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SYNCOPE
NEW TREATMENT OPTIONS
Sameh Mobarek, MD, FACC
Annual Coastal Cardiovascular Conference

February 18, 2017

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Case Study: RW, a 74-Year-Old Man With Worsening Lightheadedness

Chief Complaint and History

Chief Complaint
- RW is a 74-year-old retired engineer with worsening symptoms of lightheadedness and dizziness of 4 months duration
- His primary care physician has requested a cardiovascular consultation to exclude cardiac etiology

Medical History
- No frank syncope; patient has enough warning with current symptoms of dizziness to sit or get to his knees
- 10-year history of Parkinson's disease
- Recently developed symptoms of lightheadedness and imbalance
- 10-year history of hypertension
- No history of diabetes
- No history of heart disease

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Case Study: RW, a 74-Year-Old Man With Worsening Lightheadedness (Cont'd)

Medications and Social History

Medications
- Lisinopril 20 mg daily for hypertension
- Carbidopa/levodopa immediate release 25/100 QID for Parkinson's disease
- Daily multivitamin

Social History
- Nonsmoker
- RW is married with a daughter and 3 grandchildren who live out of state
- His wife has noted that he is hesitant to travel to visit his grandchildren as he is concerned he may pass out while visiting

QID, 4 times daily.

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Case Study: RW, a 74-Year-Old Man With Worsening Lightheadedness (Cont'd)

Clinical Assessment

- Office blood pressure and heart rate was 116/84 mm Hg and 72 beats/min in the sitting position
- Standing BP fell to 84/72 mm Hg within 90 seconds of standing (patient reported "feeling faint"), with accompanying heart rate of 74 beats/min
- Cardiac exam:
  - Normal S1, S2, fourth heart sound present
  - Normal LV function via echocardiogram (LVEF=60%)
  - Stress testing negative for ischemia
  - ECG normal sinus rhythm and no conduction disturbance
  - Carotid arteries with non-occlusive disease
- Serum creatinine, blood urea nitrogen, and electrolytes normal

BP, blood pressure; LV, left ventricular; LVEF, LV ejection fraction; ECG, electrocardiogram.

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Discussion

How do you recognize symptomatic nOH in your patients?

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Case Study: RW, a 74-Year-Old Man With Worsening Lightheadedness (Cont'd)

Diagnosis and Treatment

Diagnosis

- Patient is determined to have symptomatic neurogenic orthostatic hypotension secondary to preexisting Parkinson's disease

How would you manage this patient?

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Case Study: RW, a 74-Year-Old Man With Worsening Lightheadedness (Cont'd)

Treatment

Initial Treatment

- Patient is advised to increase hydration
- Patient is advised to eat small meals frequently and avoid standing up suddenly after eating
- Compression garments (compression stockings, corset, or belt) are also recommended
- Physical therapy/aquatic therapy or home exercises to increase skeletal muscle pump recommended (recumbent exercises)

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Case Study: RW, a 74-Year-Old Man With Worsening Lightheadedness (Cont'd)

Treatment

4-Week Assessment

- Symptoms persist after 4 weeks of non-pharmacologic treatment
- Standing BP is 82/72 mm Hg within 90 seconds of standing (patient reported "feeling faint"), with accompanying heart rate of 74 beats/min

How would you continue to manage this patient?

BP, blood pressure.

