Abstract: Cardiovascular disorders, such as orthostatic hypotension and supine hypertension, are common in patients with neurodegenerative synucleinopathies such as Parkinson disease (PD), and may also occur in other conditions, such as peripheral neuropathies, that result in autonomic nervous system (ANS) dysfunction. Dysfunction and degeneration of the ANS are implicated in the development of orthostatic and postprandial hypotension and impaired thermoregulation. Neurogenic orthostatic hypotension (nOH) results from sympathetic failure and is a common autonomic disorder in PD. Supine hypertension may also occur as a result of both sympathetic and parasympathetic dysfunction in conjunction with nOH in the majority of patients with PD. Management of supine hypertension in the setting of nOH can be counterintuitive and challenging. Additionally, the presence of other noncardiovascular comorbidities, such as diabetes mellitus and peripheral edema, may further contribute to the burden of disease. ANS dysfunction thus presents major healthcare implications and challenges for neurology and cardiovascular practices, necessitating an integrated neurology and cardiology management approach.

Key Words: neurogenic orthostatic hypotension, Parkinson disease, autonomic dysfunction, droxidopa, supine hypertension

The autonomic nervous system (ANS) is the hallmark manifestation of ANS dysfunction. In contrast to non-nOH, which can be caused by medications (eg, diuretics and vasodilators), impaired venous return (venous pooling), hypovolemia, or impaired cardiac output, nOH is a form of OH that results as a consequence of neurodegenerative disease of either the peripheral or central nervous system.6

Another common cardiovascular disorder that often occurs as a result of autonomic failure in synucleinopathies is supine hypertension (SH).7 The clinical management of nOH and SH may be counterintuitive and challenging (especially when they occur in combination) because of opposing hemodynamics and/or treatment incompatibility. Here, we review ANS regulation of the cardiovascular system with a focus on the sympathetic and parasympathetic nervous systems (SNS and PNS), as well as the pathophysiology, clinical manifestations, diagnosis, and management approaches for these manifestations of cardiovascular autonomic dysfunction, from both cardiology and neurology perspective.

THE AUTONOMIC NERVOUS SYSTEM

The ANS regulates bodily functions to maintain homeostasis and coordinates the acute response to threat or danger. It comprises the SNS, PNS, and enteric nervous systems (ENS).8 The SNS and PNS are anatomically and functionally distinct and use different sets of neurotransmitter systems; their activation largely results in antagonistic effects.8 The ENS, consisting of the myenteric and submucosal plexi, is involved in the control and coordination of the gastrointestinal (GI) tract, including motility, blood flow, and secretions.9,10 Although it is considered an independent system,9 the ENS may be inhibited by signals from the sympathetic component of the ANS, in accordance with relative bodily needs.11

The SNS prepares the body for the fight or flight response, and the PNS is involved in rest and digest responses.12 Upon activation, the SNS induces responses including increased heart rate (HR) and force of ventricular contraction (positive chronotropism and positive inotropism, respectively), decreased GI tract motility, pupil dilation, bronchodilation, decreased reproductive system function, slightly increased glandular secretion, and mobilization of energy substrates.8 The primary neurotransmitter of the SNS is norepinephrine.11 Upon activation of the PNS, responses include decreased HR and cardiac force of contractility (negative chronotropism and negative inotropism, respectively), enhanced GI tract motility, pupil constriction, bronchoconstriction, and substantial secretion from lacrimal and salivary glands.8 The main postganglionic neurotransmitter of the PNS is acetylcholine.14

AUTONOMIC NERVOUS SYSTEM’S REGULATION OF THE CARDIOVASCULAR SYSTEM

The intrinsic conduction system of the heart produces an impulse originating from the rhythmic discharge of the sinoatrial node, which determines the HR.13 The ANS regulates HR and cardiac output depending on physiologic conditions, ensuring that the heart performs optimally both at rest and when an acute response is needed.13,16

The anatomy of the ANS associated with regulation of the heart is depicted in Figure 1.16 Sympathetic cardiac nerve fibers stem from...
the upper thoracic region of the spinal cord; these are short preganglionic efferent nerve fibers that enter the paravertebral chains of ganglia and synapse with longer postganglionic sympathetic efferents that extend to the sinoatrial and atrioventricular nodes. Upon activation, the preganglionic efferents release acetylcholine that binds to nicotinic receptors on the postganglionic efferents; in turn, the postganglionic efferents, which are adrenergic, release norepinephrine at synapses that have β-adrenergic receptors. The results are increases in HR, force of ventricular contraction, rate of relaxation, and conduction velocity of the sinoatrial and atrioventricular nodes, all of which are fundamental for the fight or flight response.

