



## Medical Management, Orofacial Findings, and Dental Care for the Patient with Parkinson's Disease

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### ABSTRACT

Parkinson's disease (PD) is the second most prevalent neurodegenerative disease in North America, next to Alzheimer's disease. Patients who suffer from PD typically present with neuromuscular, cognitive, postural and psychiatric deficits, which make oral hygiene challenging, but extremely important. Although the cardinal signs of PD are movement-related, manifestations in the orofacial complex are ubiquitous. Weakened facial musculature, gaunt appearance, tremors of the tongue, lips and eyes, erratic mandibular movements, bruxism, xerostomia, sialorrhea, dysphagia, dysgeusia and glossitis are examples of the plethora of atypical orofacial findings associated with PD. Further complications, including angular cheilosis, attrition, temporomandibular joint disorders, burning mouth syndrome, hyposmia and hypophonia, may arise as a consequence of these orofacial manifestations. The effects of PD on the orofacial complex may result in poor nutritional habits, which can exacerbate weight loss and contribute to a negative impact on physical, psychosocial and emotional health. Dentists should be able to identify signs of PD systemically, including but not limited to the orofacial region, to optimize the management of PD patients. Here, we report practical recommendations for the medical and dental management of patients with PD in accordance with the most recently published clinical practice guidelines.

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## Epidemiology

Parkinson's disease (PD) is a progressive, chronic, incurable neurodegenerative disease characterized by the atrophy of neuromelanin-containing dopaminergic neurons in the pars compacta of the substantia nigra (SN).<sup>1</sup> Currently, PD is the second most prevalent neurodegenerative disorder in North America after Alzheimer's disease. According to the 2014 Canadian Health Report on PD, over 84000 Canadian adults are living with PD.<sup>2</sup> The prevalence of PD increases with age; however, this trend may not apply to patients > 80 years because of an increase in disease severity and mortality rate.<sup>2</sup> The mean onset age of PD is 60 years; however, young-onset PD may develop before age 40 and is believed to account for 5–10% of those diagnosed with PD.<sup>3</sup>

Across all age groups, gender differences may exist among those with PD. Although men are more likely to have PD than women, information is insufficient to explain this difference. The annual incidence of PD has been reported to be as high as 20 cases per 100000 people, and an estimated 8.7–9.3 million people worldwide will be diagnosed with PD by 2030.<sup>2,4–6</sup> With a marked proportion of the population affected by PD, it is pertinent for dentists to be familiar with its orofacial manifestations to appropriately accommodate patients, facilitate treatment planning and optimize dental care.

## Etiology and Neuromuscular Pathology

The neuromuscular system is a highly sophisticated network of neural and muscular fibers that work synergistically to facilitate movement. Normally, motor signals are initiated in the motor cortex of the brain and forwarded to the basal ganglia via motor neurons.<sup>7</sup> The striatum of the basal ganglia carries these motor signals to the SN, where dopaminergic neurons are highly concentrated, and movement is regulated. Dopamine plays an important role in producing involuntary motion via motor pathways. Also, dopaminergic neurons in the SN influence the expression of neuromelanin, a substance that helps protect these neurons from oxidative stress.<sup>8</sup> When pathologies arise within these pathways, they can manifest systemically with neuromuscular symptoms of rigidity, akinesia or dyskinesia, which are among the most prominent signs of PD.<sup>9,10</sup>

PD results in an overall deficiency of dopamine because of atrophy of the melanin-containing dopaminergic neurons within the SN and other pigmented nuclei of the brainstem.<sup>1</sup> This reduction in pigmented nuclei is the hallmark sign of PD.<sup>2</sup> Patients with PD may present with up to 80–90% depletion in dopaminergic neurons, which significantly impairs motor regulation in the SN resulting in delayed or uncoordinated movements. The precise mechanism leading to PD is unknown, and it is thought to be better classified as a syndrome of multiple etiologies rather than a stand-alone disease.<sup>11</sup>

Generally, the etiology of PD includes idiopathic, environmental and genetic factors. Idiopathic PD accounts for over 95% of cases and includes atrophy of dopaminergic neurons resulting from the accumulation of Lewy bodies.<sup>12</sup> Lewy bodies are noxious, abnormal aggregations of proteins that develop within the SN and are believed to be causal factors in neuronal atrophy.<sup>12</sup> Ultimately, the degeneration of dopaminergic and non-dopaminergic neurons in the SN is a consequence of the presence of Lewy bodies and results in impaired motor control. Therefore, idiopathic Lewy body aggregates are thought to be the most common culprit in the initiation and progression of PD.

Genetic and environmental etiologies may also play a role in the initiation and progression of PD. Genetic onset of PD accounts for 3–5% of cases and involves several monogenic forms caused by a single mutation in an inherited dominant or recessive gene.<sup>13</sup> Environmental factors may include oxidative damage via transition metals (iron, chromium, copper, zinc), which can exacerbate the progression of PD via neuromelanin atrophy.<sup>1</sup> Exposure to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine has also been identified as a potential risk factor<sup>14</sup>; however, environmental exposure to noxious substances is the least common etiology of PD.<sup>2</sup>

## Clinical Presentation

The clinical presentation of PD varies with disease severity, which is based on the extent of dopaminergic neuron atrophy in the SN.<sup>15</sup> In early stages, clinical signs and symptoms are usually absent. This asymptomatic pre-clinical phase may last for 5–20 years from the initiation of dopaminergic neurodegeneration. The clinical onset of PD unfolds once approximately 70–80% of the dopaminergic neurons in the SN have been depleted.<sup>7</sup> At this point, systemic signs and symptoms will be prominent (**Table 1**).

