Introduction to Neurogenic Orthostatic Hypotension

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Introduction

Welcome to Module 2: Neurogenic Orthostatic Hypotension!

In **Module 1: The Autonomic Nervous System**, you learned that the **autonomic nervous system (ANS)** regulates the internal environment of the organ systems to maintain **homeostasis**. It does this through regulatory circuits called **visceral reflexes**. The balance between input from the sympathetic and the parasympathetic divisions of the ANS determines the response of the target tissue.

One example of a visceral reflex is the sympathetic reflex that helps to maintain the heart's output when you stand up. When you stand up, **proprioceptors** detect the body's changed position and send a signal to the central nervous system (CNS). The sympathetic system responds by increasing the heart rate and constricting the blood vessels to increase blood pressure. This helps to prevent the blood from pooling in the legs and to keep the brain oxygenated.[1]

If the sympathetic system fails to increase the heart's output, the blood pressure within the brain decreases. This may result in symptoms such as lightheadedness, blurry vision, or even fainting.[2,3] This is called orthostatic hypotension.[1]

Orthostatic hypotension may have non-neurogenic or neurogenic causes. With non-neurogenic causes, for example if the blood volume is too low due to dehydration, the normal sympathetic response is not sufficient to restore the blood pressure.[4]

Neurogenic orthostatic hypotension (nOH) results from **autonomic failure**.[5] This means that the sympathetic neurons do not release enough norepinephrine to stimulate the compensatory mechanisms (increased heart rate and systemic blood vessel constriction) that maintain blood pressure upon standing.[5,6]

In this module, we will learn about nOH. It is divided into 3 lessons:

Lesson 1: Overview discusses the definition, classification, clinical presentation, epidemiology, and natural history of nOH

Lesson 2: Pathogenesis details the underlying pathophysiologic mechanisms that cause nOH

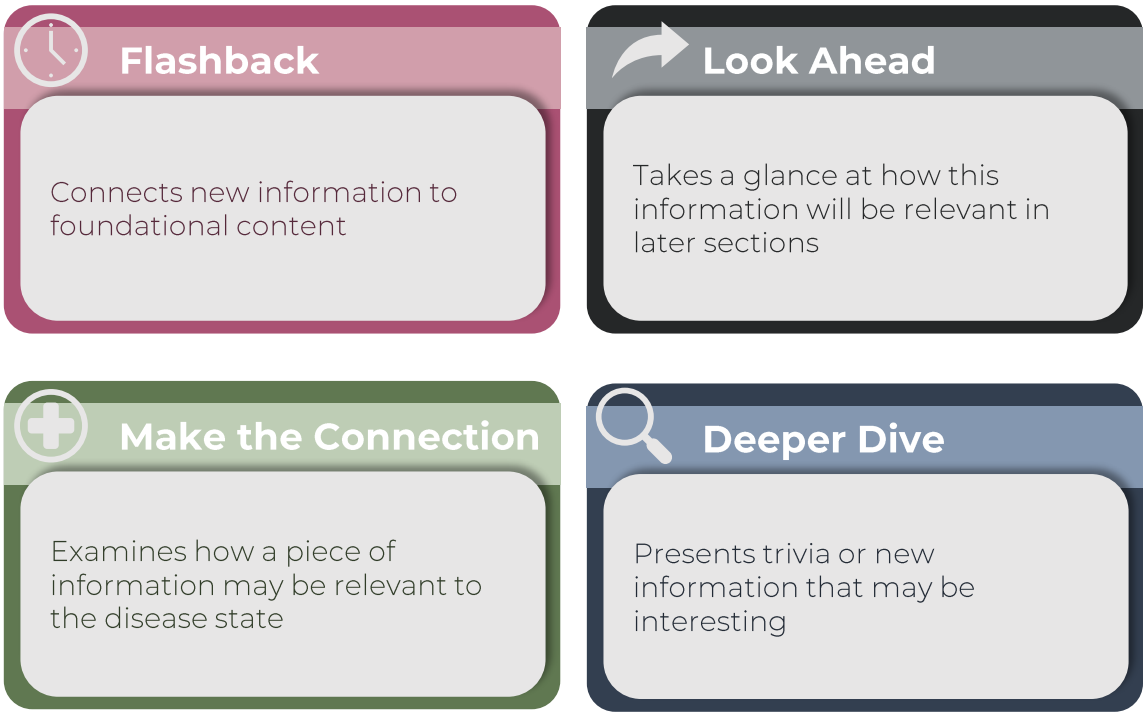
Lesson 3: Diagnosis & Management summarizes the tools and techniques used to screen and diagnose patients with nOH and describes the nonpharmacologic and pharmacologic strategies that may be used to manage these patients

By the end of this module, participants will be better equipped to:

- Describe nOH
- Explain the pathogenesis of nOH
- Summarize the diagnosis and management of nOH

Module Features

Throughout this module, **callout boxes** will help you draw connections from the material. These include:



At the end of each lesson, **Key Concepts** list the main takeaway information. The **Knowledge Check** will test your grasp of this content.

Glossary terms listed throughout the module are linked to their definition in the **Glossary**. Select the term to move between the glossary definition and the term's in-text appearance.

Select the button anytime to return to the table of contents.

Lesson 1: Overview

Orthostatic hypotension (OH) is formally defined by expert consensus as a sustained reduction of ≥20 mmHg in **systolic** blood pressure or 10 mmHg in **diastolic** blood pressure (or both) within 3 minutes of standing or upright tilt.[6,7] In practice, this means that the brain does not receive enough oxygen and the resulting symptoms leave patients struggling to remain standing.[5,7]

This lesson introduces a foundational understanding of nOH, including its clinical presentation, types, and epidemiology.

Learning Objectives

By the end of this lesson, participants should be able to:

- Define nOH
- List the signs and symptoms of nOH
- Classify nOH variants
- Recognize the natural history and prognosis of nOH
- State the prevalence of nOH in relevant populations

Clinical Presentation of nOH

Signs and Symptoms

When patients with nOH stand up, they may experience symptoms such as lightheadedness, blacking out, or falling with or without fainting (**Table 1**).[3,6] These symptoms are associated with standing and they are relieved when the patient lies down.[8]

Table 1. Symptoms of nOH[3,8]

Lightheadedness (also reported as dizziness, vertigo, or wooziness)
Fainting or almost fainting
Fatigue
Weakness
Cognitive impairment
Shortness of breath
Blurring of vision
Chest pain
Coat-hanger headache

nOH, neurogenic orthostatic hypotension.

Look Ahead

Symptoms of nOH tend to be worse during the early morning hours and after large meals.[8] These aggravating factors are discussed in more detail in **Lesson 3: Diagnosis & Management**

Patients may also report shortness of breath, visual blurring, chest pain, or neck pain (termed a "coat-hanger headache"), which are related to inadequate oxygen **perfusion** of these tissues. Other nonspecific symptoms include fatigue, weakness, mental dulling, confusion, or difficulty concentrating.[6,8] Depending on the cause of the disease, patients with nOH may have other symptoms of autonomic failure such as:[8-11]

- Digestive problems
- Urinary problems
- Sweating abnormalities
- Sexual dysfunction
- Dysfunctions of the pupil's reaction to light

Classification

There are 3 clinical variants of OH, which differ, called classical OH, delayed OH and initial OH.[8] These are summarized in **Figure 1**.

Figure 1. Classification of OH[8]

Classical OH	Delayed OH	Initial OH
• **Sustained** drop in blood pressure • ***Within 3 minutes*** of standing up	• **Sustained** drop in blood pressure • ***After 3 minutes*** of standing up • Mild and/or early manifestation of the disease • May progress to classical OH	• **Transient** drop in blood pressure • ***Within 15 seconds*** of standing up • Occurs more often in younger patients • Not associated with a disease state

OH, orthostatic hypotension.

Natural History and Prognosis

Unlike non-neurogenic OH, which resolves when the underlying cause is remedied, nOH is a chronic disorder.[11] It tends to have a worse prognosis than non-neurogenic OH and is associated with higher morbidity and mortality. The **natural history** of nOH depends on its underlying cause. For example, patients with neurodegenerative disease usually get progressively worse over time. Patients with **pure autonomic failure** tend to progress more slowly whereas patients with **multiple system atrophy** progress more quickly. For patients with **diabetes**, the rate of progression may be faster or slower depending on how well the disease is controlled.[8]

Epidemiology of nOH

Prevalence

The prevalence of OH varies depending on the age, comorbidities, and medications of the population studied.[8] OH affects approximately 5% of middle-aged adults and the prevalence tends to increase with increasing age, affecting up to 20% of adults older than 60 years.[12,13] In part, this trend is due to the normal age-related decline of autonomic functions and use of antihypertensive medication. It is also related to the increasing prevalence of autonomic neurodegenerative diseases with increasing age.[8,11]

The prevalence of OH is also higher in certain at-risk populations. For example, 25% to 35% of people with diabetes are affected by OH.[8] The prevalence is as high as 50% in patients with **Parkinson disease** and 70% in those with multiple system atrophy.[11] Populations at risk for nOH include:[6,8]

- Patients with neurodegenerative disorders (eg, Parkinson disease, multiple system atrophy, etc)
- Patients with peripheral neuropathies (eg, diabetes, **amyloidosis**, etc)
- Elderly patients (≥70 years of age)
- Hospitalized patients

At-risk patients should be routinely screened for symptoms of OH.[6] Screening is discussed further in **Lesson 3: Diagnosis & Management**.