Parasympathetic control of the heart is mediated by long preganglionic efferent nerve fibers that stem from the vagus nerve and synapse near the sinoatrial and atrioventricular nodes. Activation of the parasympathetic nerve fibers releases acetylcholine, which, in turn, activates muscarinic receptors in the sinoatrial and atrioventricular nodes. The results are decreases in HR, force of ventricular contraction, rate of relaxation, and conduction velocity of the sinoatrial and atrioventricular nodes, which are all characteristic of the rest and digest response.

The SNS has a primary role in autonomic regulation of the vasculature, innervating arteries, veins, and microvessels. Activation of sympathetic nerve fibers triggers the release of 3 main neurotransmitters—norepinephrine, adenosine triphosphate (ATP), and neuropeptide Y—all of which have a role in mediating vasoconstriction. Norepinephrine and ATP are released together to produce rapid adrenergic and purinergic vasoconstriction as a result of vascular smooth muscle cell contraction. Neuropeptide Y is released along with norepinephrine and ATP in response to moderate to intense sympathetic activation, producing slow and sustained vasoconstriction. Neuropeptide Y may also potentiate vasoconstriction in response to norepinephrine.

The ANS is also responsible for signaling the cardiovascular system for the necessary acute response to orthostatic stresses created by moving from a supine to a sitting or standing position. The role of the ANS in maintaining cardiovascular homeostasis during changes in posture is presented in Figure 2. Change from a supine or seated to a standing position triggers blood pressure (BP) regulatory mechanisms that increase HR, cardiac contractility, and vascular tone to maintain sufficient perfusion of vital organs. When moving to a standing position, blood shifts from the thorax to the lower body (venous pooling), and BP drops as a result. Baroreceptors in the cardiovascular and pulmonary vessels detect the decrease in BP and respond by withdrawing parasympathetic activity and increasing sympathetic activity, thereby increasing BP.

**PATHOPHYSIOLOGY OF AUTONOMIC NERVOUS SYSTEM FAILURE IN NEURODEGENERATIVE DISEASES**

Formation and accumulation of misfolded protein aggregates of α-synuclein is the pathognomonic feature of the synucleinopathies PD, Lewy body dementia (LBD), pure autonomic failure, and multiple system atrophy (MSA). α-Synuclein has been recognized as the main component of the Lewy body in both PD and LBD, suggesting that aggregation of α-synuclein may play a dominant role...
in the neurodegenerative processes seen in these diseases. Further evidence has confirmed that abnormal aggregation of \( \alpha \)-synuclein plays a central role in PD and related disorders; however, its normal function and mechanism of involvement in neurodegeneration are not completely understood. In PD, LBD, and pure autonomic failure, \( \alpha \)-synuclein forms intraneural aggregates as Lewy bodies and neuronal neurites, leading to both central and peripheral neurodegeneration and denervation (in PD). In MSA, \( \alpha \)-synuclein aggregation occurs mainly in oligodendritic structures termed glial cellular inclusions, resulting in only central nervous system lesions. Progressive neurodegeneration of the ANS in patients with MSA may be clinically manifested as nOH, erectile dysfunction in men, urinary incontinence, and constipation.

In addition to \( \alpha \)-synuclein aggregation, significantly lower levels of norepinephrine have been found in postmortem studies of PD in several brain regions, including the caudate, middle frontal gyrus, anterior cingulate gyrus, hippocampus, amygdala, inferior parietal lobule, precuneus, and visual association cortex. Low norepinephrine levels are associated with OH as demonstrated in a study that found significantly lower plasma levels of norepinephrine in patients who had PD with OH but not in patients who had PD without OH. Furthermore, cardiac noradrenergic denervation has been demonstrated in the thoracic region by positron emission tomography studies in patients with pure autonomic failure, PD, and MSA, although normal innervation is seen in most patients with MSA (Figure 3). Preserved innervation in MSA reflects a centrally mediated pathophysiology, whereas in pure autonomic failure and PD, it reflects a postganglionic sympathetic lesion.