Neuromuscular motor dysfunction presents clinically in PD patients as resting muscle tremors and muscle rigidity. Camptocormia is an abnormal thoracolumbar spinal flexion, or bent spine syndrome, and another clinical feature in patients with PD.<sup>16</sup> Muscle rigidity is common and is mainly a result of oxidative stress resulting from mitochondrial complex I dysfunction and skeletal muscle damage.<sup>7</sup> Sarcopenia, or muscle loss, may be seen in conjunction with muscle rigidity in PD patients because of skeletal muscle atrophy.<sup>17</sup> Slow movements, bradykinesia, or lack of movement altogether (akinesia) are also characteristic neuromuscular motor signs of PD.<sup>7,9</sup> Although most PD symptoms manifest as neuromuscular motor impairments, several non-motor signs and symptoms include neuropsychiatric deficits, postural inadequacies, stomatognathic deficiencies, autonomic dysfunction and oral complications (**Table 1**).

**Table 1:** Neuromuscular, neuropsychiatric, postural, stomatognathic and autonomic signs and symptoms of Parkinson's disease.

Category	Signs and symptoms
Neuromuscular	Resting muscle tremors, camptocormia, muscle rigidity, sarcopenia, muscle atrophy, bradykinesia, akinesia
Neuropsychiatric	Depression, anxiety, cognitive impairment, mild dementia
Postural	Facial impassiveness, postural instability, shuffling gait, retropulsion
Stomatognathic	Dysphagia, dysphonia, dysphasia, dysarthria
Autonomic	Sialorrhea, fatigue, constipation, sexual dysfunction, orthostatic hypotension
Oral	Xerostomia, temporomandibular joint disorders, bruxism/attrition

Cognitive decline and dementia are common neuropsychiatric features of PD, which often occur in conjunction with each other.<sup>18</sup> Postural inadequacies, including facial impassiveness, postural instability, shuffling gait and retropulsion, may present at diagnosis, but become more prevalent with the advancement of PD and related morbidities. Postural imbalances are extremely debilitating and often associated with increased falls and loss of independence.<sup>19</sup> Postural deformities may also affect the functionality of the extremities, shoulder, head and neck, compromising the patient's ability to walk, lift, rotate and reach. This hindrance of movement makes performing activities of daily living, such as oral hygiene, extremely challenging.<sup>20,21</sup>

The prevalence and clinical presentation of orofacial manifestations also increases with the progression of PD.<sup>20</sup> Patients are prone to the development of stomatognathic deficiencies, which alter their masticatory function.<sup>22</sup> Alterations of the stomatognathic system in PD patients may lead to temporomandibular joint disorders (TMDs), along with difficulties swallowing, chewing and speaking.<sup>22,23</sup> Several autonomic effects may also manifest clinically, including sialorrhea, fatigue, constipation, sexual dysfunction and orthostatic hypotension.<sup>20,24-26</sup> In addition, dental-specific manifestations of PD include xerostomia, dysphagia, bruxism and an increased incidence of root caries.<sup>20</sup>

## Diagnosis and Classification

The diagnosis of PD is based on several factors including patient history, physical examination, clinical presentation of signs and symptoms and a sustained response to dopaminergic medications, such as levodopa.<sup>2,7</sup> PD may present with a plethora of signs and symptoms; however, the cardinal neuromuscular signs that dentists and physicians should recognize include the "classical triad" of resting tremor, cogwheel rigidity and bradykinesia (or akinesia).<sup>2,7,10,20</sup> There is some crossover between the secondary motor symptoms of PD and those of similar neurodegenerative diseases and related Parkinsonian disorders.<sup>10</sup> Thus, it is important for clinicians to be able to differentiate PD from non-

Parkinsonian disorders by recognizing these classical signs and symptoms. Although there are no definitive tests to confirm or rule out PD,<sup>7</sup> the absence of tremor, postural instability, dementia, and other key factors, such as poor response to levodopa, might suggest other diagnoses.<sup>10</sup> Therefore, a thorough and nuanced approach should be used, and the broad spectrum of clinical manifestations considered to reach an accurate diagnosis.

Medical imaging modalities may aid physicians in evaluating patients who are suspected to be suffering from PD. Specifically, dopaminergic uptake of the 123I-iodoflupane radiotracer in nigrostriatal tracts may be visualized with single photon-emission computed tomography. This facilitates the detection of PD and may provide insight regarding disease severity and duration.<sup>27</sup> The stage of PD can be evaluated by determining the extent of the uptake of 123I-iodoflupane at the presynaptic terminal of dopaminergic neurons, which reflects the extent of functional dopaminergic neurons present. In early stages of PD, there is a relative decrease in the intensity of tracer uptake bilaterally, whereas, in advanced stages of the disease, this decrease in uptake becomes more noticeable.<sup>15,18</sup> Patients with unilateral neurodegeneration of dopaminergic neurons will also reflect these changes in diagnostic imaging, and may present clinically with contralateral motor dysfunction.