Comorbidities and Mortality

Regardless of the cause, OH is associated with a higher risk of mortality. One meta-analysis reported a 1.5-fold increase in mortality risk over a 5-year period in patients with OH. Another study reported a 10-year mortality of 64% in individuals with OH compared to 9% of the control population. In patients with neurodegenerative disease such as Parkinson disease, the risk of mortality is more than 2 times higher in patients with OH compared to patients without OH.[8] The higher risk of mortality may be related to the effects of **supine hypertension**, which affects about half of individuals with nOH.[8,11]

Supine hypertension refers to blood pressure that is high when laying down.[3] Over time, it may impair kidney function and cause cardiovascular dysfunction, which increases the risk of cardiovascular events.[8] OH also increases the risk of falls, especially for older patients. Thus, patients with OH have a higher risk of head injuries and fractures, which can reduce quality of life and lifespan.[14] Given these risks, appropriate management is vital for patients with OH. Treatment and management of nOH is discussed further in **Lesson 3: Diagnosis & Management**.

Key Concepts

- Orthostatic hypotension (OH) is formally defined by expert consensus as a sustained reduction of ≥20 mmHg in systolic blood pressure or 10 mmHg in diastolic blood pressure (or both) within 3 minutes of standing or upright tilt[6,7]
- Symptoms of nOH include lightheadedness, fainting, fatigue, weakness, cognitive impairment, shortness of breath, blurring of vision, chest pain, and coat-hanger headache[3,8]
- These symptoms are associated with standing and they are relieved when the patient lies down
- The 3 clinical variants of OH are classical OH, delayed OH, and initial OH[8]
- nOH is a chronic disorder that has a worse prognosis than non-neurogenic OH and is associated with higher morbidity and mortality[11]
- The prevalence of OH varies depending on the age, comorbidities, and medications of the population studied[8]
- OH affects approximately 5% of middle-aged adults and the prevalence tends to increase with increasing age, affecting up to 20% of adults older than 60 years[12,13]
- Regardless of the cause, OH is associated with a higher risk of mortality, which may be related to the effects of supine hypertension and falls[8,11,14]

Knowledge Check

1. The formal definition of OH is defined as a sustained reduction of ___ in systolic blood pressure and/or ___ in diastolic blood pressure within 3 minutes of standing.

   A. ≥20 mmHg; 10 mmHg
   B. >15 mmHg; 5 mmHg
   C. ≥10 mmHg; 2 mmHg
   D. >5 mmHg; 1 mmHg

2. List 3 signs and symptoms of nOH.

   _____

   _____

   _____

3. Match the nOH variant to its definition.

   A. Classical
   B. Delayed
   C. Initial

   ____ Sustained drop in blood pressure after 3 minutes of standing

   ____ Transient drop in blood pressure within 15 seconds of standing

   ____ Sustained drop in blood pressure within 3 minutes of standing

Check Answers

Knowledge Check Continued

4. Patients with multiple system atrophy tend to:
   A. Have stable, non-progressive disease
   B. Progress slowly
   C. Progress quickly
   D. Spontaneously improve

5. What proportion of adults over age 60 are affected by OH?
   A. 5%
   B. 20%
   C. 50%
   D. 80%

Check Answers

Lesson 2: Pathogenesis

In this lesson, we will highlight the normal physiology of the sympathetic nervous system, which you learned in **Module 1**, and connect these concepts to the pathogenesis of nOH.

Learning Objectives

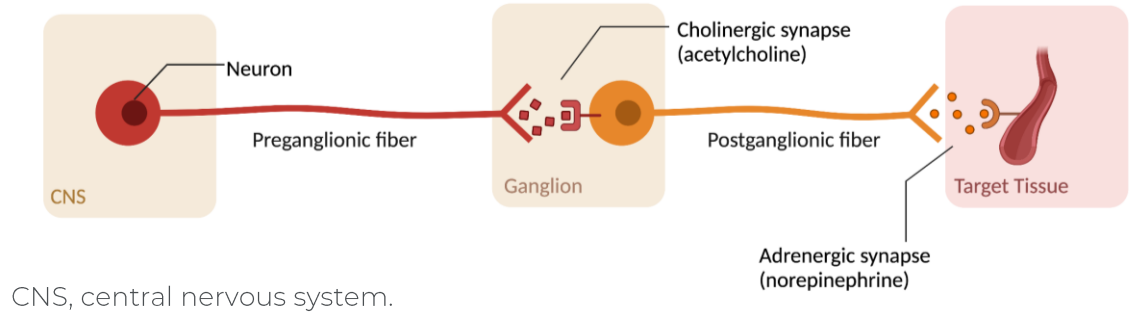
By the end of this lesson, participants should be able to:

- Summarize the pathogenesis of nOH
- Identify the mechanisms of autonomic failure
- Recognize the primary and secondary etiologies of nOH

Normal Baroreflex

In Module 1, you learned that a signal from the sympathetic nervous system travels from the CNS to the sympathetic **ganglion** and then on to the target tissue (**Figure 2**). The preganglionic fiber carries the signal to the ganglion. This junction is classified as a cholinergic synapse because it releases acetylcholine as a signaling chemical. The postganglionic fiber carries the signal to the target tissue and this synapse is classified as adrenergic because it releases norepinephrine.[1] These signaling systems help to maintain balance within the body. For example, sympathetic signaling helps to compensate for the effects of gravity during changes in posture.

Figure 2. Sympathetic nervous system



CNS, central nervous system.

Adapted from "Organization of the Sympathetic and Parasympathetic Nervous System", by BioRender.com (2022). Retrieved from https://app.biorender.com/biorender-templates

When an individual stands up, gravity causes blood to pool in the lower body and baroreceptors in the blood vessels sense the drop in blood pressure.[8] This triggers a sympathetic reflex, called the baroreflex, that increases sympathetic signaling.

Look Ahead

Some pharmacologic treatment strategies for nOH target the adrenergic and cholinergic signaling systems.[8] You will learn more about these treatments in **Lesson 3: Diagnosis & Management**.

The released norepinephrine activates adrenergic receptors in the walls of the blood vessels and heart tissue to induce vasoconstriction, increase the heart rate, and thus elevate the blood pressure. The baroreflex maintains the heart's output of blood during the gravitational challenge to ensure that cognitive and neural processes are not disrupted by decreased oxygen delivery.[1,2,8] When the function of the sympathetic nervous system is compromised and disrupts the baroreflex, this is called autonomic failure or dysautonomia.[1,15,16]

Autonomic Failure

Autonomic failure in nOH is associated with insufficient release of norepinephrine from the sympathetic nerves.[16] It is related to dysfunction or damage within the central (eg, brain or spinal cord) or peripheral components of the neural pathway of the baroreflex.[3,8]

Autonomic failure may be **primary**, as with genetic conditions or neurodegenerative diseases such as Parkinson disease.[16,17] It may also be **secondary** to damage caused by autoimmune disease, systemic disease, viral infection, or toxins.[16-19] These common **etiologies** are summarized in **Table 2**.

Deeper Dive

A clinical variant of nOH called hyperadrenergic OH (hyperOH) has been described in a subset of patients. These patients have paradoxically high norepinephrine levels instead of low norepinephrine. The pathogenesis of this disease is not well understood. The mechanism may involve impaired sensitivity to norepinephrine.[20]

Table 2. Etiologies of autonomic failure associated with nOH

	Etiology	Examples
Primary	Neurodegenerative disease[8,16]	• Parkinson disease • Multiple system atrophy • Pure autonomic failure • Dementia with Lewy bodies
	Genetic[5,16,21,22]	• Familial dysautonomia • Dopamine beta-hydroxylase deficiency
Secondary	Autoimmune[9,16]	• Autoimmune autonomic ganglionopathy • Guillain-Barré syndrome
	Systemic disease[5,9,19]	• Diabetic autonomic **neuropathy** • Amyloidosis
	Viral infection[18,23]	• COVID-19
	Toxins[19]	• Alcoholic neuropathy • Chemotherapy

COVID-19, coronavirus disease of 2019.

Primary Etiologies

Primary nOH occurs due to diseases that are intrinsic to the nervous system.[3] Primary causes of nOH include neurodegenerative diseases and genetic diseases.[16,17] These conditions are summarized next.

Neurodegenerative Diseases

Several neurodegenerative diseases present with nOH as a significant feature. They include:[8]

- Parkinson disease
- Multi-system atrophy
- Pure autonomic failure
- Dementia with Lewy bodies

These diseases have a common pathology, which is characterized by abnormal accumulation of a misfolded protein called **alpha-synuclein** within the cells of the nervous system.[8,24] Thus, they are collectively referred to as alpha-synucleinopathies.[25] These deposits are toxic and autonomic failure results as alpha-synuclein causes dysfunction throughout the cell and ultimately leads to cell death and neurodegeneration.[26-28]

The clinical presentation of each disease differs based on the pattern of protein accumulation and also by which neuronal fibers of the central or peripheral nervous systems are affected.[8,15,27] Patients with these diseases may have other symptoms of autonomic failure such as:[8-10]

- Digestive problems
- Urinary problems
- Sweating abnormalities
- Sexual dysfunction
- Dysfunctions of the pupil's reaction to light

Genetic Diseases

Many genetic diseases cause autonomic failure such as nOH.[10] Familial dysautonomia is a genetic disease that impairs development of the nervous system and causes dysfunction of the sensory and autonomic nerves. Patients with this condition have widespread autonomic failure including dysfunction of the cardiovascular, respiratory, and gastrointestinal systems. They also present with decreased sensitivity to pain and temperature.[29]

Dopamine beta-hydroxylase deficiency is another genetic disease that presents with nOH. This condition is marked by a mutation of the key enzyme in norepinephrine production.[1,22] Thus, these patients have no circulating norepinephrine or epinephrine. Without norepinephrine to stimulate the baroreflex, they present with severe nOH as well as a range of other signs of autonomic failure.[22]

Secondary Etiologies

Besides neurologic disease, nOH may also occur as a complication due to diseases or agents outside the nervous system.[3] These secondary causes include autoimmune disease, systemic diseases, viral infections, and damage due to toxic substances.[16,17] These causes of nOH are discussed in more detail next.