The resulting impairment of cardiovascular homeostasis in PD manifests as increased difficulty in making HR adjustments to changes in BP and in the development of nOH, baroreflex dysfunction, and nighttime fluid retention. In MSA, cardiovascular dysregulation resulting in nOH is a prevalent characteristic. \( {\left[ {^{123}I} \right]} \)-Metaiodobenzylguanidine scintigraphy can also be used to assess cardiac sympathetic innervation to distinguish between conditions of peripheral (PD and pure autonomic failure) versus central (MSA) autonomic failure. Decreased baroreflex-cardiovagal gain occurs with normal aging and has also been observed in patients with PD and patients with OH. Baroreflex-cardiovagal gain is normally measured through determination of the cardiac interbeat interval (RR interval) response in relation to systolic BP changes after intravenous injection of a vasoconstrictor or vasodilator. Together with sympathetic failure resulting in a sustained drop in BP when standing, HR increases to compensate for low BP and consequently decreases the cardiac interbeat interval. Decreased baroreflex-cardiovagal gain manifests as dizziness and may lead to blackout.

**COMMON CONDITIONS THAT MAY RESULT FROM AUTONOMIC DYSFUNCTION**

**Neurogenic Orthostatic Hypotension**

In healthy individuals, venous return of blood to the heart is increased by muscle contraction to prevent pooling in lower parts of the body. ANS responses to changes in position include vasoconstriction and increased HR and cardiac contractility. However, in individuals with nOH, autonomic dysfunction results in hemodynamic abnormalities that are clinically manifested as a drop in BP upon standing. nOH is a form of OH defined as a sustained reduction of systolic BP of \( \geq 20 \text{ mm Hg} \) or diastolic BP of \( \geq 10 \text{ mm Hg} \) within 3 minutes of standing or using a head-up tilt table for autonomic testing. nOH occurs when the ANS does not respond adequately to counteract the gravitational shift in blood volume; thus, there is a sustained fall in BP that is associated with an insufficient increase in HR (typically \( < 15 \text{ bpm} \)).

nOH is considered to be a manifestation of norepinephrine deficiency, as described previously for synucleinopathies. The prevalence of nOH is reported at 30% to 40% in PD, 1% to 50% in LBD, 75% to 97% in MSA, and 97% in pure autonomic failure.

Several studies have suggested an impact of OH/nOH on the risk of falls and injuries, societal costs, and psychosocial effects (eg,
The diagnosis of nOH is based on clinical manifestations including dizziness/lightheadedness, presyncope, syncope, weakness, and falls. Screening questions are used to identify suspected OH/nOH, and a stepwise approach is recommended for diagnosis. Steps include in-clinic monitoring of BP and HR after 5 minutes in a supine position, which is repeated after 1 and 3 minutes of standing, and at-home BP and HR monitoring after 5 minutes in a supine position or before arising in the morning, which is repeated after 3 minutes of standing, and again while standing when symptomatic. A sit-to-stand test, with at least 5 minutes of sitting and then monitoring of BP immediately before standing and 1, 3, 5, and 10 minutes (as tolerated) after standing, may be a suitable alternative to monitoring BP upon standing after spending 5 minutes in a supine position. A review of medications should be performed to assess the necessity for reduction or modification of medications that may cause OH. The patient’s medical history, including cardiovascular comorbidities, review of systems, and current medication list, should be assessed, and a reasonable physical examination and 12-lead electrocardiogram should be performed to delineate potential causes of OH/nOH. Finally, specialty testing may be considered; possible tests include autonomic testing, plasma catecholamines, sudomotor function testing, and 24-hour ambulatory BP monitoring to help distinguish OH from nOH.

The main goals for treatment per nOH consensus recommendations include reduction of symptom burden (especially falls), prolongation of standing time, and improvement of physical capabilities to enable the patient to perform activities of daily living. The consensus recommendations advise initial interventions, which entail implementation of a 4-step algorithm, with patient reassessment every 2 weeks to discern the benefits of such interventions. Assessment and adjustment of current medications should be performed first, followed by the use of nonpharmacologic approaches. If nOH persists, implementation of single-agent pharmacologic treatment should be considered, and finally combination pharmacologic treatments can be applied with careful assessment of symptomatic benefits, impact on BP, and tolerability.