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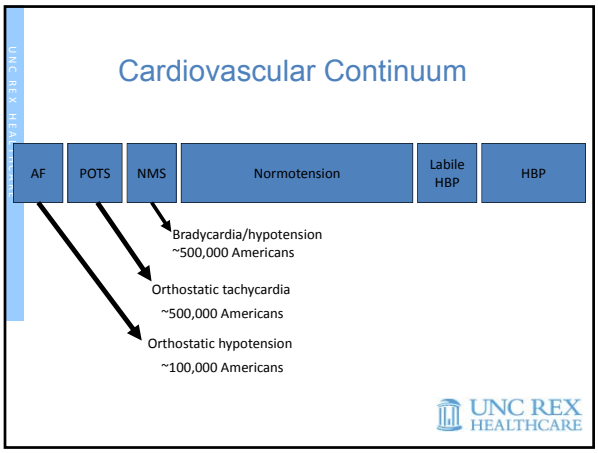
Cardiovascular Continuum
AF
POTS
NMS
Normotension
Labile HBP
HBP
Bradycardia/hypotension
~500,000 Americans
Orthostatic tachycardia
~500,000 Americans
Orthostatic hypotension
~100,000 Americans
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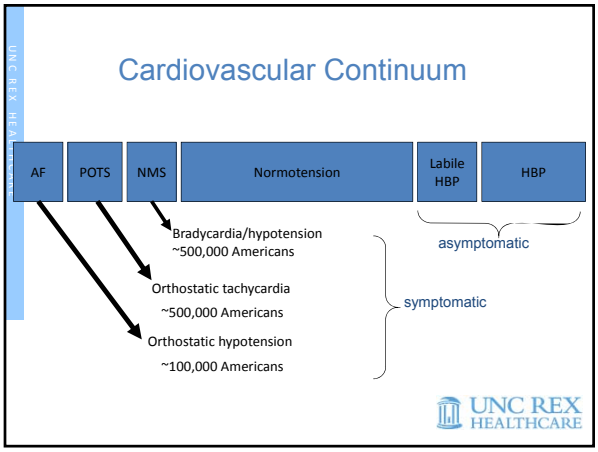
Cardiovascular Continuum
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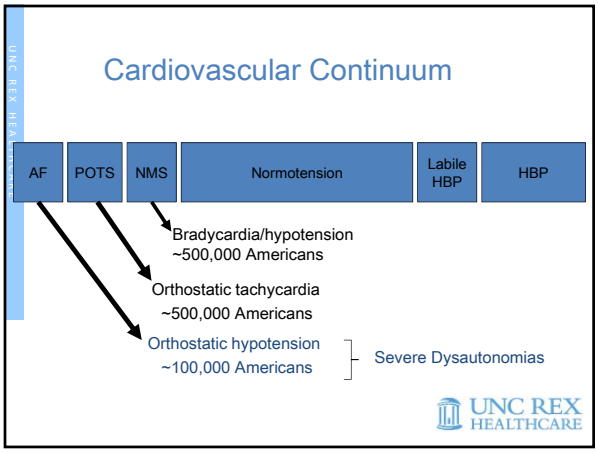
Cardiovascular Continuum
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HBP
Bradycardia/hypotension
~500,000 Americans
Orthostatic tachycardia
~500,000 Americans
Orthostatic hypotension
~100,000 Americans
Severe Dysautonomias
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Orthostatic Hypotension

- Orthostatic hypotension
  - Defined as a fall in blood pressure on standing[1]
  - Can result in symptoms of cerebral hypoperfusion
  - Is underdiagnosed[2]

1. Freeman R. *N Engl J Med.* 2008;358(6):615-624; 2. Lahrmann H, et al. In Gilhus NE, et al, eds. *European Handbook of Neurological Management.* Oxford, UK: Blackwell Publishing Ltd; 2011:469-475.

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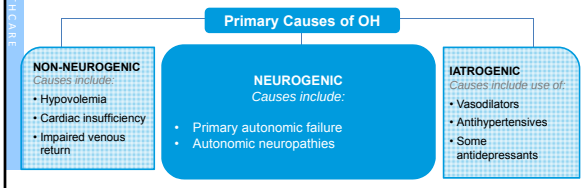
Primary Causes of Orthostatic Hypotension (OH)



Goldstein DS, Sharabi Y. *Circulation.* 2009;119(1):139-146.