Autoimmune Disease

Autoimmune disease occurs when the immune system reacts against normal cells and attacks and destroys the body's normal tissue.[3]

Some autoimmune diseases destroy the fibers of the ANS, which disrupts the baroreflex and leads to nOH. For example, patients with autoimmune autonomic ganglionopathy (AAG) have antibodies against the receptors of the preganglionic synapse.[1,9] These individuals present with a clinical triad of nOH, sweating abnormalities, and digestive problems.[3,9]

Another example is Guillain-Barré syndrome, which is an autoimmune disease that primarily targets the somatic system responsible for movement and thus causes an ascending paralysis. However, it also targets autonomic fibers, leading to cardiovascular and gastrointestinal dysfunction in up to two-thirds of patients.[1,3,9]

Systemic Disease

Systemic diseases affect the body as a whole rather than a specific location or organ system.[3] Some systemic diseases damage the nerve fibers of the ANS and cause autonomic neuropathy. Diabetes is the most common cause of autonomic neuropathy.[19] This disease, resulting from dysfunction of **insulin** production, secretion, or sensitivity, leads to chronically high levels of glucose in the blood.[1] The excess sugar damages neurons directly and may also indirectly affect cell function.[1,30] Patients with diabetic autonomic neuropathy present with pandysautonomia including nOH.[9,15,19]

Amyloidosis is another systemic disease that results in autonomic neuropathy. It is characterized by the abnormal buildup of protein throughout the tissues of the body, which produce severe, progressive symptoms of pandysautonomia.[9]

Viral Disease

Certain viral infections such as COVID-19 have been associated with dysautonomia, including nOH.[18,23] The mechanism of this association is not clear but it is thought that between 2.15 to 6.45 million people globally are affected by COVID-19-associated dysautonomia.[18,31]

Toxins

Some toxins damage nerve fibers. Alcoholic neuropathy is a complication of chronic excessive alcohol consumption. Alcohol may directly damage nerves and may also cause neuropathy through alcohol-related vitamin deficiencies.[19]

Chemotherapy-induced peripheral neuropathy (CIPN) is a side effect of chemotherapy-based cancer treatments. It affects 19% to over 85% of cancer patients depending on the agent used. It predominantly causes sensory symptoms such as numbness or tingling but may also lead to autonomic symptoms such as nOH.[32]

Key Concepts

- The baroreflex responds to changes in blood pressure by increasing sympathetic norepinephrine signaling to induce vasoconstriction, increase the heart rate, and thus elevate the blood pressure
    - These changes maintain the heart's output of blood and oxygen delivery when standing[1,2,8]
- Autonomic failure or dysautonomia results when the baroreflex is compromised due to dysfunction or damage within the central or peripheral neural components of the baroreflex
    - This causes the sympathetic nerves to release insufficient amounts of norepinephrine[8,16]
- Primary causes of nOH include neurodegenerative diseases and genetic diseases[16,17]
    - Neurodegenerative diseases that present with nOH as a significant feature are collectively called the alpha-synucleinopathies and include Parkinson disease, multisystem atrophy, pure autonomic failure, and dementia with Lewy bodies[8,25]
    - Genetic diseases such as familial dysautonomia or beta-hydroxylase deficiency disrupt the development and/or function of the ANS, leading to nOH[1,22,29]

Key Concepts Continued

- Secondary causes of nOH include damage caused by autoimmune disease, systemic disease, viral infection, or toxins[16-19]
    - Some autoimmune diseases such as AAG or Guillain-Barré syndrome destroy the fibers of the ANS, which disrupts the baroreflex and leads to nOH[9]
    - Diabetes, a systemic disease in which excess sugar damages neurons and disrupts cell function, is the most common cause of autonomic neuropathy[1,19,30]
    - Amyloidosis is a systemic disease in which abnormal protein buildup disrupts the function of neurons[9]
    - Viral infections such as COVID-19 are associated with dysautonomia although the causal mechanism is still unclear[18]
    - Toxins such as alcohol or chemotherapy damage nerves and may lead to nOH[19,32]

Knowledge Check

6. Select 3 correct answers. Sympathetic norepinephrine signaling:
   A. Increases heart rate
   B. Increases blood cell count
   C. Stimulates coagulation
   D. Induces vasoconstriction
   E. Elevates blood pressure

7. The baroreflex responds to changes in:
   A. Heart rate
   B. Blood volume
   C. Blood cell count
   D. Blood pressure

8. Mark each etiology as primary or secondary.

   A. Primary
   B. Secondary

   ____ Viral infection
   ____ Systemic disease
   ____ Neurodegenerative disease
   ____ Toxins
   ____ Autoimmune disease
   ____ Genetic disease

Check Answers

Knowledge Check Continued

9. The most common cause of autonomic neuropathy is:
   A. Beta-hydroxylase deficiency
   B. Autoimmune autonomic ganglionopathy
   C. Diabetes
   D. COVID-19

10. Select 4 correct answers. The alpha-synucleinopathies include:
   A. Pure autonomic failure
   B. Guillain Barré syndrome
   C. Multisystem atrophy
   D. Parkinson disease
   E. Dementia with Lewy bodies

11. When the baroreflex is disrupted, the sympathetic nerves release insufficient amounts of _____.

Check Answers

Lesson 3: Diagnosis & Management

nOH causes disabling symptoms that reduce quality of life and impair normal daily activities and cognitive functioning.[11,13] It is also associated with significant morbidity including falls, fainting, coronary artery disease, stroke, and heart failure.[2] Thus, timely diagnosis and management are vital to improve the patient's quality of life and reduce health care costs.

In this lesson, we discuss the tools and methods used to screen and diagnose patients with nOH as well as nonpharmacologic and pharmacologic management strategies.

Learning Objectives

By the end of this lesson, participants should be able to:

- Recognize the practices used to screen patients for nOH
- Describe the techniques and methods used to diagnose nOH
- List triggers and medications that aggravate nOH
- Summarize nonpharmacologic strategies for management of nOH
- Identify pharmacologic treatment options for nOH

Screening

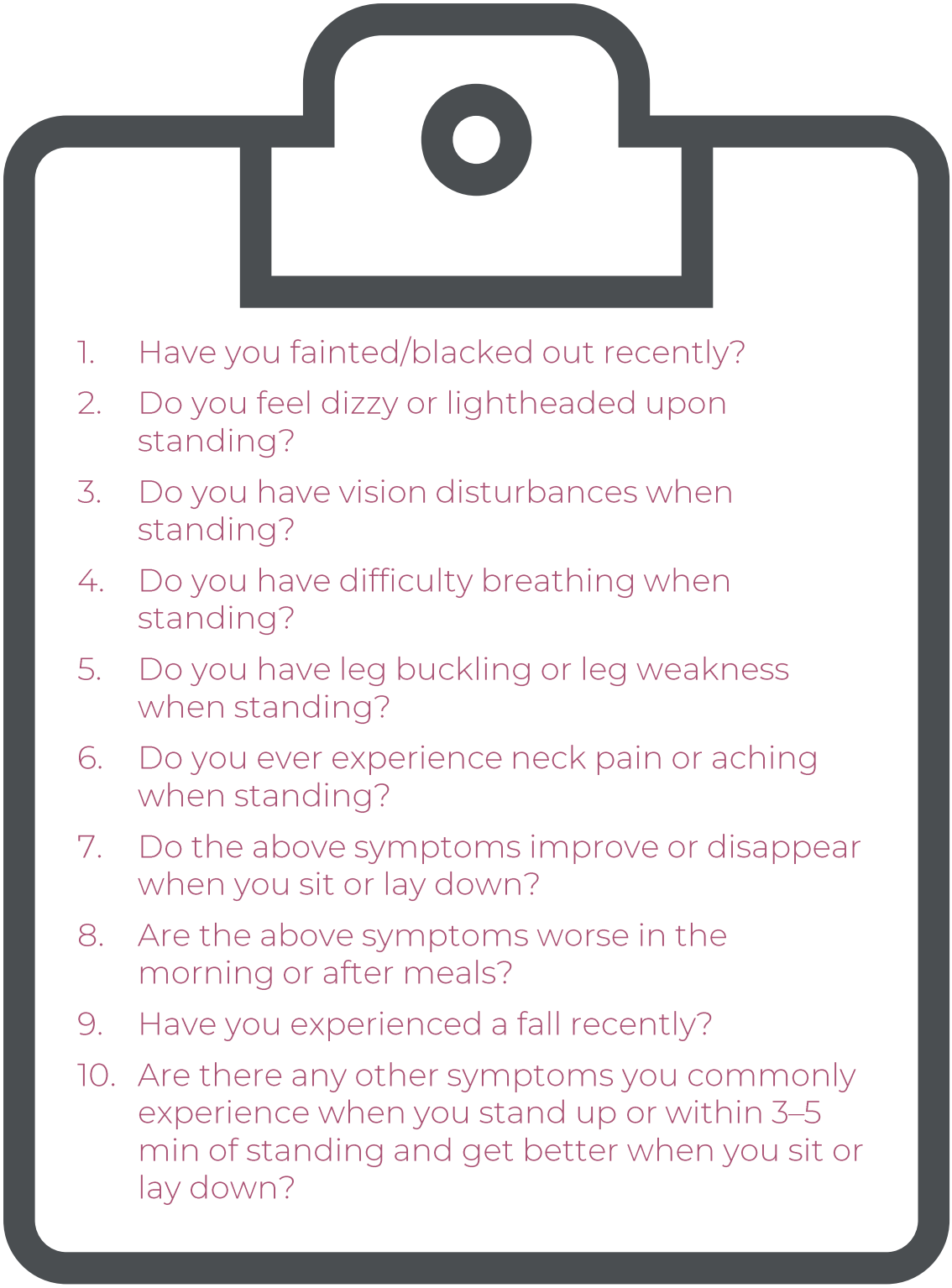
Certain categories of patients are at higher risk of nOH compared to the general population. These include patients:[6]