Pharmacologic options for the management of nOH currently include both approved and off-label medications. The 2 agents currently approved by the US Food and Drug Administration for the treatment of OH and nOH are midodrine, an α-1 adrenergic agonist, and droxidopa, a prodrug of norepinephrine, respectively. Both drugs increase BP by improving vasoconstriction, although a slowing of HR is associated with midodrine administration. Droxidopa has limited effects on HR. Systematic reviews and meta-analyses evaluating the short-term (1 day to 4 weeks) effects of midodrine on BP and symptoms of OH found that midodrine treatment may result in small but positive effects on clinical outcomes in patients with OH. However, the evidence for midodrine was considered low quality because of the small number of studies and heterogeneity among the studies analyzed. Three short-term (1–8 weeks of treatment), randomized, placebo-controlled, double-blind phase 3 studies with droxidopa in patients with symptomatic nOH due to synucleinopathy (PD, MSA, and pure autonomic failure) demonstrated improvement in specific symptoms of nOH (eg, dizziness/lightheadedness). Drugs frequently used off label for the treatment of OH/nOH include fludrocortisone, a glucocorticoid that acts to expand plasma volume, and pyridostigmine, a cholinesterase inhibitor that enhances sympathetic activity by increasing baroreflex sensitivity. The use of β-blockers may worsen the symptoms of nOH because the resultant decreased sympathetic activity, in turn, generates a negative impact on the inotropic/chronotrophic state. It is noteworthy that pacemakers are not recommended for the treatment of nOH.

Coexistent Neurogenic Orthostatic Hypotension and Supine Hypertension

SH coexistent with nOH is associated with negative clinical sequelae, including cardiovascular outcomes, and is part of the underlying disease process in patients with autonomic failure. SH in patients with nOH is defined as systolic BP ≥ 140 mm Hg and/or diastolic BP ≥ 90 mm Hg while in the supine position for ≥ 5 minutes. SH frequency has been reported for PD (34%; 71% mild), MSA (37%; 28% severe), and MSA with OH (49%; 44% severe). In PD, SH is associated with a history of cardiovascular comorbidities and more pronounced drops in BP with orthostatic challenge. SH has been associated with target end-organ damage (eg, left ventricular hypertrophy and kidney dysfunction) and negative cardiovascular outcomes, such as the occurrence of stroke.

SH has been shown to coexist with nOH in 50% to 90% of patients with PD. Dilemmas in management arise with concurrent disease because SH and nOH represent opposite hemodynamics, and as such, when these conditions are coexistent, specific treatments for nOH or SH may exacerbate the other condition. For example, pressor medications used to treat nOH may exacerbate SH, whereas short-acting antihypertensives used to treat SH may worsen symptoms of nOH. A change in mean BP over a period of 24 hours can include abnormally low BP during the day due to orthostatic stress and abnormally high BP at night due to prolonged recumbence (Figure 4). Impairment of the sympathetic network activation underlies the development of nOH; together with other consequences of sympathetic failure (eg, baroreflex dysfunction, adrenergic hypersensitivity, and nocturnal fluid retention), parasympathetic dysfunction may also contribute to aggravation or development of nocturnal SH. In patients with autonomic failure, a nocturnal dipping pattern (circadian-related ≥ 10% decrease in mean BP at night) is absent—referred to as nondipping or reverse dipping—and results in nocturnal SH. Because untreated long-term SH has known cardiac consequences, it is reasonable to seek treatment options; however, coexistent SH and nOH should be managed with care. A substantial benefit of prioritizing nOH versus SH treatment exists because of a reduction in the risk of falls and the associated complications. Patients with nOH and severe SH can, however, be treated with short-acting antihypertensive agents in the evening, with awareness of the risks of worsening nOH.

Clinical studies directly comparing the risk of SH for droxidopa and midodrine have not been performed. However, a meta-analysis using clinical trial data determined the relative risk for SH with droxidopa (4 studies including 485 patients) was not statistically significant [1.4 (95% CI, 0.71–2.7) vs placebo]. In contrast, midodrine (2 studies including 349 patients) was associated with a significant relative risk for SH [5.1 (95% CI, 1.6–24.0) vs placebo].

Distinguishing Between Other Possible Cardiovascular Manifestations of Autonomic Nervous System Dysfunction

Other cardiovascular conditions that may arise because of ANS dysfunction include (but are not limited to) vasovagal syncope,
postural orthostatic tachycardia syndrome (POTS), and inappropriate sinus tachycardia (IST). A summary of these conditions is provided in Table 1.37,38,40,69–72

**Vasovagal Syncope**

Vasovagal syncope, the most common type of reflex syncope, occurs from a vasovagal reflex that causes vasodilation and/or bradycardia resulting in a rapid and transient loss of consciousness as a consequence of cerebral hypoperfusion, which is followed by complete recovery.68–71 Orthostatic stress (upright position for > 30 seconds), emotional stress, or pain are associated with vasovagal syncope.69,71 Prodromal symptoms in the minute before losing consciousness include pallor, diaphoresis, nausea, abdominal discomfort, yawning, sighing, and hyperventilation. These symptoms are then followed by visual, auditory, and cognitive difficulties.37 Physiologic mechanisms that contribute to vasovagal syncope include decreased cardiac output and reduced systemic vascular resistance.73