Several scales have been used to rate and categorize the severity of PD based on the extent to which patients experience related signs and symptoms. The Hoehn and Yahr scale is the grandfather of these evaluation scales and is most commonly used to provide a general assessment of the progression of PD in terms of neuromuscular deficiency (**Table 2**).<sup>28</sup> Currently, the most widely employed and well-established system for assessing disability and impairment among PD patients is the Unified Parkinson's Disease Rating Scale (UPDRS), which was revised in 2007.<sup>29-31</sup> The UPDRS has 4 major components: (1) mental state, behaviour and mood, (2) activities of daily living, (3) motor symptoms and (4) complications of therapy.<sup>30</sup> The UPDRS provides additional information over the Hoehn and Yahr scale, implying variable differences in the rate of progression of PD, specifically during

earlier stages. The progression of PD is not linear and requires robust medical and dental management strategies to maximize patient comfort and attain patient-specific treatment goals.<sup>10,32</sup>

## Medical Management

Unfortunately, there is not yet a cure for PD. Currently, we are limited to treating the symptoms of PD by addressing its hallmark sign: an absolute decrease in dopaminergic neurons in the SN.<sup>33</sup> Various methods exist to increase the concentration of dopamine and, therefore, combat the dopamine-dependent signs and symptoms of PD; they include pharmacotherapy, lifestyle changes and surgical intervention.<sup>20</sup> Here, we discuss current pharmacological interventions useful for the management of PD along with their associated systemic and orofacial implications.

## Pharmacotherapy

Pharmacological interventions are most commonly used to treat PD-related signs and symptoms. Several classes of drugs may be used to increase the concentration of dopamine in the brain by increasing the synthesis of dopamine, decreasing the metabolism of dopamine and increasing the presynaptic release of dopamine (**Table 3**). Levodopa (dopamine precursor) combined with carbidopa (DOPA decarboxylase inhibitor) is considered the gold standard therapy for early PD.<sup>34</sup> Novel pharmacological strategies target other neurotransmitters in addition to the dopaminergic system, including serotonin (5-HT), gamma aminobutyric acid (GABA) and acetylcholine (ACh). These have been proposed to treat symptoms associated with advanced stages of PD.<sup>35</sup>

Nonetheless, all pharmacotherapies for PD rely on the fundamental principle of increasing the concentration of dopamine in the brain. This can be accomplished by either stimulating dopamine synthesis or inhibiting dopamine metabolism with monoamine oxidase (MAO-B) inhibitors or catechol-O-methyltransferase (COMT) inhibitors. Dental professionals should be wary of patients who are taking COMT-inhibitors because of potential interactions with vasoconstrictors, such as epinephrine and levonordefrin<sup>36-38</sup> and may, therefore, consider the use of dental anesthesia without vasoconstriction, when clinically applicable.<sup>20</sup>

### Dopamine Agonists and Levodopa

Dopamine replacement therapy is the most common first-line treatment for PD-related signs and symptoms.<sup>39</sup> Levodopa is a precursor to dopamine, which is naturally metabolized following decarboxylation. The metabolism of levodopa results

in increased levels of serum dopamine because of the chemical equivalence between levodopa and dopamine. Unlike levodopa, dopaminergic agonists directly stimulate the postsynaptic dopamine receptors in the nigrostriatal system, rather than increase the production of dopamine.<sup>39</sup> Dopamine agonists are the first choice for mild rigidity; whereas dopamine precursors become necessary as signs and symptoms worsen.<sup>34,39</sup>

Dopamine agonists are mainly derived from 2 subgroups: ergoline and non-ergoline.<sup>40</sup> Bromocriptine and cabergoline are ergoline-based drugs for anti-PD therapy, while pramipexole and ropinirole are non-ergoline derivatives (**Table 3**).<sup>34,29,40</sup> Although the differences in their mechanisms of action are unclear, ergoline derivatives are associated with more severe adverse effects with extended use, including retroperitoneal and pleuropulmonary fibrosis. Certain ergoline-based drugs, such as pergolide, may also cause valvular heart disease. Therefore, ergoline-derived medications are more often used as a second-line therapy for PD. Non-ergoline drugs may promote impulsive behaviour, such as gambling, and have a higher tendency to promote somnolence than ergoline-derived medications.<sup>40</sup> Both ergoline and non-ergoline derived dopamine agonists produce similar orofacial manifestations, as described in **Table 3**; however, the extent and severity of oral adverse effects seems to be on an individual drug basis rather than a subgroup trend.

### DOPA Decarboxylase Inhibitors

Carbidopa is a DOPA decarboxylase inhibitor often prescribed in combination with levodopa (Sinemet). Research suggests the combination of carbidopa and levodopa may be the most effective treatment regimen to manage the dopaminergic symptoms of PD.<sup>41</sup> The mechanism of action of Sinemet involves an increase in the post-synaptic release of dopamine, which is achieved by levodopa, while carbidopa prevents the peripheral conversion of levodopa into dopamine. This synergistic combination increases the half-life and bioavailability of levodopa in the brain.<sup>39,41</sup> The combination of levodopa and carbidopa is exceptional at inhibiting the metabolism of dopamine, though DOPA decarboxylase inhibition by carbidopa is non-specific. Therefore, the treatment of dopaminergic symptoms of PD using Sinemet is associated with various adverse effects, including but not limited to gastrointestinal upset, cardiac arrhythmias and orthostatic hypotension (**Table 3**).

