

Although considered sporadic, it is recognized that PD risk is likely influenced by genetic factors. Genome-wide association studies have identified a number of variants/mutations that potentially contribute to PD risk in a polygenic manner [13–15]. Therefore, PD risk is likely to be determined by interactions between such genetic predisposition and environmental risk factors. Furthermore, about 5–10% of PD is familial, with single gene mutations that may be inherited in a Mendelian (i.e. autosomal dominant or recessive) manner. Genes associated with autosomal dominant familial PD include the alpha synuclein (SNCA) gene and the leucine-rich repeat kinase 2 (LRRK 2) gene, while those associated with autosomal recessive forms of PD include parkin (PRKN) gene, the PTEN-induced kinase 1 (PINK 1) gene, and

the Daisuke-Junko 1 (DJ-1) gene [16, 17]. Mutation of the glucocerebrosidase (GBA) gene is increasingly being recognized as a genetic risk factor for PD and is considered by some to constitute the single most important genetic risk factor for PD [18, 19].

Pathology

Macroscopically, the external surface of the brain in PD is similar to that of age-matched controls. On cut sections, PD is characterized by loss of melanin pigment in the substantia nigra (and locus coeruleus). Microscopically, the pathologic hallmark of PD is the presence of Lewy bodies and neuronal loss in the substantia nigra, other brainstem structures, and in advanced cases and cortical areas [14, 20]. Lewy bodies are intraneuronal eosinophilic inclusion bodies that consist primarily of alpha synuclein as demonstrated using immunohistochemical techniques [14, 20]. Braak and colleagues have postulated a hypothesis of PD pathology progression. According to this hypothesis, PD pathology begins in vagal and other medullary nuclei and olfactory bulb (stages 1 and 2), thereafter progressing to more rostral structures like the substantia nigra and basal forebrain structures (stages 3 and 4), with more widespread neocortical involvement in advanced stages (5 and 6) [21].

Pathogenesis

While the entire picture of PD pathogenesis is yet to be completely elucidated, environmental and genetic elements are believed to play synergistic roles. Monogenic forms of PD have shone much-needed light on some of the mechanisms involved in its pathogenesis. These mechanisms include abnormal alpha synuclein aggregation and accumulation, dysfunction of cellular protein homeostasis, mitochondrial dysfunction, neuroinflammation, and oxidative stress [14]. It is likely that recognized environmental risk factors induce changes in some of these molecular pathways, the dysfunction of which ultimately result in PD. For example, protein homeostatic mechanisms become less efficient with advancing age, potentially leading to intracellular toxic protein accumulation. Similarly, pesticides and other toxins known to interfere with mitochondrial function are documented environmental risk factors for PD. Both processes (impaired protein degradation and mitochondrial dysfunction) are implicated in PD pathogenesis as discussed below.

Alpha synuclein is involved in synaptic vesicle transportation, docking, fusion, and neurotransmitter release [22]. Abnormal alpha synuclein folding and aggregation and/or impairment of its clearance are thought to be a central mechanism in the pathogenesis of PD. Indeed, Lewy bodies – the pathologic hallmarks of PD – consist primarily of alpha synuclein. The accumulated misfolded protein is toxic to neurons and leads to cell death and

neurodegeneration [23, 24]. Mutations in the SNCA gene that codes for alpha synuclein can cause excessive accumulation and/or impaired degradation of the protein. SNCA mutation was the first identified cause of genetic PD [25].

Impairment of protein degradation either due to impaired lysosomal autophagy pathways or dysfunction of ubiquitin-proteasome pathways leading to toxic protein accumulation and eventual neuronal cell death is also recognized pathways in PD pathogenesis. These protein homeostatic mechanisms become less efficient with age [26, 27], potentially causing accumulation of misfolded senescent proteins in cells. Such protein aggregates are implicated in many neurodegenerative diseases, including PD; age-related perturbations of protein homeostasis may underlie the increased occurrence of these diseases with advancing age [26]. The ubiquitin and lysosomal systems are involved in alpha synuclein metabolism, and their dysfunction results in impairment of its degradation [14]. Conversely, pathologic aggregation and accumulation of alpha synuclein impair its proteasome- or lysosome-mediated degradation [28].