- with suspected or diagnosed neurodegenerative disorders associated with dysautonomia
- who have reported fainting or an unexplained fall
- with peripheral neuropathies that are associated with autonomic dysfunction
- who are elderly, frail, or on multiple medications
- who report dizziness or nonspecific symptoms that occur only when standing

Patients in these categories should be routinely screened for nOH. The American Autonomic Society and National Parkinson Foundation jointly recommend screening at-risk patients by asking questions to identify symptoms of OH. Clinicians should ask about the **cardinal** symptoms of OH including the frequency and severity of these symptoms and whether they impact daily activities as shown in **Figure 3**.[6]

If a patient reports a positive response to 1 or more screening questions, a complete evaluation should be done to confirm a diagnosis of nOH.[6]

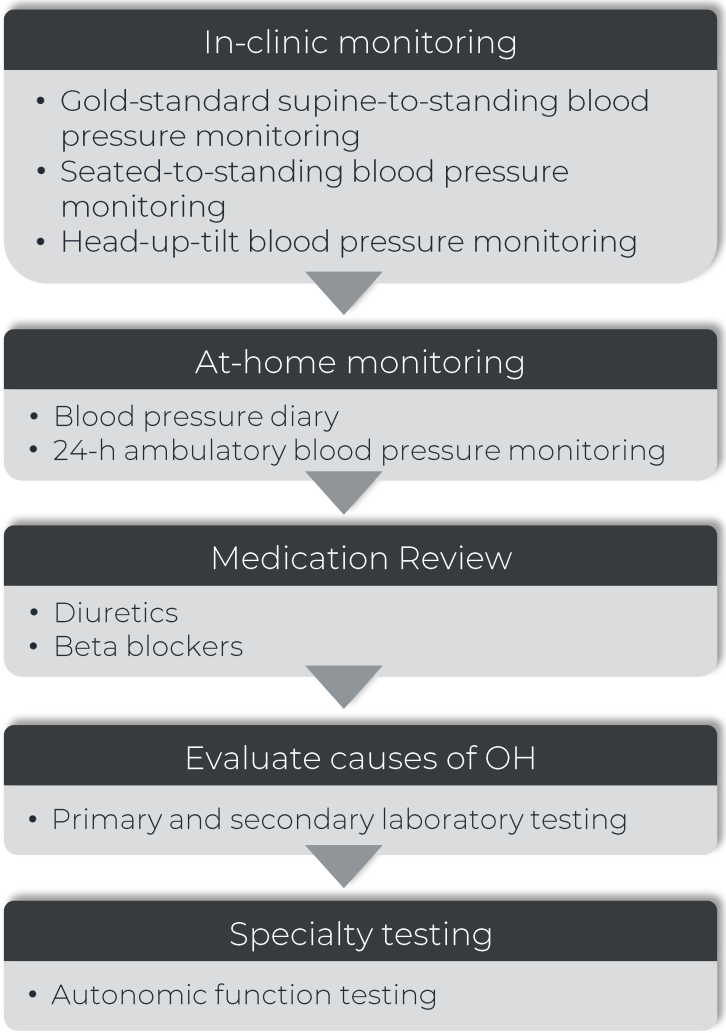
Figure 3. Screening questions for suspected nOH[6]



Diagnosis

If screening reveals that a patient is at risk for nOH, a full diagnostic evaluation is performed to confirm a diagnosis of nOH, find the underlying cause, and determine the appropriate management strategy. The American Autonomic Society and National Parkinson Foundation jointly recommend a stepwise approach to diagnose nOH as shown in **Figure 4**.[6]

Figure 4. American Autonomic Society and National Parkinson Foundation stepwise approach to nOH diagnosis[6]



OH, orthostatic hypotension.

In-Clinic Monitoring

Diagnosis begins with in-clinic monitoring of the patient's blood pressure and heart rate. The gold standard is to measure **supine**-to-standing blood pressure. During this process, the patient's blood pressure is checked after being supine (eg, lying down) for 5 minutes then have them stand up for 3 minutes while checking their blood pressure at 1 minute and 3 minutes. Seated-to-standing or **head-up tilt** blood pressure may be used as an alternative if needed. The patient is diagnosed with OH if the test is positive (ie, the patient's blood pressure drops more than 20/10 mmHg when standing or with head-up tilt.)[6]

For patients with suspected initial OH, the time for blood pressure drop and recovery is quick. Therefore, continuous blood pressure and heart rate measurements should be used with a 10-minute supine baseline measurement.[19]

At-Home Monitoring

Symptoms of OH vary throughout the day, which may lead to inconclusive results for in-clinic testing.[19] Patients with a negative result for in-clinic testing but who have symptoms strongly suggestive of OH may be instructed to keep a diary of blood pressure measurements.[6,19]

Make the Connection

A diary may also be used after any changes to therapy to determine whether the change was effective.[6]

The diary includes 7 days of measurements upon waking up in the morning (before taking medication), when symptomatic, and at bedtime.[6] In some cases, 24-h **ambulatory** blood pressure monitoring with a portable blood pressure monitor may be useful.[3,6]

Medication Review

Certain drugs can disrupt the baroreflex and cause OH.[6] When evaluating a patient with suspected OH, their prescription drugs should be reviewed to identify any offending medications.[19]

Evaluate Causes of OH

After a patient is diagnosed with OH, it is important to differentiate neurogenic from non-neurogenic causes because nOH is associated with greater morbidity and mortality.[6] Laboratory tests may be ordered to identify causes of hypotension or neuropathy.[19] These tests are summarized in **Table 3**.

Specialty Testing

In some cases, patients may need to be referred to a specialized tertiary center for autonomic function testing.[6,19] These tests, such as the **Valsalva maneuver**, may help to discriminate between certain causes of nOH.[6]

Table 3. Laboratory tests used in OH diagnosis[3,6,15,19]

Laboratory Test	Purpose
Primary Tests	
Electrocardiogram	Evaluate electrical activity of the heart
Complete blood count	Identify anemia or infection that may contribute to non-neurogenic OH
Basic metabolic panel (Includes sodium, potassium, chloride, **bicarbonate**, **blood urea nitrogen**, **creatinine**, and fasting glucose)	Identify disorders such as: • Electrolyte disorders • Acid-base disorders • Blood volume depletion • Kidney failure • Diabetes
Thyroid-stimulating hormone, **cortisol**	Identify thyroid or adrenal dysfunction
Vitamin B_{12} level, **methylmalonic acid**	Identify vitamin B_{12} deficiency
Secondary Tests for Select Patients	
Albumin	Identify malnutrition or chronic illness
Liver enzyme testing, albumin	Identify liver dysfunction in patients with weight loss, suspected alcoholism, or symptoms of systemic disease
Neurological antibody studies	Identify autoimmune diseases
Serum electrophoresis	Identify protein aggregation
Anti-virus antibody studies	Identify recent infections associated with nOH
Fractionated **catecholamine** testing	Identify low norepinephrine levels associated with certain neurodegenerative diseases

nOH, neurogenic orthostatic hypotension; OH, orthostatic hypotension.

Grading of nOH

After a patient is diagnosed with nOH, it is important to establish the severity. The grading scale is used to help decide when a patient should be referred to a specialist.[6] The grading scale, shown in **Figure 5**, is based on the magnitude of the blood pressure drop, the amount of time the patient tolerates standing, and the magnitude of symptoms and their impact on daily activities.[6,15] Clinicians should consider referral to a specialist for patients with grade 3 or 4 nOH.[6]

Figure 5. American Autonomic Society–National Parkinson Foundation Grading Scale for nOH[6]

Grade 1	• Infrequent symptoms • Unrestricted standing tolerance • 20-30 mmHg drop in systolic blood pressure during supine-to-standing test
Grade 2	• Moderate impact on daily activities • ≥5 minutes standing tolerance (but not unrestricted) • >30 mmHg drop in systolic blood pressure
Grade 3	• Severe impact on daily activities • <5 minutes standing tolerance • >30 mmHg drop in systolic blood pressure
Grade 4	• Incapacitated • <1 minute standing tolerance • >30 mmHg drop in systolic blood pressure

Differential Diagnosis

Several disorders may mimic the symptoms of nOH and should be ruled out during diagnosis. These include:[19]

- Vasovagal syncope
- Postural orthostatic tachycardia syndrome (POTS)
- Afferent baroreflex failure

These disorders are briefly described in **Table 4**.