### Monoamine Oxidase-B Inhibitors

Although dopamine agonists aim to sustain levels of dopamine by stimulating its postsynaptic release, monoamine oxidase inhibitors (MAOIs) reduce the metabolism of dopamine by MAO enzymes. Despite the difference in their mechanism of action,

both dopamine agonists and MAOIs may be used alone as a first-line therapy or in combination with levodopa to synergistically control the motor symptoms of PD.<sup>34</sup> Rasagiline, selegiline and safinamide are anti-PD medications that specifically inhibit MAO-B, an enzyme responsible for the post-synaptic breakdown of dopamine (**Table 3**).<sup>42</sup> Both selegiline and rasagiline have the potential to selectively and irreversibly inhibit MAO-B in PD treatment; however, selegiline seems to have a higher affinity.<sup>42</sup> Furthermore, selegiline and rasagiline are both known to potentiate the release of dopamine by levodopa in combination therapy. Safinamide also has an inhibitory effect on the N-methyl-D-aspartate (NMDA) glutamate receptor by sodium and calcium channel antagonism.<sup>42</sup> Rasagiline and safinamide are efficacious in the treatment of motor symptoms of PD; however, MAO-B inhibitors alone are generally less efficacious than dopamine agonists.<sup>39,42</sup> Nevertheless, MAO-B inhibitors are typically associated with less severe adverse effects, which makes them attractive for the medical management of PD.<sup>42</sup>

### Catechol-O-methyltransferase Inhibitors

Catechol-O-methyltransferase (COMT) inhibitors hinder the conversion of dopamine into its inactive metabolites by COMT enzymes.<sup>37</sup> To potentiate the release of dopamine and sustain serum levels, COMT inhibitors are also prescribed in combination with levodopa. Entacapone is a peripherally acting COMT inhibitor used in the treatment of PD (**Table 3**).<sup>42</sup> Tolcapone is also a COMT inhibitor used as an anti-PD agent; however, tolcapone more readily crosses the blood-brain barrier and it has a higher potency. Consequently, tolcapone is associated with a higher risk of hepatotoxicity and other significant adverse effects.<sup>42</sup> Therefore, it is only prescribed to patients in advanced stages of PD or those who do not respond to entacapone. COMT inhibitors are often used as an adjunctive therapy in PD treatment, specifically for patients who do not respond well to first-line treatment regimens with dopamine agonists and MAO-B inhibitors.<sup>20,43</sup>

### Acetylcholine Antagonists

Anticholinergic medications regulate the autonomic nervous system (ANS). Although PD is not specifically an ANS disorder, many PD patients suffer from muscarinic symptoms, including sialorrhoea. Consequently, anticholinergic drugs are prescribed as an adjunctive therapy. As listed in **Table 3**, the most prescribed anticholinergic drugs for PD treatment include trihexyphenidyl, benztropine, orphenadrine and procyclidine. Anticholinergic medications are the first choice for mild tremors, as they are effective at improving motor symptoms.<sup>44</sup> Unfortunately, motor improvements with anticholinergic drugs are made at the cost of increased neuropsychiatric symptoms and reduced cognitive function.<sup>44</sup> Ultimately, as PD progresses into more advanced psychotic stages, the pharmacologic treatment regimens shift from

dopamine replacement therapies to psychological interventions. Furthermore, there are significant oral consequences associated with the use of anticholinergic medications. Xerostomia, reduced salivary flow, dry throat and nasal dryness have been reported as common orofacial adverse effects of anticholinergic drugs.<sup>37,45</sup> The absence of saliva and its buffering capacity may have serious dental consequences, including the development or exacerbation of dental caries, periodontal diseases or oral fungal infections.<sup>20</sup>

### Glutamate Antagonists

NMDA receptor antagonists were recently described as novel targets for PD therapy.<sup>46</sup> Although the exact mechanism involved is unknown, glutamate receptors have been identified to contribute to the alterations in neurotransmission that are seen in PD.<sup>46</sup> NMDA receptors are also involved with the excitation of neurons in the striatum and SN, where dopaminergic neurons are highly concentrated. Research has shown that NMDA-sensitive glutamate binding in these dopamine-concentrated regions of the brain may result in excitotoxicity, which is believed to accelerate neurodegeneration of dopaminergic neurons, as seen in PD.<sup>46,47</sup> Thus, NMDA receptor antagonists, such as amantadine have been identified as potential anti-PD agents to combat the excitotoxic effects of NMDA binding in such fragile locations. Because of the novelty associated with NMDA antagonists in the treatment of PD and the lack of certainty in terms of an exact pathophysiological mechanism, research in this field is ongoing. Nonetheless, amantadine has produced promising results in the treatment of PD by improving patient survival, therefore supporting its use as a neuroprotective agent.<sup>46,48</sup>

In addition to those described above, several other classes of drugs have been reportedly used in the medical management of PD. These include, but are not limited to, adenosine receptor A2 antagonists, GABA-A receptor agonists, selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, 5-HT 2A inverse agonists and prototypical agents that have yet to be approved by the Food and Drug Administration in the United States.<sup>35,43</sup>

### Orofacial Manifestations

Although resting tremor, postural instability, bradykinesia and cogwheel rigidity are the cardinal systemic signs of PD, several orofacial manifestations may present clinically.<sup>49</sup> These signs may be seen in early stages of the disease, but they become more noticeable with disease progression.<sup>20</sup> Perhaps the most concerning are a result of impairment in performing routine activities of daily living, such as brushing teeth and flossing. Reduced competence with oral hygiene in patients with PD may lead to increased frequency of caries, periodontal disease and tooth loss.<sup>50</sup> In addition, the various pharmacotherapies of PD may cause xerostomia, which

may exacerbate the progression of dental caries, periodontal disease, halitosis and tooth loss.<sup>45,50</sup> Xerostomia also contributes to dysarthria, dysphagia, dysgeusia, glossitis and decreased prosthodontic retention, thereby worsening quality of life for patients with PD.<sup>51</sup> Dysphagia and dysgeusia also have psychosocial and physical implications, which may further discourage or impede the ability of PD patients to eat, thereby reinforcing the importance of proper nutrition and dietary supplementation for them.<sup>52</sup>