Mitochondrial dysfunction has also been implicated in PD pathogenesis. Animal studies have indicated that toxins such as MPTP and rotenone known to inhibit mitochondrial complex I are toxic to nigrostriatal neurons [29, 30]. Furthermore, rotenone can induce clinical and neuropathological features (like dopaminergic neuronal degeneration and alpha synuclein accumulation) similar to those of PD [31] and has been associated with increased PD risk in farmers exposed to it [32]. Finally, reduced nigral mitochondrial complex 1 activity relative to non-PD controls has been demonstrated in postmortem studies of PD brains [33]. The foregoing lines of evidence all point to a putative role for mitochondrial dysfunction in PD pathogenesis.

Additionally, impairment of mitophagy (autophagy of senescent mitochondria) leading to the accumulation of damaged mitochondria and proteins, ultimately causing neuronal cell death is another pathogenetic mechanism in PD. Indeed, mutations in the genes that code for PARKIN and PINK 1, both proteins that are involved in mammalian mitophagy [34], are now known to cause hereditary PD [35, 36].

Apart from the aforementioned mechanisms, neuroinflammation and increased oxidative stress are also thought to play a role in the pathogenesis of PD [37]. There is also increasing evidence for a contributory role of the gut in PD pathogenesis. Alpha synuclein has been shown to be present in the submucosal plexuses of the gut, and its retrograde spread to the brain via the vagus nerve has been suggested [38, 39]. Indeed, one large Danish observational study with a follow-up period of over 20 years suggested that prior full truncal vagotomy is associated with reduced

risk of subsequent PD [40]. Gut microbiota alterations and gut wall inflammation may also play a role [41].

Clinical presentation and diagnosis

PD is characterized by a variety of motor and non-motor symptoms. The core motor symptoms of PD are bradykinesia, rigidity, rest tremors, and postural instability. The motor symptoms of PD characteristically begin on one side of the body, and this asymmetry may persist as the disease progresses, with the initially affected side often more affected than the other. As the disease advances, patients begin to experience motor fluctuations or 'on-off' states, dyskinesias, freezing, and frequent falls.

Non-motor symptoms may predate the onset of the more easily recognizable motor symptoms. These non-motor symptoms span various systems and include autonomic symptoms like constipation, urinary, and dysfunction; psychiatric symptoms like depression, anxiety, and psychosis; sensory symptoms like anosmia and pain; and cognitive symptoms.

In advanced stages of disease, patients may become wheelchair-bound, develop severe dysphagia with drooling and dementia, and require institutional care. PD patients are also at a higher risk for developing aspiration pneumonia later in the disease course.

The diagnosis of PD is essentially clinical, but neuroimaging techniques such as magnetic resonance imaging (MRI) or dopamine transporter (DaT) scans maybe useful for the occasional difficult case. Definitive diagnosis can only be made post-mortem by demonstration of typical PD pathology in autopsy samples. Some clinical diagnostic criteria have been proposed with a view to increasing premortem diagnostic accuracy of PD. For example, the United Kingdom Parkinson's Disease Society Criteria [42] involve a three-step process: 1) establishing the presence of parkinsonism, defined as bradykinesia plus at least one of rigidity, rest tremors, or postural instability, 2) excluding other causes of parkinsonism (e.g. vascular, drugs, and postinfectious) that may mimic PD, 3) ascertaining at least three features that support the diagnosis of PD over other causes of parkinsonism (e.g. unilateral onset, persistent asymmetry, excellent response to levodopa, among others).

More recently, the International Parkinson and Movement Disorder Society has also published criteria for the clinical diagnosis of PD [43]. To diagnose clinically established PD, there should be the presence of parkinsonism (defined as bradykinesia plus one of rigidity or 4–6 Hz rest tremors), absence of absolute exclusion criteria (unequivocal cerebellar signs, presence of vertical supranuclear gaze palsy, absent response to levodopa treatment, prior documentation of conditions known to cause parkinsonism, including the use of neuroleptics or other dopamine-depleting agents with a time course

consistent with drug-induced parkinsonism), and at least two supportive criteria, with no red flags. The supportive criteria are as follows: clear and dramatic beneficial response to levodopa and anosmia, while red flags include early severe bulbar dysfunction, early severe autonomic failure, complete absence of disease progression, and absence of common non-motor signs 5 years into the disease [43]. PD severity can be staged clinically using the Hoehn and Yahr scale with scores ranging from stage 0 to 5 [44, 45] or the more comprehensive Unified Parkinson's Disease Rating Scale, UPDRS [46].