Table 4. Differential diagnosis of nOH[3,19]

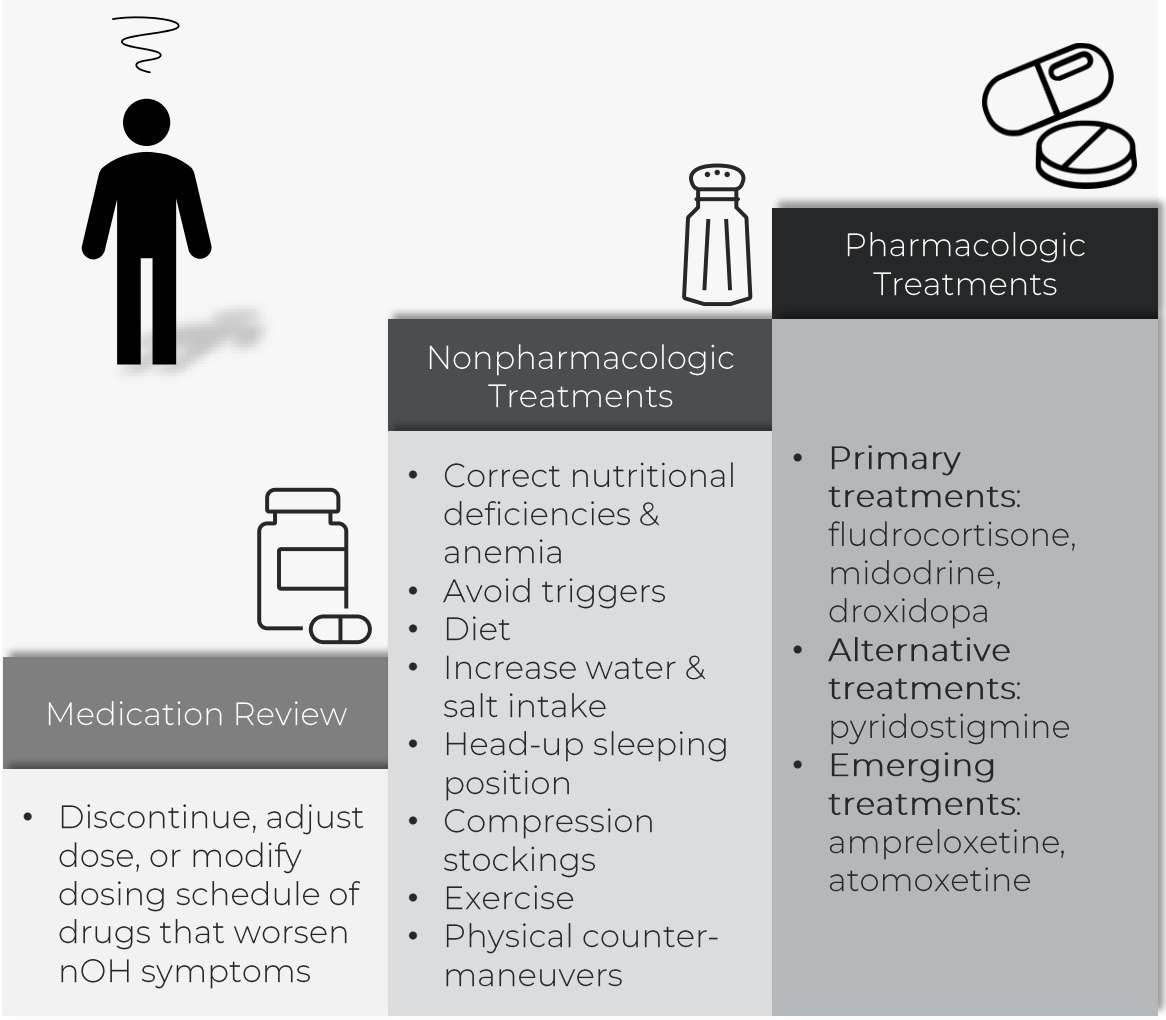
Disorder	Description
Vasovagal syncope	• Common fainting spell after a stressful event that is characterized by wooziness, nausea, and weakness prior to a brief loss of consciousness
POTS	• Autonomic disorder characterized by chronic symptoms of orthostatic intolerance similar to nOH • Heart rate increases abnormally upon standing without a drop in blood pressure
Afferent baroreflex failure	• Dysfunction of the baroreflex due to injury of the neural components that causes unrestrained sympathetic stimulation • Most commonly results from injury during surgical removal of neck tumors • Characterized by volatile blood pressure changes that occur in response to a range of stimuli and are not associated with postural changes

nOH, neurogenic orthostatic hypotension; POTS, postural orthostatic tachycardia syndrome.

Management

The goal of treatment is not to normalize the standing blood pressure. Rather, the goal of treatment is to reduce the patient's symptom burden and improve their quality of life.[33] The key components of management are shown in **Figure 6**. Each of these components are discussed in more detail next.

Figure 6. Treatment algorithm for nOH management[6,8,33]



nOH, neurogenic orthostatic hypotension.

Medication Review

Certain drugs that reduce blood volume, dilate blood vessels, or block norepinephrine activity may make nOH symptoms worse by lowering blood pressure.[1,2] These include agents such as **diuretics** and **beta blockers**. Modifying the patient's medication regimen by discontinuing the drug, adjusting the dose, or changing the dosing schedule may mitigate or even resolve nOH symptoms in some patients.[6]

Nonpharmacologic Management

Nonpharmacologic management is crucial to improve symptom burden and quality of life for patients with nOH.[33] These simple measures are incorporated into the patient's daily routine and may be used independently or with pharmacologic agents to address the patient's symptoms.[6]

Correct Nutritional Deficiencies

Anemia may exacerbate OH symptoms by reducing the blood's capacity to carry oxygen.[2] Vitamin B_{12} deficiency is also associated with OH. These conditions should be corrected with vitamin and iron supplementation as needed.[6]

Avoid Triggers

Elevated core body temperature causes blood vessels to dilate throughout the body, which lowers blood pressure and worsens nOH symptoms.[1,6,33]

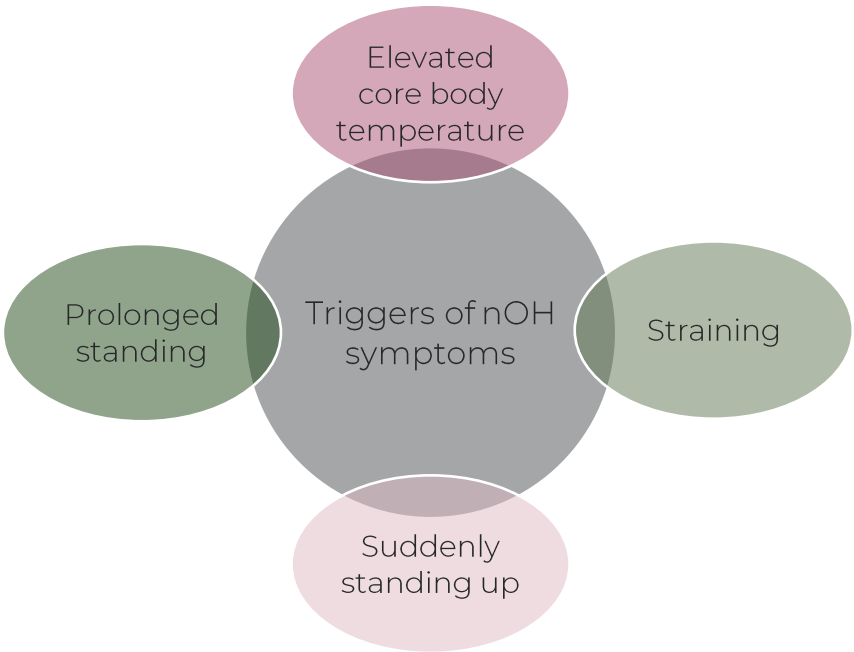
Patients should avoid triggers that may increase their core body temperature including:[6]

- hot and humid environments
- hot baths or showers
- high-intensity exercise
- hot tubs, saunas, or spas

Furthermore, patients with nOH may have other signs of autonomic failure such as impaired regulation of body temperature. In addition to worsening symptoms of nOH, these patients may be at risk for hyperthermia.[6]

Other triggers may also exacerbate nOH (**Figure 7**). Straining, especially while holding breath (such as during a bowel movement), suddenly standing up, or standing for extended periods of time can cause symptoms.[2,8]

Figure 7. Triggers of nOH symptoms[2,6,8]



nOH, neurogenic orthostatic hypotension.

Diet

For patients with nOH who have deficient sympathetic stimulation of blood vessel constriction, eating causes blood to pool within the abdominal organs, leading some patients to have severe drops in blood pressure within 2 hours of eating. This is called **post-prandial hypotension**. The effect is worse after meals that are rich in carbohydrates or sugar, which stimulate the release of hormones with vasodilatory properties.[2,3,34] Small frequent meals and a low-glycemic diet may help nOH symptoms.[6] Patients should also be aware of the diuretic effects of caffeine, alcohol, and tea, which can lower blood pressure.[1,2]

Increase Water and Salt Intake

Reductions in blood volume may cause and/or worsen symptoms of nOH.[2] Thus, maintaining and expanding blood volume is an important step for managing nOH symptoms.[6] This may be done through ingesting more fluids and salt. For long-term management, recommendations include 2-2.5 L of fluid per day and 2-3 g of salt, which may be obtained by adding salt to food or ingesting salt tablets.[2,8] For patients with severe nOH, salt intake may even be increased to 10 g per day.