Burning mouth syndrome (BMS), affecting the tongue, floor of mouth, lips and cheeks, is also seen in patients who suffer from PD.<sup>20</sup> Although its etiology is not certain, research suggests that dopamine replacement therapy with carbidopa/levodopa may cause the onset of BMS and is correlated with its severity.<sup>53</sup> Further hypotheses regarding the appearance of BMS in PD patients include drug-induced xerostomia and parafunctional activities, such as purposeless chewing.<sup>20</sup> Olfactory dysfunction and altered sense of taste also present in patients with PD, affecting their appetite and frequency of ingestion, thereby contributing to poor dietary and nutritional habits.<sup>20,43,52,54</sup> The currently accepted mechanism responsible for a decrease in these senses is loss of neurons in the anterior olfactory nucleus as a result of incidental Lewy body disease, which may be a precursor to PD.<sup>55</sup>

Neuromuscular pathologies associated with PD affect the physiological function of the orofacial musculature, which can present in various manners clinically. TMDs are frequently observed in patients with PD.<sup>23</sup> They are multifactorial and may impair the functions of the muscles of mastication and the temporomandibular joint (TMJ) synergistically or independently.<sup>23,56</sup> In PD patients, the electromyographical activity of the masticatory muscles is altered, resulting in bradykinesia. Consequently, patients with PD may often present with chewing difficulties.<sup>57</sup> The reduction in masticatory efficiency is also attributed to a decreased bite force.<sup>22,57</sup> Further manifestations of TMDs may result in myofascial pain, limited mandibular opening, dislocation of the articular disc and corresponding asymmetry in occlusal contacts.<sup>23</sup> Neuromuscular pathologies that may have an effect on mastication also include tremors and rigidity of the orofacial musculature, which can lead to cracked teeth, orofacial pain, TMJ pain, bruxism, attrition and decreased denture retention.<sup>20</sup>

Neuromuscular abnormalities in patients with PD include involuntary movement and/or tremors of the eyelid, forehead, mandible, lips and tongue, which make dental care and oral hygiene challenging.<sup>58</sup> Patients with PD often present with an impassive or gaunt facial appearance resulting from hypomimia, a reduction in the movement of small facial muscles.<sup>20</sup> Gaunt appearance is a consequence of several factors, including poor nutrition and weight loss from excessive energy consumption by involuntary movements.<sup>20</sup>

Deficiencies in orofacial musculature are also associated with fungal infections, such as angular cheilosis, which seems to have a multifactorial etiology in patients with PD. The primary factor in skin disorders in PD patients is suggested to be autonomic dysfunction, which manifests as sialorrhea.<sup>20,58,59</sup> Together with forward leaning because of postural instability and decreased lip competence from deficits in orofacial musculature, sialorrhea may result in drooling, which can influence the onset of angular cheilitis.<sup>20,59</sup> Drooling may also occur because of swallowing inadequacies and result in loss of saliva from the oral cavity. Patients with PD may present with vocal problems caused by oropharyngeal deficits in neuromuscular function. Specifically, these include decreased tone of orofacial musculature, hypokinesia and rigidity.<sup>20</sup> These oropharyngeal deficiencies may result in hypophonia which could compromise the communicative effectiveness of PD patients.<sup>60</sup> The severity of hypophonia increases as PD progresses and may eventually reach nearly inaudible levels comparable to a whisper.

## Dental Management

### General Considerations

The plethora of orofacial manifestations of PD make dental management critical. Therefore, before considering treatment for patients with PD, dentists must consult the most recent clinical practice guidelines, as described in **Table 4**.<sup>58</sup>

It is important that dentists are familiar with the systemic and orofacial manifestations of PD, as they may be the first health care providers to observe clinical signs and symptoms of early PD.<sup>11</sup> For patients who have a history of PD, the dentist's primary goal should be to manage the potential orofacial complications associated with the disease and make the patient's experience at the dental office as comfortable as possible. To do so, the dentist must consult with the patient's family physician and understand the various treatment regimens to be implemented for different disease stages.<sup>58</sup> Before dental treatment, dentists should also be aware of potential conflicts associated with informed consent because of the cognitive decline in patients with advanced PD.<sup>10</sup> It is advantageous to have family, friends or caretakers present when treating patients with PD to avoid potential misunderstandings over informed consent, as well as to reinforce oral hygiene, preventive strategies and at-home care.

Given the challenges associated with treating PD patients, additional techniques may be employed chairside to aid in their dental management (**Table 5**). As with all patients, dentists should obtain a comprehensive medical history and review any pertinent information with the patient's family physician for clarity. It may be useful to consult with a neurologist to determine the patient's

stage of PD. Those who are suffering severely advanced stages may benefit from dental procedures in hospital dental clinics rather than at in-office dental appointments. However, this may be unrealistic in some cases, specifically in remote locations with limited access to care.

The use of minimal conscious sedation may facilitate the dental treatment of PD patients. Minimal conscious sedation with intravenous midazolam has been reported to reduce PD-related dyskinesias during dental extractions.<sup>61</sup> Furthermore, PD patients administered benzodiazepines for sedation have shown a reduction in post-operative confusion.<sup>62</sup> Although nitrous oxide is among the most popular agents for achieving minimal conscious sedation, there are limited studies to demonstrate its efficacy and safety for PD patients. One case report even suggests that chronic occupational exposure to nitrous oxide might exacerbate dopaminergic degeneration and the onset of PD.<sup>63</sup> Currently, there are no reports of short-term exposures to nitrous oxide, such as those provided during a dental appointment, having significant adverse effects on PD patients.