It is now recognized that PD has a long prodromal phase that may predate the motor symptoms by as many as 20 years [22]. During this period, symptoms, usually non-motor, that are not initially attributed to PD occur. Common prodromal PD symptoms include anosmia, constipation, psychiatric symptoms like depression, or sleep disturbances (rapid eye movement [REM] sleep behavior disorders) [47]. Unfortunately, these symptoms are not specific for PD, and since they occur so remotely from the more easily recognizable motor symptoms, other diagnoses are often considered and should, indeed, be excluded. Conversely, the presence of such a long prodromal period offers great hope for the development of disease biomarkers that may predict motor symptom onset, and disease modifying therapies that may halt or alter disease progression altogether.

Basis for dopamine replacement therapy in Parkinson's disease

Neurodegeneration in PD results in loss of pigmented dopaminergic neurons that originate in the substantia nigra pars compacta and project to the striatum, the so called 'nigrostriatal pathway'. These neurons play an important modulatory role in basal ganglia circuitry. The striatum receives cortical projections, serving as the basal ganglia's input structure, while basal ganglionic output is via the duo of the internal part of the globus pallidus and the reticular portion of the substantia nigra.

Briefly, connections within the basal ganglia consist of circuits that originate in the motor cortex and project to the basal ganglia; the loop is completed by projections back to the cortex via the thalamus. These circuits are arranged into two main pathways: the direct pathway that is ultimately facilitatory to movement and the indirect pathway that is inhibitory to movement. The dopaminergic neurons of the nigrostriatal pathway modulate these pathways by facilitating transmission through the direct pathway while simultaneously inhibiting transmission through the indirect pathway [48]. Therefore, the degeneration of nigrostriatal neurons results in poverty of movement, which manifests clinically as bradykinesia and rigidity. This forms the basis for dopamine replacement/replenishment as the mainstay of medical treatment in PD.

It must, however, be emphasized that while this simplified model of basal ganglia circuitry enables understanding, the reality is more complex. Evidence shows that loss of dopaminergic neurons does not only cause an imbalance in dopaminergic neurotransmission but also results in abnormal firing patterns and firing rates by neurons within the motor circuit [48, 49]. The modulation of these abnormal firing rates and patterns forms the basis for deep brain stimulation (DBS) for PD treatment [50].

The loss of dopaminergic neurons upsets the balance between central dopaminergic and cholinergic neurotransmission [51]; therefore, anticholinergics are also useful in PD treatment especially for troublesome tremors. Indeed, anticholinergics were the main agents used in PD treatment before the discovery of the central role of dopamine in PD biochemistry.

History of Parkinson's disease pharmacotherapy

Late in the 19th century, the treatment of PD was mostly with plant-derived alkaloids such as atropine and hyoscyne. These alkaloids were derived from members of the nightshade family of plants such as *Atropa belladonna* (deadly nightshade) and *Hyoscyamus niger* (henbane) [52]. Their use in PD was largely popularized by Jean-Martin Charcot as documented by his trainee, Leopold Ordenstein [52]. These alkaloids were subsequently discovered to exert central anticholinergic effect, which probably explains their efficacy in PD patients. By the middle of the 20th century, anticholinergics were the mainstay of PD treatment, and synthetic anticholinergics such as trihexyphenidyl (Artane) were commercially available. Writing in 1954, Doshay and colleagues in their 5-year follow-up study of 411 PD patients treated with trihexyphenidyl noted that roughly three out four patients derived benefit from the medication, and no other treatment available at the time was equally efficacious [53]. These anticholinergics were either prescribed alone or in conjunction with other compounds such as amphetamines or antihistamines [54, 55].

A slew of basic science discoveries in the mid-20th century eventually culminated in the trials that cemented the efficacy of L-DOPA for PD treatment [52, 56, 57]. Dopamine was demonstrated to be present in high concentrations in the striatum of mammals [58] and humans [59]. Hornykiewicz and colleagues in autopsy studies of the brains of patients with PD, post-encephalitic parkinsonism and Huntington's disease (HD) demonstrated severe (90%) depletion in the striatal dopamine levels in the Parkinsonian disorders but not HD [60]. They also demonstrated severe reduction in nigral dopamine levels in PD [61]. Carlsson and colleagues had earlier demonstrated that in rabbits with parkinsonism induced by reserpine-mediated dopamine depletion, administration of L-DOPA reversed the parkinsonian features [62].