**Postural Orthostatic Tachycardia Syndrome**

POTS, a sustained sinus tachycardia upon standing [HR of ≥ 30 bpm in the absence of OH (or ≥ 40 bpm in individuals 12–19 years of age) within 10 minutes of standing or head-up tilt], without notable change in BP, is typically accompanied by symptoms, such as lightheadedness, palpitations, tremulousness, generalized weakness, blurred vision, exercise intolerance, fatigue, presyncope, and syncope.73

![FIGURE 4. Comparison of normal circadian blood pressure variation with supine hypertension and neurogenic orthostatic hypotension.31 In patients with coexistent neurogenic orthostatic hypotension and supine hypertension, episodes of orthostatic hypotension alternate with episodes of supine hypertension during the day. At night, the normal pattern of physiologic blood pressure dipping is absent or reversed, and supine hypertension becomes more sustained because of prolonged recumbence. Mean blood pressure = systolic + diastolic blood pressure/2. OH indicates orthostatic hypotension; SH, supine hypertension. Reprinted from Espay et al.31 Copyright (2016) with permission from Elsevier.](image)

![TABLE 1. Cardiovascular Manifestations of Autonomic Nervous System Dysfunction](table)

| Condition                  | Causes                                                                 | Clinical Manifestations                                                                 |
|----------------------------|------------------------------------------------------------------------|----------------------------------------------------------------------------------------|
| Neurogenic orthostatic     | Autonomic dysfunction                                                  | BP drop of ≥ 20 mm Hg systolic or ≥ 10 mm Hg diastolic upon standing                   |
| hypotension                |                                                                        | Insufficient compensatory HR increase upon standing (< 15 bpm)                        |
|                            |                                                                        | Lightheadedness, dizziness, weakness, fatigue, cognitive and visual problems, leg      |
|                            |                                                                        | buckling, and pain including headache, neck pain, orthostatic dyspnea, or chest pain   |
| Vasovagal syncope          | Orthostatic stress (upright position for > 30 seconds), emotional stress, or pain | Loss of consciousness preceded by pallor, diaphoresis, nausea, abdominal discomfort, |
|                            |                                                                        | yawning, sighing, and hyperventilation                                               |
|                            |                                                                        | Cerebral and retinal hypoperfusion                                                    |
|                            |                                                                        | Auditory and cognitive difficulties                                                   |
| Postural orthostatic       | Autonomic denervation, recent viral illness, chronic fatigue syndrome,  | Sustained HR increase of ≥ 30 bpm (or ≥ 40 bpm in individuals 12–19 years of age)     |
| tachycardia syndrome       | hypovolemia, hyperadrenergic stimulation, or hypervigilance implicated  | within 10 minutes of standing without notable change in BP                             |
|                            |                                                                        | Standing HR typically ≥ 120 bpm                                                        |
|                            |                                                                        | Lightheadedness, palpitations, tremulousness, generalized weakness, blurred vision,   |
|                            |                                                                        | exercise intolerance, fatigue, presyncope, and syncope                                |
| Inappropriate sinus        | Possible mechanisms include dysautonomia, neurohormonal imbalance, and   | Persistent resting sinus HR > 100 bpm (mean 24-hour HR > 90 bpm unrelated to primary   |
| tachycardia                | intrinsic sinus node hyperactivity                                     | causes)                                                                                 |
|                            |                                                                        | Weakness, fatigue, lightheadedness, exercise intolerance, and palpitations              |

BP indicates blood pressure; bpm, beats per minute; HR, heart rate.

Data from Freeman et al,37,38 Shibao et al,49 Sheldon et al,49 Shen et al,50 Brignole et al,71 and Page et al.72
consciousness is not a major feature, although presyncope is frequent. The exact causes of POTS remain unknown, and it is likely that multiple factors contribute to the development of this syndrome including autonomic denervation, recent viral illness, chronic fatigue syndrome, hypovolemia, hyperadrenergic stimulation, and hypervigilance. Importantly, because the symptoms of POTS overlap considerably with vasovagal syncope, the diagnoses of these 2 conditions are often not mutually exclusive. 