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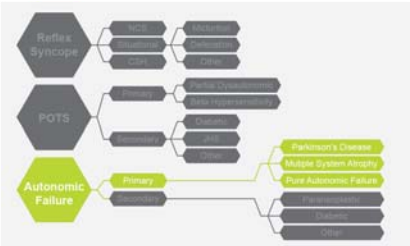
Diagnosing Autonomic Failure as a Cause of Symptoms in Neurogenic OH



OH, orthostatic hypotension; NCS, neurocardiogenic syncope; CSH, carotid sinus hypersensitivity; POTS, postural orthostatic tachycardia syncope; JHS, joint hypermobility syndrome.

Grubb B. *Circulation.* 2005;111:2997-3006.

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	NORMAL PHYSIOLOGY	"VASOVAGAL" SYNCOPE	POTS
Venous return	↓	↓	↓
Stroke volume	↓	↓	↓
Pulse pressure	↓	↓	↓
Sympathetic tone	↑		↑↑↑
Vagal tone	↓	↑	
Heart rate	↑ (10 – 15 bpm)	↓	↑↑↑ (>30 bpm)
Systolic pressure	Stable	↓↓	↓
Diastolic pressure	↑ (~10 mm)	↓	↓

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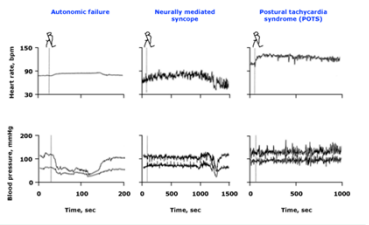
Heart rate and blood pressure patterns observed in head-up tilt table testing



Shown are the heart rate and blood pressure responses seen during tilt table testing in patients with various etiologies of syncope, including autonomic failure, neurally mediated syncope, and postural tachycardia syndrome (POTS). The absence of an appropriate reflex-induced increase in heart rate as the blood pressure falls is a useful clue to the presence of autonomic failure. During neurally mediated syncope, parasympathetic (vagal) activity increases as blood pressure declines, slowing the heart. With POTS, tilt table testing typically reproduces the clinical symptoms in association with a heart rate increase ≥30 beats/min or a maximum heart rate ≥120 beats/min within the first 10 minutes; these changes are not associated with hypotension.

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UpToDate

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Autonomic Disorders Associated With Symptomatic Neurogenic Orthostatic Hypotension (nOH)

Parkinson's Disease
- Affects ~1 million patients in the US[1]
- Slow-progressing neurodegenerative disorder[2]
- ~18% of patients will experience symptomatic nOH[3]

Multiple System Atrophy (Shy-Drager)
- Estimated mean incidence 0.6-0.7 cases per 100,000 person-years[4]
- Mean survival of 6-10 years from onset of symptoms
- Characterized by autonomic dysfunction, parkinsonism, and ataxia[5]
- ~96% will experience neurogenic bladder symptoms and/or incontinence[6]
- ~81% of patients will experience symptomatic nOH[3]

Pure Autonomic Failure (Bradbury-Eggleston)
- Very rare, exact incidence unknown[7]
- Idiopathic disorder characterized by nOH with evidence of more widespread autonomic failure[8]
- No evidence of cerebellar or Parkinson's symptoms[7,8]
- 100% will experience symptomatic nOH[8]

1. American Parkinson Disease Association. Understanding the basics. http://www.apdaparkinson.org/parkinsons-disease/understanding-the-basics. Accessed March 17, 2015; 2. Kalia LV, Lang AE. *Lancet*. Epub ahead of print. April 19, 2015. doi:10.1016/S0140-6736(14)61393-3; 3. He AD, et al. *Parkinsonism Relat Disord*. 2011;17(8):625-628; 4. Fanciulli A, Wenning GK. *N Engl J Med*. 2015;372(3):249-263; 5. Orphanet. Multiple System Atrophy. http://www.orpha.net. Accessed March 5, 2015; 6.Sakakibara R, et al. *J Neurol Neurosurg Psychiatry*. 2000;68:65-69; 7. Orphanet. Pure autonomic failure. http://www.orpha.net. Accessed March 5, 2015; 8. Kaufmann H. *Clin Auton Res*. 1996;6(2):125-126.