They also subsequently showed that L-DOPA administration replenishes brain dopamine levels that were depleted by reserpine [63]. In experiments that involved lesions in relevant areas of rat brains, and employing fluorescence histochemistry techniques that were novel at the time, the same group demonstrated the presence of a dopaminergic nigrostriatal pathway. The cell bodies of these neurons originated in the substantia nigra pars compacta, ascended through the cerebral peduncles and internal capsules, and terminated in the striatum [64]. Poirier and Sourkes showed that experimental lesions of the substantia nigra in monkeys led to striatal dopamine depletion and completed the picture of a dopamine-deficiency disease [65, 66].

In summary, PD results from degeneration of neurons in the pars compacta substantia nigra, causing dopamine depletion in the striatum. The ensuing striatal dopamine loss results in several of the motor symptoms of PD. (We now know that the nigrostriatal dopaminergic neurons play a modulatory role in basal ganglia circuitry, and loss of these neurons alters firing patterns in the basal ganglia.) [48]. The stage was, thus, set for trials of dopamine replacement for PD therapy.

The landmark studies that showed unequivocal benefit of high-dose DOPA were those by Cotzias et al. [67, 68]. Their subjects experienced significant benefits from DOPA administration at high doses. They also documented that with the co-administration of carbidopa, a peripheral decarboxylase inhibitor, the required doses of L-DOPA, could be reduced without compromising benefit [68]. Their findings were later corroborated by Yahr, Hoehn, and coworkers, who tested L-DOPA in a double-blind study and reported varying degrees of benefit [69]. Other studies followed suit, all showing positive results, leading to United States Food and Drug Administration (FDA) approval of L-DOPA use for PD [52].

Drug treatment and other aspects of management

The cornerstone of pharmacotherapy for the motor symptoms in PD is dopamine replacement. Dopamine poorly crosses the blood-brain barrier, so its precursor L-DOPA is administered instead. Once within the central nervous system (CNS), DOPA is converted by a decarboxylase into dopamine. Dopamine is metabolized by two enzyme systems within the CNS: monoamine oxidase (MAO) and catechol O-methyl transferase (COMT). Because of the risk of peripheral decarboxylation, most L-DOPA preparations contain a peripheral decarboxylase inhibitor such as carbidopa or benserazide.

Another 'dopamine replacement' strategy is the use of dopamine receptor agonists that directly stimulate dopamine receptors. Examples include ergot derivatives like bromocriptine and cabergoline and non-ergot dopamine agonists such as ropinirole and pramipexole. Inhibitors

of dopamine metabolism which increase brain dopamine levels by preventing its breakdown are also used in PD pharmacotherapy. They may be prescribed as monotherapy in mild disease or as adjuncts to L-DOPA later in the disease course to treat motor fluctuations. Examples include MAO inhibitors such as selegiline and rasagiline and COMT inhibitors like entacapone and tolcapone. MAO inhibitors may also be prescribed as monotherapy, especially early in the disease course [70, 71]. Conversely, COMT inhibitors are typically used as adjuncts to L-DOPA. Side effects of dopamine replacement therapy include gastrointestinal symptoms (nausea and vomiting), dyskinesias, hallucinations and other psychotic symptoms, and impulse control disorders. Because PD is a progressive neurodegenerative disorder, response to dopamine replacement becomes less satisfactory as the disease advances. Motor fluctuations begin to set in as do freezing and dyskinesias. At this stage, patients often require higher doses of L-DOPA more frequently, as well as addition of drugs from other classes mentioned earlier.

Amantadine, an old drug and an antiviral agent, is useful in the treatment of dyskinesias [72]. Its mechanism of action is not clearly known. Strategies for managing late-stage PD with fluctuations include the use of delayed- or extended-release medication formulations, adjustment of medication doses, and increased frequency of medication intake. Furthermore, factors that have been shown to contribute to reduced medication efficacy (and therefore fluctuations) need to be excluded. These include heavy protein diet, which impede L-DOPA absorption, and an abundance (especially in patients with constipation and intestinal bacterial overgrowth) of bacterial decarboxylases that reduce L-DOPA bioavailability [73]. In some instances, patients with severe on-off phenomena may benefit from L-DOPA holidays with or without co-administration of amantadine [74, 75].