Regardless of the method used, dentists should not surpass minimal conscious sedation while treating PD patients because of the potential consequences of respiratory depression. Respiratory dysfunction in PD patients is highly variable,<sup>64</sup> and it may be difficult to maintain an airway. Muscular rigidity and postural inadequacies might also make it difficult to perform basic life support (e.g., head tilt, chin lift and/or tongue thrust) to maintain a patent airway.

### **Treatment Planning for PD Patients**

When devising dental treatment plans for PD patients, it is important to ensure that the regimen is suited to the individual patient and their stage of PD. For early PD patients, the oral health team should focus on mitigating the progression of the disease and treating its symptoms. For severe/advanced PD patients, the team should attempt to alleviate clinical symptoms to make the dental experience as comfortable as possible.<sup>20</sup>

Salivary control in PD patients can be difficult to balance between PD-induced sialorrhea and medication-induced xerostomia. Dentists should be careful to select the appropriate treatment option on an individual basis. High-dose botulinum toxin A (BoNT-A) has demonstrated effectiveness at reducing salivary outflow in PD patients without inducing intolerable adverse effects.<sup>65</sup> A recent review supported the use of BoNT-A treatment for sialorrhea; however, long-term studies with larger

sample sizes are required to confirm this.<sup>66</sup> Future studies may also aim to quantify the reduction in saliva outflow to provide dentists a numerical tool to aid in treatment planning. Drug-induced xerostomia may be equally as debilitating as sialorrhea, or perhaps worse, in PD patients on polypharmacy regimens. Therefore, increasing salivary flow for these patients should be limited to basic strategies to avoid potential complications. Methods, such as improving hydration and using topical agents may provide symptomatic relief to avoid prescription of another drug.<sup>67</sup>

Dysphagia is another significant symptom of PD that may have serious implications for dental treatment. The use of high-volume suction and proper isolation methods is imperative to avoid aspiration and to mitigate the effects of dysphagia. For procedures, such as crown insertion or extraction, extreme care should be taken. Practical aids, such as a C-sponge or cotton gauze pad, should be placed to protect the airway. For scaling and root planing, dental professionals may opt to use hand instruments rather than ultrasonic handpieces to avoid excessive use of water spray. Dentists would be prudent to review pharmacotherapies that patients with PD may be currently prescribed to avoid any adverse drug reactions.

As PD generally affects patients who are older than 60 years, a large proportion of PD patients are likely to be either partly or fully edentulous. The extent of edentulism in patients with PD is likely higher because of an increased prevalence of periodontal disease and, correspondingly, tooth loss. Dental management of edentulous patients with PD must be carefully planned and removable dental prostheses should be avoided, whenever possible, to prevent potential aspirations that could result in a life-threatening emergency.<sup>68</sup> Fixed dental prostheses, such as bridges and implants, may be considered where clinically applicable; however, studies show that poor oral hygiene, bruxism and dyskinesias in PD patients may lead to their early failure.<sup>69</sup> Therefore, dentists should use sound clinical judgement and consider all potential options for tooth replacement, including removable and fixed dental prostheses and implants, where clinically applicable. If properly placed and maintained, dental implants are an effective treatment option for edentulous patients with PD. It was recently reported that the duration of use of dental prostheses may affect masticatory efficiency more than the degree of severity of neuromuscular pathology itself.<sup>70</sup> Research also suggests that implant-supported overdentures may increase masticatory efficiency and nutrition in PD patients, which leads to better quality of life.<sup>71,72</sup>

**Table 2:** Stages of Parkinson's disease based on the Hoehn and Yahr scale,<sup>28</sup> modified.

Severity	Stage	Symptoms
Early/ mild	I	Only 1 side of the body is affected (for example, tremor of 1 limb), usually with minimal or no functional impairment
	II	Both sides of the body are affected but posture and balance remain normal
Moderate	III	Both sides of the body are affected, and there is mild imbalance when standing or walking; however, the person remains independent
Advanced/ severe	IV	Both sides of the body are affected, and there is disabling instability while standing or walking; a person in this stage requires substantial help and cannot live independently
	V	Fully developed disease present; the person is often cachectic, restricted to bed or wheelchair unless aided

**Table 3:** Common agents used to treat various signs and symptoms of Parkinson's disease, including mechanism of action, adverse effects and important dental manifestations.

Drug classification	Generic name (proprietary name)	Mechanism of action	Adverse effects	Dental considerations
Dopamine precursor	Levodopa (Inbrija)	Converted into dopamine after decarboxylation	Cough, nausea, vomiting, fatigue, constipation, drowsiness, confusion, delusions, hallucinations, syncope, compulsive behaviours, anxiety, sedation, dyskinesia, asthenia, psychosis, arrhythmias, restless leg syndrome, peripheral edema, valvular heart disease, retroperitoneal fibrosis, pleuropulmonary fibrosis	Oropharyngeal pain, orthostatic hypotension
Dopamine agonists				
Ergoline derivatives	Bromocriptine (Parlodel)	D2 receptor agonist; D1 receptor partial agonist		Orthostatic hypotension
	Cabergoline (Dostinex)	Long-acting D2 receptor agonist		Xerostomia, non-odontogenic tooth pain, throat irritation
Non-ergoline derivatives	Pramipexole (Mirapex)	Selective D2 agonist		Xerostomia, dysphagia
	Ropinirole (Requip)	High affinity D3 receptor agonist; D2 receptor agonist – increases the release of dopamine at the presynaptic terminal	Xerostomia, dysphagia, orthostatic hypotension	
DOPA decarboxylase inhibitors	Carbidopa (Lodosyn)	Inhibits the metabolism of levodopa into dopamine; does not cross blood-brain barrier	Nausea, vomiting, cardiac arrhythmias, delusions, dyskinesia	No significant effects reported†