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The Autonomic Nervous System Maintains Blood Pressure Upon Standing by Releasing Norepinephrine

Standing results in the pooling of ~500-1000 mL of blood in the lower extremities and splanchnic circulation[1]

- **Decrease in venous return to heart**
- **Reduction in cardiac output**

Triggering of venous and arterial baroreceptors[2]

↓

Sympathetic activation[2]

↓

- Venoconstriction and increased venous return[3]
- Increased heart rate
- Increased blood pressure

This compensatory reflex response is regulated by the autonomic nervous system and the release of norepinephrine[1,3]

1. Freeman R. *N Engl J Med*. 2008;358(6):615-624; 2. Low PA, Singer W. *Lancet Neurol*. 2008;7(5):451-458.
3. Isaacson SH. *Vasc Health Risk Manag*. 2014;10:169-176.

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THE ORTHOSTATIC RESPONSE

- The orthostatic response is divided in 3 phases:

1. Initial Response (the first 30 seconds)
   -SV remains normal for 6 beats despite fall in venous return (due to pulmonary blood) then
   -Gradual decline in both cardiac filling and arterial pressure
   -This results in activation of 2 groups of pressure receptors: High pressure sites in the carotid sinus and aortic arch and low pressure sites in the cardiac and pulmonary areas

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THE ORTHOSTATIC RESPONSE

- Local axon reflex called “veno-arterial axon reflex” also constricts arterial flow to muscle, skin, and adipose tissue which can account for up to half of the increase in limb resistance seen during standing

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THE ORTHOSTATIC RESPONSE

2. Early Steady State Period (after 1-2 minutes)
   -Steady increase in diastolic BP of 10%
   -Little or no change in systolic BP
   -Increase in heart rate about 10 bpm
   -30% less blood volume in the thorax
   -Cardiac output is 30% less

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THE ORTHOSTATIC RESPONSE

3. Prolonged Orthostasis (5 minutes post standing)
   -Activation of the RAAS
   -Activation of Vasopressin & Endothelin
   -However, the arterial baroreceptors especially the carotid sinus is principal mechanism

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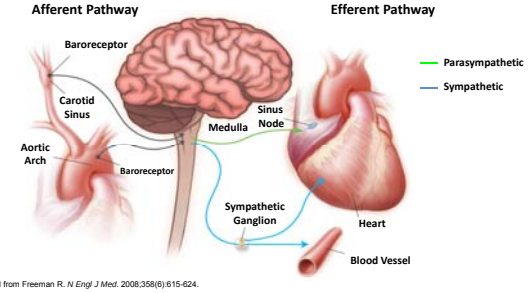
The Role of the Baroreflex in Maintaining Blood Pressure



Adapted from Freeman R. *N Engl J Med*. 2008;358(6):615-624.

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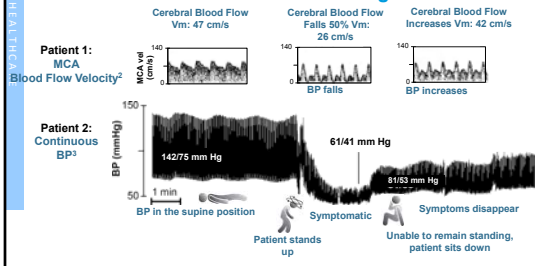
Symptoms of nOH Can Occur When BP Falls Below Lower Limit of Cerebral Autoregulation[1]



nOH, neurogenic orthostatic hypotension; BP, blood pressure; MCA, middle cerebral artery; Vm, velocity measurement.

1. Isaacson SH. *Vasc Health Risk Manag*. 2014;10:169-176; 2. Figure supplied by Horacio Kaufmann;
3. Schroeder C, et al. *Drugs*. 2013;73(12):1267-1279.

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Supine Hypertension Is Common in Neurogenic OH Patients[1]

Percentage of Patients[2]	MSA (n=25) %	PD (n=23) %	Control (n=26) %
With reduced BP fall at night	68	48	8
With reversed circadian BP	48	22	4
With supine hypertension	60	48	12

OH, orthostatic hypotension; BP, blood pressure; MSA, multiple system atrophy; PD, Parkinson's disease.