The concern that early initiation of L-DOPA hastens neurodegeneration because of its ability to induce oxidative stress [76], thus accelerating occurrence of motor fluctuations and dyskinesias has more or less been laid to rest. Recent evidence from a randomized controlled trial suggests no difference in disease progression rates with early versus delayed L-DOPA use [77]. Rather, it appears that disease duration and higher daily dose of L-DOPA are associated with increased risk of these motor complications [78]. With regard to relief of motor symptoms, L-DOPA remains the most efficacious/potent weapon in the PD pharmacotherapy arsenal (more so than dopamine agonists) [79–81], and its early commencement once the decision to treat has been made is recommended [70, 82].

Anticholinergic medications like trihexyphenidyl and benzotropine are still prescribed for PD, especially for tremors (which may occasionally not respond to dopamine

replacement) particularly in resource-constrained settings [83]. Their use is often limited, particularly in the elderly, by side effects such as memory impairment, confusion, blurred vision, and urinary retention.

In patients who experience troublesome fluctuations and dyskinesias despite optimal medical therapy, device-based therapies may be an alternative. These include DBS [84] and ablative lesional therapies utilizing focused ultrasound waves under MRI guidance [85, 86]. In DBS, electrodes are surgically inserted in the target structure (usually one or both subthalamic nuclei or globus pallida interna). The electrodes are connected to a subcutaneously placed neurostimulator located either on the chest or abdomen. After sufficient time is allowed for postoperative recovery, the desired stimulation parameters are programmed. Impulses can, thereafter, be delivered from the stimulator to the brain to interrupt the abnormal motor circuit firing patterns associated with PD. Modern-day ablative lesional therapy typically involves unilateral thalamotomy or sub-thalamotomy using MRI-guided focused ultrasound waves. With MRI guidance, ultrasound waves are focused on the desired brain structure to ablate it, obviating the need for open surgery. This procedure is particularly useful for tremor-dominant PD.

Treatment of non-motor features of Parkinson's disease

Non-motor manifestations of PD are treated symptomatically [87]. These include dietary modification and use of laxatives for constipation; glycopyrrolate oral spray or sublingual atropine drops for drooling; cognitive-behavioral therapy and/or antidepressants such as selective serotonin reuptake inhibitors (SSRIs), serotonin-noradrenaline reuptake inhibitors (SNRIs), or tricyclic antidepressants (TCAs) for depression [71]; avoidance of prolonged standing, use of compression stockings and/or pressor agents like midodrine or fludrocortisone for orthostatic hypotension; and dopaminergic medication dose adjustment and use of antipsychotics for hallucinations and other psychotic symptoms.

Since most antipsychotics are dopaminergic antagonists, their use in PD can be quite challenging because of worsening of parkinsonism. The new antipsychotic drug, pimavanserin, has recently been approved for the treatment of psychosis in PD patients [88]. It acts mainly by serotonergic inverse agonism and is, thus, less likely to cause extrapyramidal side effects [89]. In its absence, the atypical antipsychotics clozapine and quetiapine are also useful; quetiapine is often preferred to clozapine because of the risk of granulocytopenia associated with clozapine [71]. Drooling can be treated with oral glycopyrronium bromide or botulinum toxin A injection [70]. Cognitive impairment in PD can be managed with acetylcholinesterase inhibitors; rivastigmine has the strongest

evidence of efficacy for this indication, but donepezil and galantamine are also considered useful [87].

Other aspects of care

Physiotherapy, especially aerobic exercises, is also useful for the relief of motor symptoms in PD patients. In a recently conducted randomized clinical trial, home-based aerobic exercises were found to improve off-state motor scores relative to stretching exercises [90]. Terminally, PD patients may become immobilized and suffer cognitive impairment. Patients with severe dysphagia may also require feeding gastrostomy/jejunostomy tubes. At this stage, institutional and hospice care may be required to maintain comfort and preserve human dignity. End-of-life decisions may also need to be discussed at this time. It is vital to stress that at any stage, PD management should involve multidisciplinary teams that include neurologists, geriatricians, primary care physicians, specialist nurses, rehabilitation specialists, nutritionists, occupational therapists, speech and language therapists, among others [91].

Recent advancements in treatment and research

Advancements in PD research, specifically regarding treatment and disease modification, have been recorded in recent years. Some of these are highlighted below.