Table 3 continued ►



Drug classification	Generic name (proprietary name)	Mechanism of action	Adverse effects	Dental considerations
<b>Monoamine oxidase-B inhibitors</b>	Rasagiline (Azilect)	Irreversible selective inhibition of brain MAO — decreases the metabolism of dopamine	Headache, nausea, diarrhea, vomiting, dyskinesia, trauma, peripheral edema, weight loss, arthralgia, back pain, neck pain, constipation, dyspepsia, skin rash (topical), hallucination, confusion, tinnitus, rhinitis, pharyngitis, urinary retention, increased serum ALT, increased serum AST	Xerostomia, orthostatic hypotension, dyspnea
	Selegiline (Eldepryl)	High-affinity irreversible MAO-B inhibitor — decreases the catabolism of dopamine		Xerostomia, dysphagia, stomatitis, dysgeusia
	Safinamide (Xadago)	Low-dose selective inhibition of MAO-B enzyme — exact mechanism unknown‡		No significant effects reported
<b>Catechol-O-methyltransferase inhibitors</b>	Entacapone (Comtan)	Reversible and selective peripherally-acting COMT inhibitor — decreases the metabolism of levodopa; increased levels of dopamine	Nausea, dyskinesia, muscle cramps, syncope, dizziness, fatigue, anxiety, diaphoresis, abdominal pain, constipation, vomiting, urine discoloration, purpura, hyperkinesia, hypokinesia, sleep disorders, hallucination, dystonia	Xerostomia, dysgeusia, orthostatic hypotension, dyspnea
	Tolcapone (Tasmar)	Reversible and selective CNS-acting COMT inhibitor — decreases the metabolism of levodopa; increased levels of dopamine in the brain		Significant xerostomia, orthostatic hypotension
<b>Acetylcholine antagonists</b>	Trihexyphenidyl (Artane)	Smooth muscle relaxant, anticholinergic	Urinary retention, confusion, hallucinations, tachycardia, agitation, dizziness, euphoria, skin rash, constipation, nausea, toxic megacolon, parotitis, vomiting, muscle weakness, blurred vision, mydriasis, dysuria, tremor, nasal congestion	Xerostomia
	Benzotropine (Cogentin)	Anticholinergic, antihistamine		Xerostomia, dry throat, nasal dryness
	Orphenadrine (Norflex)	Anticholinergic, analgesic		Xerostomia
	Procyclidine (Kemadrin)	Anticholinergic, blocks excess acetylcholine at cerebral synapses, antispasmodic, mydriatic		Xerostomia, dry throat, nasal dryness
<b>Glutamate antagonists</b>	Amantadine (Symmetrel)	Weak NMDA receptor non-competitive antagonist — exact mechanism unknown§	Syncope, peripheral edema, dizziness, delusions, hallucination, paranoia, falling, constipation, livedo reticularis, insomnia, anxiety, depression, headache, ataxia, nausea, urinary tract infection, benign prostatic hypertrophy, arthritis, blurred vision	Xerostomia, orthostatic hypotension, nasal dryness

Table 3 continued ►

Drug classification	Generic name (proprietary name)	Mechanism of action	Adverse effects	Dental considerations
Combination therapies	Levodopa + benserazide (Prolopa)	Increased dopamine serum level which is sustained by inhibition of the peripheral plasma breakdown of levodopa	Cough, nausea, vomiting, fatigue, constipation, drowsiness, arrhythmias, chest pain, flushing, ataxia, anxiety, alopecia, rash, hematuria, agranulocytosis, hemolytic anemia, akinesia paradoxa, dystonia, blepharospasm, blurred vision, diplopia, bilirubin increased, sporadic breathing pattern, cough, hoarseness, diaphoresis, hiccups, hypersensitivity reactions, dystonia	Bruxism, postnasal drip, lip/mouth/tongue tightness, orthostatic hypotension
	Levodopa + carbidopa (Sinemet)	Increased dopamine serum level which is sustained by DOPA decarboxylase inhibition		Orthostatic hypotension, xerostomia, dysgeusia, oropharyngeal pain, dyspnea, upper respiratory tract infection
	Levodopa + carbidopa + entacapone (Stalevo)	increased dopamine serum level which is sustained by DOPA decarboxylase and COMT inhibition		No significant effects reported

*Note: CNS = central nervous system, COMT = catechol-O-methyltransferase, DOPA decarboxylase = aromatic L-amino decarboxylase, MAO = monoamine oxidase, NMDA = N-methyl-D-aspartate.*  
*\*Pharmaceutical data were obtained from Lexicomp for the Canadian Dental Association.*  
*†Carbidopa in combination with levodopa is associated with orthostatic hypotension.*  
*‡Safinamide contributes to an increased dopaminergic activity in the brain although its exact mechanism of action in the treatment of PD is unknown.*  
*§Amantadine exhibits anticholinergic-like adverse effects although it has not been shown to possess direct anticholinergic activity.*