1. Freeman R. *N Engl J Med*. 2008;358(6):615-624; 2. Schmidt C, et al. *Mov Disord*. 2009;24:2136-2142.

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Recognizing Symptomatic Neurogenic OH in Your Patients

COMMON SYMPTOMS[1]:
- Lightheadedness
- Dizziness
- Presyncope
- Syncope

LESS COMMON SYMPTOMS[1]:
- Weakness
- Leg buckling
- Fatigue
- Cognitive slowing
- Visual blurring
- Headache
- Neck pain
- Orthostatic dyspnea
- Chest pain

- Common symptoms occur on standing[1]
- Symptoms typically worse in the early morning[2]
- May also worsen after meals
- Occur in patients with diseases associated with specific neurodegenerative disorders such as Parkinson's disease[1]

OH, orthostatic hypotension.

1. Freeman R. *Clin Auton Res*. 2011;21(2):69-72; 2. Low PA, Singer W. *Lancet Neurol*. 2008;7(5):451-458.

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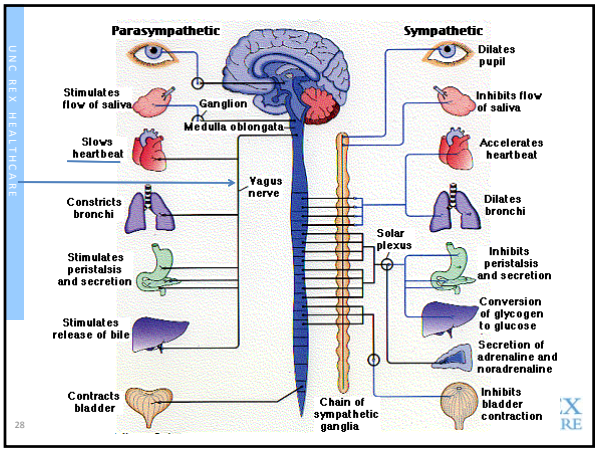

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Measuring Orthostatic Blood Pressure[1]

- Have patient lie down for 5 minutes
- Measure patient's blood pressure and pulse rate while lying down
- Have patient stand
- Measure blood pressure and pulse rate after standing for 1 minute, then again at 3 minutes

nOH is defined by a sustained drop in systolic blood pressure of ≥20 mm Hg or diastolic blood pressure of ≥10 mm Hg within 3 minutes of standing due to an underlying neurologic disorder[2,3]

1. CDC, Measuring Orthostatic Blood Pressure, http://www.cdc.gov/homeandrecreationalsafety/pdf/steadi-2015.04/Measuring Orthostatic_Blood_Pressure-a.pdf, accessed May 15, 2015; 2. Low PA, Singer W. *Lancet Neurol*. 2008;7(5):451-458; Goldstein DS, Sharabi Y. *Circulation*. 2009;119(1):139-148.

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Head-Up Tilt (HUT) Testing

- Cardiovascular response to HUT can be used to diagnose neurogenic OH in patients for whom standing BP is not an option[1]
  - Patient rests supine for 15 minutes prior to HUT while beat-to-beat BP and heart rate are recorded
  - Automated table is tilted slowly (~10 seconds) to an upright angle of 70°
  - Patient remains upright for 5 minutes, followed by a 5-minute supine measurement interval

OH, orthostatic hypotension; BP, blood pressure.

1. Berger MJ, Kimpinski K. *Can J Neurol Sci*. 2014;41(2):156-163.

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Management Strategies to Consider in Neurogenic OH Patients

- Goal of therapy: Reduce postural symptoms without introducing unacceptable side effects[1]

Non-Pharmacologic Approaches[2]

- Increase salt and fluid intake
- Elevate head of bed
- Remove aggravating factors
- Recommend compression stockings

Pharmacologic Approaches

Expand intravascular volume and/or Increase vascular tone

OH, orthostatic hypotension.