New routes of L-DOPA delivery

Newer routes of L-DOPA administration have been developed to circumvent fluctuations in L-DOPA levels that may predispose to wearing off phenomena. These include continuous intestinal delivery of levodopa-carbidopa gel via percutaneous gastrojejunostomy [92], which, according to some studies, is comparable to DBS for the treatment of motor fluctuations in advanced PD [93]. Others include inhaled levodopa-carbidopa [94] and a subcutaneous levodopa-carbidopa infusion [95].

New medications

The adenosine receptor antagonist, istradefylline, received United States FDA approval in 2019 for use as an adjunct treatment for PD. It was demonstrated in clinical trials to reduce 'off time' in advanced PD and has a tolerable side effect profile [96]. A novel COMT, opicapone, also received FDA approval in 2020 for use as adjunctive treatment to reduce off times in PD patients after demonstrating efficacy and reduced risk of hepatotoxicity in clinical trials [97–99].

Neuroprotective/disease-modifying agents

Significant research efforts have been dedicated to the discovery of agents that can modify disease progression by slowing down or altogether halting neurodegeneration in PD. The long prodrome in PD makes this prospect

appealing because if administered during the preclinical phase, it is theoretically possible to prevent the onset of debilitating motor symptoms. Previous trials of the monoamine amine oxidase inhibitors selegiline [100] and rasagiline [101] did not produce convincing results of their disease-modifying effects [22, 102]. Improved understanding of pathogenetic mechanisms in PD has led to trials of pathogenesis-specific neuroprotective strategies for PD. For instance, trials of monoclonal antibodies against aggregated forms of alpha synuclein are ongoing [103, 104]. Another approach involves the repurposing of drugs previously used for other indications, but which can potentially modulate certain pathogenetic pathways in PD. One such example is the use of ambroxol, a cough suppressant that has been shown to increase glucocerebrosidase activity, in genetic forms of PD caused by glucocerebrosidase deficiency [105]. Other drugs that are being repurposed for use in PD treatment and/or modification include exenatide [106] and terazosin [107].

Dopaminergic cell transplantation

Prior studies of striatal dopaminergic cell transplantation have yielded mixed results [108]. While some studies did not meet the prespecified endpoints [109, 110], they showed some trends toward clinical benefit. There is evidence of clinical benefit from some studies, while others revealed that patients may not benefit from the procedure despite proof of graft survival and functionality [111]. Insights gained from these trials have informed more careful design of newer studies of dopaminergic cell transplants derived from fetal mesencephalic tissue [112] and human stem cells [113]. It is hoped that the results from these trials will be translated to widespread clinical practice sooner than later.

Gene therapy

Gene therapy approaches have also been investigated, including disease-modifying and non-disease-modifying targets. Examples of the latter include nigral, striatal, or subthalamic delivery of genes that code for enzymes involved in dopamine [114, 115] or gamma-aminobutyric acid (GABA) synthesis [116] with the aim of boosting dopaminergic transmission or inhibiting abnormal neuronal firing, respectively. A recent uncontrolled open-label trial of MRI-guided surgical delivery of a viral vector containing genetic codes for DOPA decarboxylase into the putamina of PD patients demonstrated increased enzyme activity as measured by positron emission tomography (PET) scans, reduced need for dopaminergic medications as evidenced by reduced doses, and increased 'on time' without troublesome dyskinesias among participants [117]. The same group also demonstrated enhanced response to L-DOPA following surgical delivery of the therapeutic agent [118]. Disease-modifying therapeutic

targets include nigral and/or striatal delivery of genes coding for different neurotrophic factors in a bid to induce overexpression of these neuroprotective factors, thereby halting or slowing neurodegeneration. Results from different trials have been mixed – some positive and others negative. For example, a recently conducted randomized placebo-controlled trial of MRI-guided putaminal delivery of glial cell line-derived neurotrophic factor (GDNF) did not meet its primary end point though post-hoc analysis showed that 43% of participants in the active arm experienced clinically significant motor improvement [119]. Ongoing research in the field continues to show promise [120].

Development of disease biomarkers

Research into potential biomarkers for PD is ongoing. Given its long prodrome, the utility of a disease marker that can be used to detect premotor PD, and thus identify potential candidates for preventive, disease-modifying therapy cannot be overemphasized. While most are still currently at an investigational stage, some have shown promise. One of such – neurofilament light chain (NfL), measured in serum or cerebrospinal fluid – has been found to 1) discriminate between PD and atypical parkinsonism disorders [121], 2) correlate with disease severity (measured by Hoehn and Yahr staging) and progression of motor and cognitive symptoms [122], and 3) discriminate between PD patients and controls when combined with a panel of cerebrospinal fluid alpha-synuclein assays [123].