However, these measures should be used with caution for patients who also have cardiovascular disease.[8] The long-term risks of a high-salt diet for patients with nOH have not been well studied.[6]

As a rescue measure, patients can quickly drink 500 mL (16 oz) of water over 3-4 minutes to create a **pressor** effect.[6,8] The water stimulates a reflex through the blood circulation of the liver, which raises blood pressure within 5 minutes. This may help to quickly improve symptoms and the effects may last for up to an hour.[3,6]

Head-Up Sleeping Position

Raising the head of the bed 6 to 9 inches can help to reduce symptoms in the morning upon waking in certain patients.[6] Some patients with nOH also present with supine hypertension. Elevated blood pressure while lying in bed creates pressure in the renal system that increases the production of urine and thus reduces blood volume.[3,6] Elevating the head of the bed mitigates this phenomenon and thus improves the morning drop in blood pressure.[6]

Compression Garments

Compression garments such as stockings or compression bandages may help to reduce the amount of blood pooling in the lower body, which improves the drop in blood pressure upon standing and therefore improves symptoms.[8] Compression of 30-40 mmHg is needed to have a measurable improvement on blood pressure.[6]

Compression garments that extend to the waist are the most effective because most blood pooling happens around the abdominal organs.[3,8] Thigh-high stockings may also be used, however evidence suggests that knee-high stockings are not effective. Patient compliance is low for compression garments, unfortunately, because they are difficult to put on and may be uncomfortable to wear.[6]

Exercise

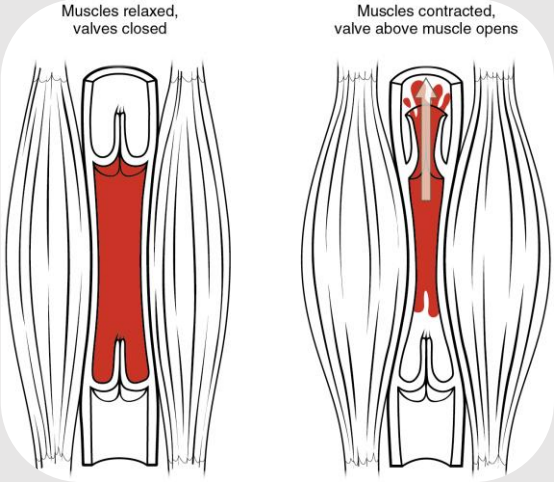
Because patients with nOH may experience intolerable symptoms when they stand, they may avoid movement and physical activity.[11,33] However, bed rest causes physical deconditioning that:[3,5,6,35]

- reduces and redistributes blood volume
- causes atrophy of the cardiac and skeletal muscles
- changes the activity of the body's **baroreflex**, which responds to changes in blood pressure
- reduces the body's **vasoconstriction** response to pressor drugs, which are prescribed to increase blood pressure
- reduces the function of the skeletal muscle pump in the legs
- reduces bone density

Make the Connection

The skeletal muscle pump refers to a mechanism by which the muscles in the legs contract to increase the blood pressure within the veins of that region as shown in **Figure 8**. The contraction puts pressure on the veins. This effect increases the blood pressure and pushes the blood back to the heart through one-way valves. Without a functional skeletal muscle pump, blood begins to pool in the legs instead of returning to the heart and the brain does not receive enough oxygen.

Figure 8. Skeletal muscle pump[1]



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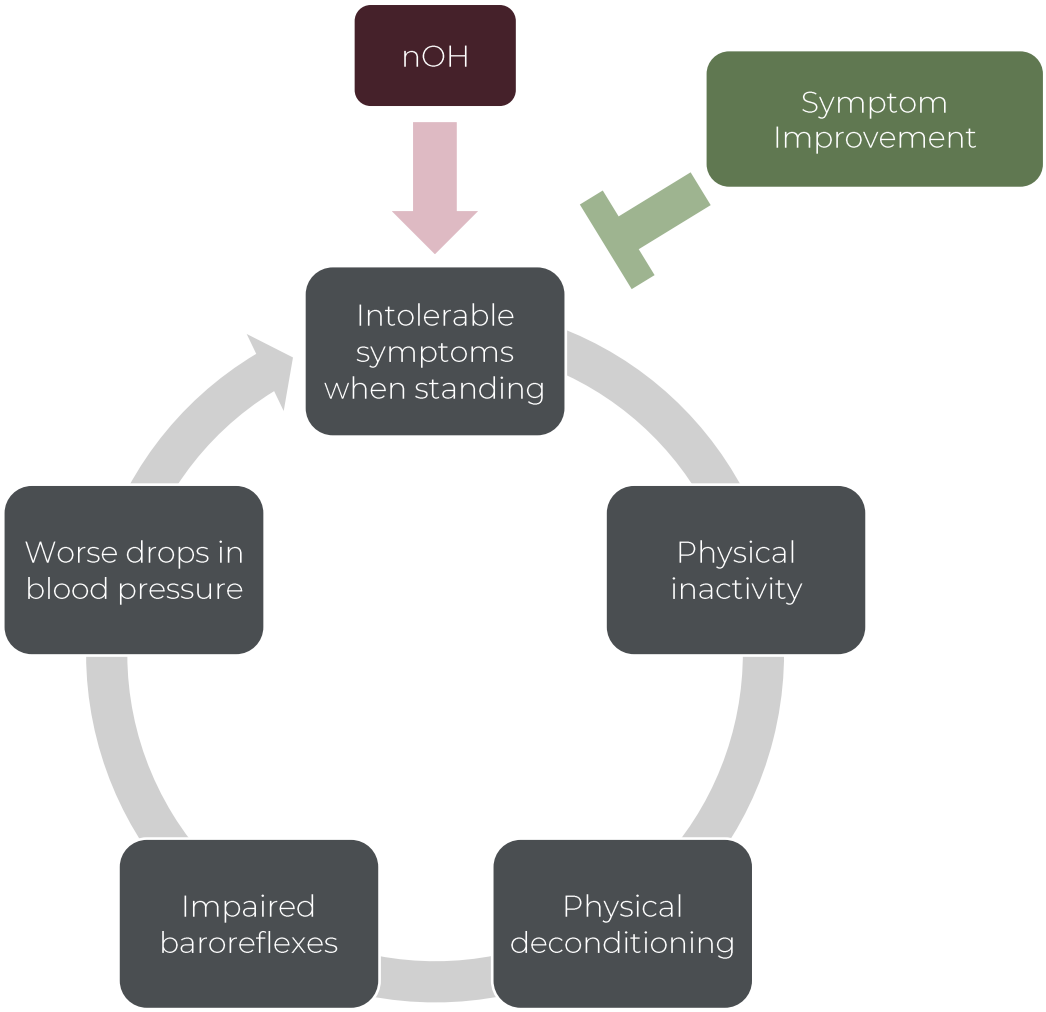
These changes occur rapidly, even within 24 hours of bed rest, and are well known to worsen the burden of symptoms.[5,6] This creates a perpetual cycle of deconditioning and worsening symptoms as shown in **Figure 9**. Improving the patient's symptoms may help to break this cycle.[33]

Figure 9. Perpetual cycle of physical deconditioning[33]



nOH, neurogenic orthostatic hypotension.

Exercise is thus absolutely vital for patients to avoid and/or reverse deconditioning.[8] Patients can do exercises while sitting or lying down (eg, stationary bike or rowing machine) to improve their tolerance. Exercise in a pool also improves tolerance because the hydrostatic pressure of the water mitigates the gravity-induced drop in blood pressure.[11]

Flashback

Previously, you learned that elevated core body temperature worsens nOH symptoms by dilating blood vessels throughout the body and thus dropping blood pressure.[1,6,33] While moderate exercise is extremely important for patients with nOH, these individuals should take care to avoid high-intensity activity that could increase their body temperature and worsen their symptoms.[6]

Physical Counter-Maneuvers

Patients should be educated about the relationship between how fluid shifts through the body due to gravity and its effects on blood pressure and nOH symptoms.[2] They should be taught to stand up gradually from sitting or lying down.[33]

Additionally, certain physical counter-maneuvers can be used throughout the day to reduce blood pooling and increase blood pressure (**Figure 10**).[8] A fundamental maneuver is to flex the leg muscles (eg, by standing on tiptoes) to activate the skeletal muscle pump. Other maneuvers including crossing the legs or flexing/clenching the muscles of arms, abdomen, or buttocks.[2,8] Squatting and stooping can also help to temporarily improve symptoms, but these maneuvers may also exacerbate symptoms when returning to a standing posture and should be used with caution.[8]

Figure 10. Physical counter-maneuvers to increase blood pressure.[2,8]

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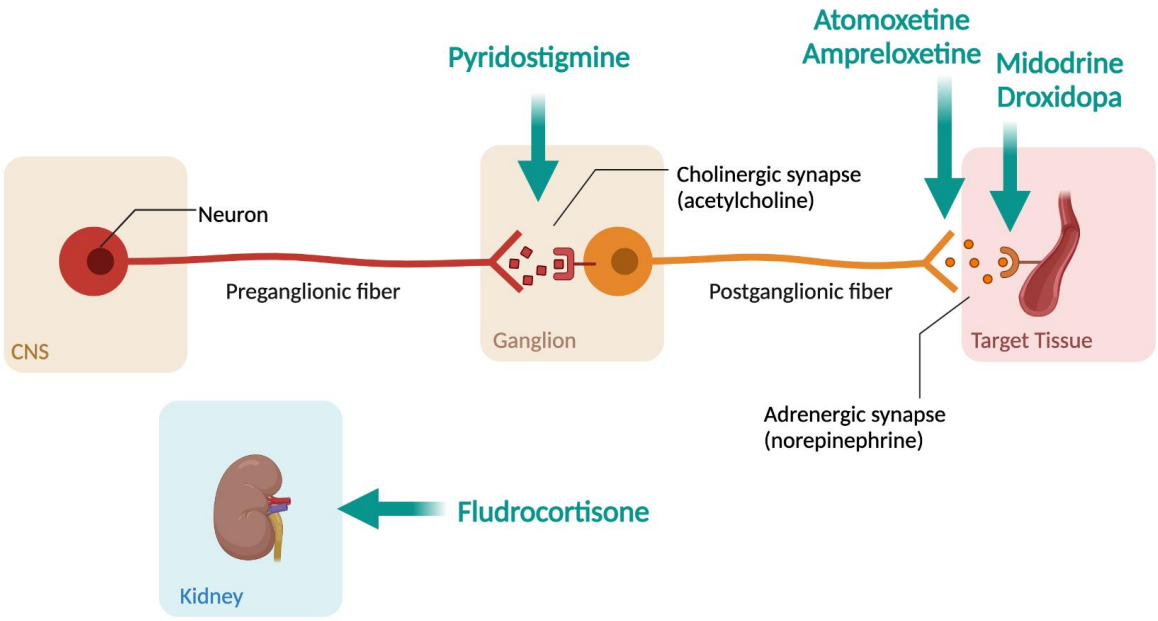
Pharmacologic Treatments