1. Maule S, et al. *Cardiovasc Hematol Disord Drug Targets*. 2007;7(1):63-70; 2. Freeman R. *N Engl J Med*. 2008;358(6):615-624.

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ABOUT NORTHERA® (droxidopa)

NORTHERA is indicated for the treatment of orthostatic dizziness, lightheadedness, or the "feeling that you are about to black out" in adult patients with symptomatic neurogenic orthostatic hypotension (NOH) caused by primary autonomic failure [Parkinson's disease, multiple system atrophy, and pure autonomic failure], dopamine beta-hydroxylase deficiency, and non-diabetic autonomic neuropathy. Effectiveness beyond 2 weeks of treatment has not been demonstrated. The continued effectiveness of NORTHERA should be assessed periodically.

WARNING: SUPINE HYPERTENSION

Monitor supine blood pressure prior to and during treatment and more frequently when increasing doses. Elevating the head of the bed lessens the risk of supine hypertension, and blood pressure should be measured in this position. If supine hypertension cannot be managed by elevation of the head of the bed, reduce or discontinue NORTHERA.

NORTHERA [package insert]. Deerfield, IL: Lundbeck; August 2014.

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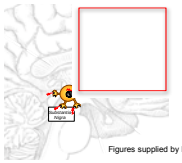
Both Parkinson's Disease and nOH Are Characterized by Deficiencies in Neurotransmission

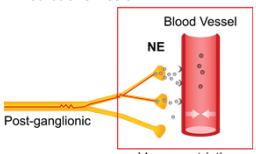
The exact mechanism of action of NORTHERA® (droxidopa) in the treatment of symptomatic nOH is unknown[1]

Parkinson's disease: a disorder of dopaminergic neurotransmission[2]



Figures supplied by Horacio Kaufmann.

nOH: a disorder of noradrenergic neurotransmission[3]



NORTHERA is a prodrug of norepinephrine[1]

nOH, neurogenic orthostatic hypotension; DA, dopamine; NE, norepinephrine.

1. NORTHERA [package insert]. Deerfield, IL: Lundbeck; August 2014; 2. Kalia LV, Lang AE. *Lancet*. Epub ahead of print. April 19, 2015. doi:10.1016/S0140-6736(14)61393-3; 3. Kaufmann H, et al. *Circulation*. 2003;108(6):724-728.

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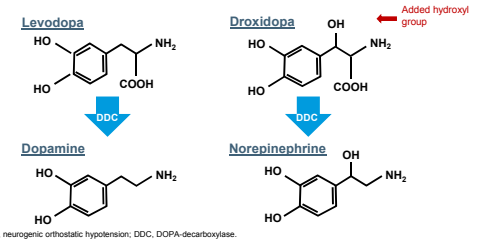
In Both Parkinson's Disease and nOH, Therapies Replenish a Deficient Neurotransmitter

- Levodopa and droxidopa are both metabolized by DDC



nOH, neurogenic orthostatic hypotension; DDC, DOPA-decarboxylase.

Kaufmann H, et al. *Circulation.* 2003;108(6):724-728.

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Droxidopa Pharmacokinetics in Healthy Subjects

- Mean peak plasma concentrations (C_{max}): ~2 hours post-dose (range, 1-4 hours)
  - High-fat meals delay C_{max} by ~2 hours
- Peak norepinephrine plasma levels: within 3-4 hours post-dose (<1 ng/mL)
- Mean elimination half-life: ~2.5 hours
  - Major route of elimination is via the kidneys
- The clinical relevance of the plasma pharmacokinetics of droxidopa has not been established

NORTHERA [package insert]. Deerfield, IL: Lundbeck; August 2014.