Challenges of Parkinson's disease management in low resource settings

The treatment of PD in low resource settings is often fraught with several challenges. In SSA, these include misconceptions about stigma associated with PD, manpower shortage, limited availability of medications or financial barriers to their purchase when available, very limited access to advanced therapeutics such as DBS, and limited PD research capacity [9, 124, 125]. The seriousness of PD-related stigma is exemplified by the fact that about one-third of participants in a survey of the South African general public attributed PD to witchcraft and nearly half thought PD patients should not live within their community [126].

Regarding availability and affordability of PD medications in developing countries, Ogunniyi had earlier observed that anticholinergics were more widely available and more affordable than L-DOPA medications [83]. This observation has been corroborated by more recent surveys assessing accessibility of PD medication in Kenya and Nigeria [127, 128]. In their survey of 48 pharmacy outlets spanning all eight of Kenya's provinces, Mokaya et al. found that anticholinergic agents were more widely available and considered more affordable by respondents; only half of the pharmacy outlets surveyed stocked L-DOPA,

and it was typically in formulations (ratio 10:1 with carbidopa) that are more likely to cause side effects [127]. Okubadejo et al. [128] in their survey of 123 pharmacies covering Nigeria's six geopolitical zones found that bromocriptine and the anticholinergic trihexyphenidyl (benzhexol, Artane®) were the most available medications for managing PD; they attributed the high availability of bromocriptine to its use for other non-neurologic indications such as hyperprolactinemia and infertility treatment. Only anticholinergics were found to be affordable in their study [128]. Indeed, according to WHO's Atlas of Country Resources for Neurological Disorders, only 3% of African countries reported constant availability of PD medications at the primary care level [129].

Apart from a few centers in South Africa [130] and North Africa (Egypt [131] and Morocco [132]), expertise and facilities for DBS are in short supply across Africa. This, therefore, limits treatment options for many patients with advanced disease who no longer get benefits from dopaminergic medications and would otherwise benefit from this procedure. Despite these challenges, there are several bright spots of progress. The International Parkinson Disease and Movement Disorder Society has a vibrant Africa section [133], which offers in-person and virtual online courses to African practitioners who are also eligible for a no-fee membership of the society. More PD research, including setting up of registries [134] and genetic studies, is also being conducted on the continent. Several of these (mostly candidate gene) studies have shown that common genetic mutations known to cause PD in other populations are rare in SSA [9, 135]. This rarity may point to the possibility that her populations bear novel, as yet unidentified PD-causing mutations, thus presenting a distinct opportunity for PD genetics research. The recently launched International Parkinson's Disease Genetics Consortium Africa – an international collaboration between academic and research institutions in 12 African countries, the United Kingdom, and the United States of America – will no doubt pioneer this research [136]. Indeed, in a recent study utilizing targeted next-generation sequencing of some candidate genes among indigenous black South Africans and Nigerians with PD, investigators identified novel variants earmarked for future study [137].

Another area of ethnopharmacological interest in PD research in SSA and other low-income countries is the use of plant-based medicines for symptomatic PD treatment. Seeds of the leguminous plant *Mucuna pruriens* (velvet bean), which is found in many tropical regions including Africa, South America, and India, have been found to contain varying amounts of L-DOPA [138]. Some small trials have shown the non-inferiority of roasted *Mucuna pruriens* seeds to L-DOPA-carbidopa preparations for the relief of motor symptoms of PD,

albeit with a slightly increased risk of gastrointestinal side effects [139–141]. Larger placebo-controlled studies need to be conducted to determine effective dosages, tolerability, side effect profile, and to prove efficacy. A multicenter trial is currently ongoing in Ghana to answer some of these questions [138].

In conclusion, PD remains an important cause of neurologic morbidity globally. Much has been unraveled about its genetic, neuropathological, and neurochemical underpinnings, yet there is still much to learn about its precise pathogenetic mechanisms with a view to developing neuroprotective therapy. PD research remains an active field, and despite many challenges, research from the African continent is poised to contribute significantly to our understanding, including the genetics, of this condition.

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Ethical approval

There are no ethical concerns as no patients were studied.

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