Patients with severe symptoms that are not adequately controlled by non-pharmacologic strategies may require pharmacotherapy.[14] There are 3 primary drugs that are used to treat nOH: fludrocortisone, midodrine, and droxidopa, which are summarized in **Table 5**.[6]

These and other key agents fall into 3 main treatment strategies (**Figure 11**):

- *Expanding blood volume*: Agents that expand blood volume (eg, fludrocortisone) may work by mimicking hormones called **mineralocorticoids**, which affect the body's fluid and electrolyte balance.[1,14] They cause the body to retain salt, which then increases blood volume and blood pressure.[1]
- *Increasing vascular resistance*: Some drugs elevate blood pressure by causing vasoconstriction. Vasoconstriction increases the resistance to blood flow (termed "**vascular resistance**") and thus elevate blood pressure.[3,11] These agents, which include midodrine and droxidopa, work by mimicking or converting to norepinephrine, which then exerts its effects on the blood vessels to cause them to constrict.[2] They are also called **sympathomimetic drugs**.[8]
- *Increasing sympathetic signaling*: Other drugs work by enhancing the signaling of the sympathetic nervous system. Norepinephrine reuptake inhibitors (eg, atomoxetine, ampreloxetine) increase the concentration of norepinephrine in the synapse. This leads to vasoconstriction and increased blood pressure.[2,11] Acetylcholinesterase inhibitors such as pyridostigmine increase preganglionic signaling to ultimately increase vascular resistance and thus blood pressure.[1,2,14]

Figure 11. Treatment strategies for nOH[2]



CNS, central nervous system.

Adapted from "Organization of the Sympathetic and Parasympathetic Nervous System", by BioRender.com (2022). Retrieved from https://app.biorender.com/biorender-templates

These strategies are complementary and may be used in combination if single-agent therapy is not sufficient to control symptoms.[11]

However, clinical and comparative evidence for these agents is limited and more research is needed to elucidate long-term efficacy and safety of single-agent and combination therapies.[6] You will learn more about these therapies and their associated efficacy and safety data in **Module 3: Treatment Landscape of nOH**.

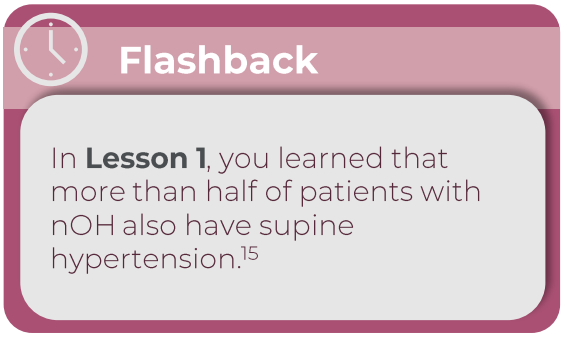
Table 5. Key pharmacologic agents used in nOH management

Agent	Mechanism	Side Effects	FDA Approval
Primary Treatments			
Fludrocortisone[14]	• Synthetic mineralocorticoid that increases salt reabsorption in the kidneys to increase blood volume • Sensitizes blood vessels to the effects of sympathetic signaling molecules such as norepinephrine	• Supine hypertension • Hypokalemia • Edema	• Off-label
Midodrine[2,3,14]	• Adrenergic agonist (ie, drug that mimics norepinephrine) • Causes vasoconstriction to elevate blood pressure	• Supine hypertension • Goose bumps • Scalp itching • Urinary retention	• FDA-approved in 1996
Droxidopa[6,11]	• Converts to norepinephrine, which increases the concentration of norepinephrine at the junctions between neurons • Causes vasoconstriction to elevate blood pressure	• Supine hypertension • Headache • Dizziness • Nausea • Fatigue	• FDA-approved in 2014
Alternative Treatments			
Pyridostigmine[3,6,8,14,36]	• Acetylcholinesterase inhibitor • Reduces preganglionic elimination of acetylcholine to enhance ganglionic signaling • Enhances sympathetic signaling to increase vascular resistance and thus elevate blood pressure	• Increased salivation • Tearing up • Diarrhea • Urinary urgency • Sweating • Slow heart rate	• Off-label
Emerging Treatments			
Ampreloxetine[11,33,37]	• Norepinephrine reuptake inhibitor • Enhances sympathetic signaling to increase vascular resistance and thus elevate blood pressure	• Headache • Urinary tract infections • Constipation	• Phase 3 clinical development
Atomoxetine[11,38]	• Norepinephrine reuptake inhibitor • Enhances sympathetic signaling to increase vascular resistance and thus elevate blood pressure	• Supine hypertension • Sleep disturbances • Irritability • Decreased appetite	• Phase 2 clinical development

FDA, Food and Drug Administration

Supine Hypertension

Supine hypertension and nOH are **hemodynamic** opposites. This makes management challenging because improving one may worsen the other.[6] Management of supine hypertension in the context of nOH is individualized. Some clinicians prioritize the treatment of supine hypertension due to the risk of end organ damage.[6,19] Other clinicians may aggressively treat nOH symptoms to mitigate debilitating symptoms and reduce the risk of falls.[6]



Minimally, all patients with both nOH and supine hypertension should avoid lying down during the day and elevate the head of their bed during the night. Short-acting anti-hypertensive agents may be used at night for patients with significant supine hypertension. However, patients should be aware that treatment of supine hypertension may worsen their nOH symptoms and may make nighttime bathroom visits dangerous.[6]

Full consideration of the management of supine hypertension is beyond the scope of this module.

Key Concepts

- At-risk patients that should be screened for nOH include those with suspected or diagnosed neurodegenerative disorders, fainting or unexplained falls, peripheral neuropathy, dizziness or orthostatic symptoms, or who are elderly, frail, or on multiple medications[6]
- When screening patients for nOH, clinicians should ask about the cardinal symptoms of OH including the frequency and severity of these symptoms and whether they impact daily activities[6]
- The gold standard for diagnosis of nOH is in-clinic supine-to-standing blood pressure monitoring; diagnosis is made if the patient's blood pressure drops more than 20/10 mmHg when standing or with head-up tilt[6]
- A diary of blood pressure measurements or 24-h ambulatory blood pressure monitoring may be useful for patients with inconclusive in-clinic testing[6,19]
- Prescription drugs should be reviewed to identify offending medications that may cause OH[19]
- Laboratory testing and, in some cases, specialized autonomic function testing may be used to differentiate neurogenic from non-neurogenic causes of OH[6,19]
- The differential diagnosis of nOH includes vasovagal syncope, POTS, and afferent baroreflex failure[19]

Key Concepts Continued

- The goal of treatment is to reduce the patient's symptom burden and improve their quality of life; management involves medication review, nonpharmacologic interventions, and pharmacologic treatment[6,8,33]
- Medications that aggravate nOH include diuretics and beta blockers[6]
- Environmental triggers that aggravate nOH include elevated core body temperature, straining, standing suddenly, prolonged standing, eating large, carbohydrate-rich meals, and diuretic substances[1-3,34]
- Nonpharmacologic interventions for nOH include correcting nutritional deficiencies and anemia, avoiding triggers, changing diet, increasing water and salt intake, sleeping in a head-up position, wearing compression garments, exercising, and using physical counter-maneuvers[6,8,33]
- The 3 primary drugs used to treat nOH include fludrocortisone, midodrine, and droxidopa[6]
- The main treatment strategies that may be used alone or in combination for nOH are to expand blood volume, increase vascular resistance, and increase sympathetic signaling[2,14]

Knowledge Check

12. What is the gold standard for diagnosis of nOH?
    A. Specialized autonomic function testing
    B. In-clinic supine-to-standing blood pressure monitoring
    C. Laboratory testing
    D. 24-h ambulatory blood pressure monitoring

13. How are patients screened for nOH?
    A. In-clinic supine-to-standing blood pressure monitoring
    B. Head-up tilt table testing
    C. Performing the Valsalva maneuver
    D. Asking about the presence, frequency, severity, and daily impact of cardinal symptoms

14. What medications aggravate nOH symptoms?
    A. Diuretics & beta blockers
    B. Adrenergic agonists & mineralocorticoids
    C. Analgesics & sedatives
    D. Insulin & metformin

Check Answers

Knowledge Check

15. List 2 environmental triggers of nOH.

_____

_____

16. Match the pharmacologic agent to its mechanism.

A. Blood volume expansion

B. Increased vascular resistance

C. Increased sympathetic signaling

____ Atomoxetine

____ Midodrine

____ Fludrocortisone

____ Pyridostigmine

____ Ampreloxetine

____ Droxidopa

17. Select 3 correct answers. Some nonpharmacologic interventions for nOH include:

A. Avoiding triggers

B. Physical counter-maneuvers

C. Lying down during the day

D. Increasing water and salt intake

E. Eating more grains

Check Answers

Glossary

Select the glossary term to return to its in-text appearance.