**Inappropriate Sinus Tachycardia**

IST is defined as a persistent resting sinus HR of > 100 bpm (mean 24-hour HR > 90 bpm not related to primary causes). The causes of IST have not been elucidated; however, dysautonomia, infarction, stroke, heart failure, and atrial fibrillation. The increased sympathetic activity may play a role. Weakness, fatigue, lightheadedness, exercise intolerance, and palpitations help to distinguish IST from secondary causes of tachycardia. Often in patients with IST, medication therapy is unsuccessful and these symptoms persist even after treatment to normalize HR.

**IMPLICATIONS FOR CARDIOLOGY PRACTICE**

High rates of general medical comorbidities are observed in up to 80% of patients with PD. The most common comorbidities in patients with PD are diabetes mellitus, dyslipidemia, arterial hypertension, and cardiomyopathy. Although noncardiovascular comorbidities are not the focus of this review, it should be noted that they can further contribute to the burden of cardiovascular disorders. Both cardiovascular and noncardiovascular disorders can develop as adverse effects to PD treatment or as a consequence of autonomic dysfunction, which is characteristic of PD pathology.

ANS disorders of the digestive system can adversely affect GI tract motility and cause hypersalivation, delayed gastric emptying, and constipation. ANS disorders of the cardiovascular system include nOH, which is the most common autonomic disorder in PD; SH, which occurs in addition to nOH in a majority of patients with PD, especially at night; and attenuated HR variability associated with cardiovascular morbidity and mortality. Any of these disorders can occur concomitantly, and management of conjunctive disease can be complicated by opposite hemodynamics and/or treatment incompatibility. Because nOH is the most common autonomic manifestation in PD, the implications of OH/nOH in clinical practice are detailed further.

Population-based epidemiologic studies have indicated that OH is associated with increased cardiovascular mortality, myocardial infarction, stroke, heart failure, and atrial fibrillation. The increased morbidity and mortality associated with OH has been demonstrated in several studies including patients with and without PD. In a Belgian study of elderly patients, OH was shown to be a significant predictor of cardiovascular deaths, nonfatal myocardial infarctions, and stroke. In middle-aged patients who participated in the American Atherosclerosis Risk in Communities Study (ARIC, 1987–2008), the presence of OH at baseline was associated with the increased risk of heart failure and stroke. Cross-sectional studies, summarized in the Fedorowski and Melander 2013 article, showed pure autonomic failure (with or without PD) or OH to be associated with reverse or nondipping of nocturnal BP, left ventricular hypertrophy, peripheral arterial disease, and plasma fibrinogen concentration.

In studies that investigated nOH in patients with PD and related conditions, comorbidity resulted in shorter overall survival. In a prospective cohort study of middle-aged and elderly patients, survival differed depending on the type of synucleinopathy (PD, MSA, and pure autonomic failure); mean survival from symptom onset ranged from 7 years in patients with MSA to 16 years in patients with PD without nOH. The presence of nOH in patients with PD was associated with a significantly higher mortality risk versus patients with PD without nOH. A retrospective study of middle-aged and elderly patients with nOH and synucleinopathy (MSA, PD with autonomic neuropathy, and pure autonomic failure) evaluated comorbidities and causes of death. Observed comorbidities included hypertension, benign prostatic hypertrophy, cerebrovascular accidents, cancer, and gastroenterologic-, psychiatric-, respiratory-, and cardiac-related (including heart failure and atrial fibrillation) comorbidities. Causes of death were infectious/respiratory, cardiac, cachexia, stroke, cancer, and trauma. From the findings of these studies, it is clear that nOH often presents with or results in a myriad of comorbidities and complications, all of which adversely affect patient quality of life, morbidity, and mortality.

**CONCLUSIONS**

PD and other synucleinopathies are characterized by autonomic dysfunction, which also severely affects the cardiovascular and noncardiovascular systems under sympathetic and parasympathetic control. Although nOH is the most common ANS dysfunction-mediated cardiovascular manifestation in patients with PD, its coexistence with SH is a clinical challenge. Furthermore, attenuated HR variability, sinus node dysfunction, and chronotropic incompetence can also occur in conjunction with OH. Management of conjunctive disease can be complicated by opposite hemodynamics and/or treatment incompatibility. Additionally, the presence of other noncardiovascular comorbidities may further contribute to the burden of cardiovascular disease and synucleinopathy. Multiple comorbidities effectively impair quality of life and shorten survival in patients with synucleinopathy; this presents major healthcare implications in synucleinopathy and cardiovascular management practices, necessitating an integrative therapeutic approach.

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