**Table 4:** Clinical practice guidelines (CPGs) for the dental management of patients with Parkinson's disease.

CPG	Quality of evidence	Associated risks
Early and frequent oral health assessment	Very low	Increased discomfort, inconvenience, financial considerations
Timing and length of dental appointments	Very low	Additional costs, discomfort and inconvenience if more dental appointments are required
Collaboration between dentists and medical providers	Very low	None identified
Chlorhexidine product use	Very low	May cause tooth staining, altered taste perception, minor irritation to soft tissues, increase in supragingival calculus formation
Minimize risk of aspiration during dental procedures	Low	None identified
Patient and caregiver education	Moderate	None identified
Powered toothbrushes with large handles and other assistive devices	Moderate	Improper use of electric toothbrushes may increase sensitivity and recession. The noise and vibration may induce anxiety and irritation in Parkinson's patients with cognitive decline; cost of power toothbrush vs. manual
Treatment of xerostomia	Moderate	Xylitol may cause abdominal discomfort in large doses and should be kept away from pets Products with citric acid may cause enamel erosion and should be used in conjunction with fluoride products

Table 4 continued ►

CPG	Quality of evidence	Associated risks
Fluoride product use	High	Excessive use may lead to fluorosis
Treatment of sialorrhoea	High	Potential side effects of botulinum toxin injections include xerostomia and transient swallowing difficulties including severe dysphagia (rare)

Source: Gosnell et al.<sup>58</sup>

**Table 5:** Techniques for managing patients with Parkinson's disease in the dental environment.

<b>1</b>	<p><b>Obtain and update a complete medical history</b></p> <ul style="list-style-type: none"> <li>• Ensure that medical history is up to date and prescriptions are updated regularly</li> <li>• Avoid drug interactions and note the progression of the disease through changes or additions to the medications list</li> <li>• Be familiar with the cardinal signs and symptoms of Parkinson's disease along with oral manifestations (xerostomia, dysphagia, etc.)</li> </ul>
<b>2</b>	<p><b>Consult with the patient and his/her neurologist before treatment to determine the stage of Parkinson's disease</b></p> <ul style="list-style-type: none"> <li>• In later stages of the disease, patients may need to be referred to a hospital dental clinic for treatment</li> </ul>
<b>3</b>	<p><b>Be aware of potential informed-consent issues</b></p> <ul style="list-style-type: none"> <li>• Discuss treatment needs with the patient, family members and/or caregivers who have power of attorney</li> </ul>
<b>4</b>	<p><b>Preventive oral hygiene is integral</b></p> <ul style="list-style-type: none"> <li>• Patient, family members and/or caregivers should be instructed on proper oral hygiene techniques for their loved ones</li> <li>• Emphasize the importance of good oral care</li> <li>• Recommend that family or a friend accompany the patient to dental visits to ensure clear communication</li> </ul>
<b>5</b>	<p><b>Dental visits should be short and scheduled in the morning</b></p> <ul style="list-style-type: none"> <li>• Coordinate appointments with the patient's medication schedule, if possible, to avoid manifestations of motor symptoms during dental procedures to avoid aspiration and potential for iatrogenic damage</li> </ul>
<b>6</b>	<p><b>Be mindful of the potential for orthostatic hypotension</b></p> <ul style="list-style-type: none"> <li>• Patients may require assistance to be seated in the dental chair</li> <li>• Patients should be raised slowly after completion of the procedure to prevent orthostatic hypotension</li> <li>• Orthostatic hypotension is mainly a symptom of anti-Parkinson's disease medications and should be prevented to avoid a medical emergency</li> </ul>
<b>7</b>	<p><b>Consider sedation for complex procedures</b></p> <ul style="list-style-type: none"> <li>• Sedation may ensure patient comfort and facilitate efficiency of the dental practitioner</li> <li>• Patients should not surpass the state of minimal conscious sedation to avoid respiratory distress</li> </ul>
<b>8</b>	<p><b>Avoid the use of cavitrons and piezo scalers</b></p> <ul style="list-style-type: none"> <li>• Magnetic devices may lead to transcranial stimulation and are therefore contraindicated in patients with Parkinson's disease.</li> </ul>
<b>9</b>	<p><b>Be cautious when handling small items and consider the potential for aspiration</b></p> <ul style="list-style-type: none"> <li>• Consider fixed prostheses such as implants or fixed partial dentures</li> <li>• Use extreme caution during insertion of fixed partial dentures</li> <li>• Always place a rubber dam for restorative procedures</li> <li>• Review cardiopulmonary resuscitation protocols and be prepared to act accordingly in the case of an emergency</li> </ul>

## Conclusion

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As the second most prevalent neurodegenerative disease in North America, PD affects a marked proportion of the population. Although the cardinal signs of PD are not directly related to the orofacial complex, orofacial manifestations are common in both early and advanced stages of PD. Given the sheer number of orofacial pathologies associated with PD and their multifactorial etiologies, dentists play a vital role in the interdisciplinary treatment of PD. Therefore, it is beneficial for dentists to be able to identify the systemic clinical signs and symptoms that are characteristic of the disease to aid in early diagnosis. As there is currently no

cure for PD, patients will often undergo polypharmacy treatments to manage their symptoms. Therefore, dentists should always consider consultation with family physicians and neurologists of patients with PD to maintain patient safety and minimize drug-induced adverse effects. Furthermore, dentists should be familiar with the optimal treatment regimens for patients with PD, bearing in mind that treatment plans should be re-evaluated often and modified accordingly. With the potential impact and negative consequences of PD on oral health, it is imperative that dental professionals understand the potential oral complications associated with PD and how to properly manage them to ensure optimal dental care.

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