albumin	Simple protein found in the blood that helps to maintain blood pressure and volume[3]
alpha-synuclein	Neuronal protein that is thought to help regulate the function of synapses; aggregates of misfolded versions of this protein cause a group of neurogenerative disorders called the synucleinopathies[27,39]
ambulatory	Able to walk; not bedridden[3]
amyloidosis	Metabolic disorder characterized by the deposition of an abnormal protein-sugar complex called amyloid in the tissues; may lead to organ failure[3]
autonomic failure	Compromise of the function and reflexes of the autonomic nervous system[1]
autonomic nervous system	Branch of the nervous system that regulates organ function and balance (eg, heart rate or blood pressure) through involuntary reflex arcs[1]
baroreflex	Sympathetic reflex that senses changes in blood pressure and maintains the heart's output of blood[1,2,8]
beta blocker	Drug that inhibits the sympathetic nervous system and may be used to treat conditions such as high blood pressure[3]
bicarbonate	Ion in the blood that functions to transport carbon dioxide and regulate blood pH[1]

Select the glossary term to return to its in-text appearance.

blood urea nitrogen	Metabolic product in the blood that results from the breakdown of amino acids used in energy production; elevated levels may be associated with dehydration, compromised kidney function, bleeding in the upper gastrointestinal tract, or treatment with certain drugs[3]
cardinal	Refers to a symptom that leads to the diagnosis of a disease[3]
catecholamine	Group of sympathetic signaling molecules including epinephrine and norepinephrine[1]
cortisol	Hormone produced by the adrenal glands that is involved in immunosuppression, anti-inflammation, and electrolyte balance[3]
creatinine	Molecule produced during muscle metabolism; elevated levels in the urine may be associated with advanced kidney disease[1,3]
diabetes	Group of diseases characterized by elevated blood sugar and excessive urination[3]
diastolic	Refers to the lower value of a blood pressure reading that corresponds to the pressure within the arteries during relaxation of the heart ventricle[1]
diuretic	Agent that increases output of urine; increased urinary output decreases blood volume and thus lowers blood pressure as a side effect[1]
electrocardiogram	Readout of the heart's electrical activity[3]
etiology	Cause of a disease[3]

Select the glossary term to return to its in-text appearance.

ganglion	Cluster of neuronal cell bodies within the peripheral nervous system[1]
head-up tilt	Upright position obtained using a tilt table; the patient lies strapped to the tilt table, which can be inclined to investigate the effect of body position on blood pressure or other parameters[3]
hemodynamic	Refers to the forces that move blood through the circulation[3]
homeostasis	State of balance within the body's internal conditions[1,3]
insulin	Hormone that regulates blood sugar[3]
methylmalonic acid	Molecule involved in metabolism, which may be elevated during vitamin B-12 deficiency[40]
mineralocorticoid	Hormone that regulates the balance of fluids and electrolytes (eg, sodium and potassium) in the body[1]
multiple system atrophy	Progressive neurodegenerative disorder that affects multiple structures within the central nervous system; usually begins with motor symptoms and progresses to include widespread autonomic dysfunction including genitourinary symptoms, sweating abnormalities, and orthostatic hypotension[25,27]
natural history	Expected course of a disease if it goes untreated[3]
neuropathy	Disease of the nerves[3]

Select the glossary term to return to its in-text appearance.

Parkinson disease	Progressive neurodegenerative disorder of the central nervous system that causes movement disorder and affects cognition and mood[3]
perfusion	Blood circulation through the tissue[3]
post-prandial hypotension	Pooling of the blood within the abdominal organs after a meal, which leads to have severe drops in blood pressure within 2 hours of eating[2,3,34]
pressor	Substance that causes blood pressure to increase[3]
primary disease	Disease that is the root cause of an illness (rather than a secondary disease that occurs as a complication of a primary disease)
proprioceptor	Receptor that responds to internal stimuli from the body such as pressure, position, or stretch[3]
pure autonomic failure	Progressive neurodegenerative disease of the peripheral nervous system that causes widespread symptoms of autonomic disfunction[25]
secondary disease	Disease that occurs as a complication of a primary disease[3]
serum electrophoresis	Lab test used to identify the types of proteins in a serum sample[41]
supine	Lying on the back[3]

Select the glossary term to return to its in-text appearance.

supine hypertension	High blood pressure while laying down[3]
sympathomimetic drug	Drugs such as midodrine and droxidopa that convert to or mimic norepinephrine; it then exerts its effects on the blood vessels to cause them to constrict[2,8]
systolic	Refers to the higher value of a blood pressure reading that corresponds to the pressure within the arteries during contraction of the ventricle[1]
thyroid-stimulating hormone	Hormone released from the pituitary gland that triggers the release of thyroid hormones; thyroid hormones regulate the metabolism, heat production, and protein synthesis[1]
Valsalva maneuver	Voluntary contraction of the abdominal wall and diaphragm with the throat closed, which increases the intrabdominal pressure; typically used to aid defecation; can be performed during autonomic function testing because straining in this manner produces a severe drop in blood pressure in patients with nOH[1,3,6,11]
vascular resistance	Resistance to the flow of blood through the body; increases when blood vessels constrict and decreases when blood vessels dilate[3]
vasoconstriction	Contraction of the smooth muscle of a blood vessel that makes the vessel narrower; increases resistance, decreases blood flow, and increases blood pressure[1]
visceral reflex	Circuit of autonomic signaling that regulate the organ systems; sensory neurons relay input (eg, baroreceptors detecting stretch, indicating higher blood pressure) to the central nervous system and the output response is carried back to the tissue[1]

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Knowledge Check Answers

1. The formal definition of OH is defined as a sustained reduction of ___ in systolic blood pressure and/or ___ in diastolic blood pressure within 3 minutes of standing.

   A. ≥20 mmHg; 10 mmHg

   B. >15 mmHg; 5 mmHg

   C. ≥10 mmHg; 2 mmHg

   D. >5 mmHg; 1 mmHg

2. List 3 signs and symptoms of nOH.

Symptoms of nOH include lightheadedness, fainting, fatigue, weakness, cognitive impairment, shortness of breath, blurring of vision, chest pain, and coat-hanger headache

3. Match the nOH variant to its definition.

   A. Classical

   B. Delayed

   C. Initial

   B Sustained drop in blood pressure after 3 minutes of standing

   C Transient drop in blood pressure within 15 seconds of standing

   A Sustained drop in blood pressure within 3 minutes of standing

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Knowledge Check Answers

4. Patients with multiple system atrophy tend to:
   - A. Have stable, non-progressive disease
   - B. Progress slowly
   - **C. Progress quickly**
   - D. Spontaneously improve

5. What proportion of adults over age 60 are affected by OH?
   - A. 5%
   - **B. 20%**
   - C. 50%
   - D. 80%

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6. Select 3 correct answers. Sympathetic norepinephrine signaling:
   - **A. Increases heart rate**
   - B. Increases blood cell count
   - C. Stimulates coagulation
   - **D. Induces vasoconstriction**
   - **E. Elevates blood pressure**

7. The baroreflex responds to changes in:
   - A. Heart rate
   - B. Blood volume
   - C. Blood cell count
   - **D. Blood pressure**

8. Mark each etiology as primary or secondary.

   A. Primary
   B. Secondary

   B Viral infection
   B Systemic disease
   A Neurodegenerative disease
   B Toxins
   B Autoimmune disease
   A Genetic disease

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Knowledge Check Answers

9. The most common cause of autonomic neuropathy is:
   A. Beta-hydroxylase deficiency
   B. Autoimmune autonomic ganglionopathy
   C. Diabetes
   D. COVID-19

10. Select 4 correct answers. The alpha-synucleinopathies include:
   A. Pure autonomic failure
   B. Guillain Barré syndrome
   C. Multisystem atrophy
   D. Parkinson disease
   E. Dementia with Lewy bodies

11. When the baroreflex is disrupted, the sympathetic nerves release insufficient amounts of **norepinephrine**.

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Knowledge Check

12. What is the gold standard for diagnosis of nOH?
    A. Specialized autonomic function testing
    B. In-clinic supine-to-standing blood pressure monitoring
    C. Laboratory testing
    D. 24-h ambulatory blood pressure monitoring

13. How are patients screened for nOH?
    A. In-clinic supine-to-standing blood pressure monitoring
    B. Head-up tilt table testing
    C. Performing the Valsalva maneuver
    D. Asking about the presence, frequency, severity, and daily impact of cardinal symptoms

14. What medications aggravate nOH symptoms?
    A. Diuretics & beta blockers
    B. Adrenergic agonists & mineralocorticoids
    C. Analgesics & sedatives
    D. Insulin & metformin

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Knowledge Check

15. List 2 environmental triggers of nOH.

elevated core body temperature, straining, standing suddenly, prolonged standing, eating large, carbohydrate-rich meals, and diuretic substances

16. Match the pharmacologic agent to its mechanism.

A. Blood volume expansion

B. Increased vascular resistance

C. Increased sympathetic signaling

C Atomoxetine

B Midodrine

A Fludrocortisone

C Pyridostigmine

C Ampreloxetine

B Droxidopa

17. Select 3 correct answers. Some nonpharmacologic interventions for nOH include:

A. Avoiding triggers

B. Physical counter-maneuvers

C. Lying down during the day

D. Increasing water and salt intake

E. Eating more grains

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