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Most Common Adverse Events Occurring More Frequently With NORTHERA® (droxidopa)[1]

	Studies 301 and 302 (1- to 2-Week Randomized Treatment)		Study 306 (8- to 10-Week Randomized Treatment)	
	Placebo (N=132) n (%)	NORTHERA (N=131) n (%)	Placebo (N=108) n (%)	NORTHERA (N=114) n (%)
Headache	4 (3.0)	8 (6.1)	8 (7.4)	15 (13.2)
Dizziness	2 (1.5)	5 (3.8)	5 (4.6)	11 (9.6)
Nausea	2 (1.5)	2 (1.5)	5 (4.6)	10 (8.8)
Hypertension	0	2 (1.5)	1 (0.9)	8 (7.0)

- The table displays adverse reactions that were reported in >5% of patients in the NORTHERA group and with ≥3% greater incidence in the NORTHERA group in relation to the placebo group

1. NORTHERA [package insert]. Deerfield, IL: Lundbeck; August 2014.

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Supine Systolic BP in Study 306

Study 306	During 1- to 2-Week Titration Phase (% of patients)		At End of 8-Week Treatment Phase (% of patients)	
	Placebo (n=108)	NORTHERA (n=112)	Placebo (n=93)	NORTHERA (n=86)
Supine Systolic BP >200 mm Hg	0	2.6	0	0
Supine Systolic BP >180 mm Hg	1.9	2.6	0	0
Supine Systolic BP >160 mm Hg	19.4	16.7	8.3	2.6

- **Evaluation of blood pressure (BP) at each visit was a secondary endpoint**
- Supine BP measurements were taken with the upper body at 30° elevation
- Sustained severe hypertension (systolic BP ≥180 mm Hg or diastolic BP ≥110 mm Hg in the seated or supine position) at the screening visit was an exclusion criterion
  - Dose escalation stopped if supine systolic BP rose to ≥180 mm Hg or diastolic BP to ≥110 mm Hg

Data on file. Deerfield, IL: Lundbeck; 2014.

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Management of Supine Hypertension with NORTHERA® (droxidopa)

- Supine hypertension with NORTHERA
  - NORTHERA carries a black box warning for supine hypertension[1]
  - Monitor blood pressure[1]
  - Consider non-pharmacologic interventions such as:
    - Elevate head of the bed[1,2]
    - Advise patient to avoid lying flat[2]
- Avoid NORTHERA dosing within 3 hours before bedtime[1]
  - Blood pressure (including lying down) should also be monitored as NORTHERA dose is up-titrated
  - For more severe or persistent blood pressure elevations, NORTHERA dose can be reduced or NORTHERA can be discontinued
  - Short-acting antihypertensive agents were allowed in the NORTHERA pivotal trial[3]

1. NORTHERA [package insert]. Deerfield, IL: Lundbeck; August 2014; 2. Arnold AC, Biaggioni I. *Curr Opin Nephrol Hypertens*. 2012;21(5):481-485; 3. Hauser RA, et al. *Mov Disord*. 2015;30(5):646-654.

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Cardiac Conduction and Heart Rate Were Not Affected by NORTHERA® (droxidopa)

- In **Study 102,** no effects of droxidopa were observed on conduction parameters following 600 mg and 2000 mg in a thorough QT study (52 healthy volunteers)

Study 102 (mean Δ from baseline)	Placebo	600 mg Droxidopa	2000 mg Droxidopa	400 mg Moxifloxacin
Heart rate (bpm)	0.0	–1.3	–1.5	1.1
PR (ms)	–0.3	0.4	0.7	–1.6
QRS (ms)	0.0	–0.1	–0.5	–0.3
QTcF (ms)	–3.1	–2.8	–2.6	6.1
QTcB (ms)	–3.1	–4.2	–4.2	7.4

QTc, corrected QT interval; nOH, neurogenic orthostatic hypotension; TID, 3 times daily; bpm, beats per minute; ms, milliseconds.
Data on file. Deerfield, IL: Lundbeck; 2014.

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Important Safety Information

WARNING: SUPINE HYPERTENSION

Monitor supine blood pressure prior to and during treatment and more frequently when increasing doses. Elevating the head of the bed lessens the risk of supine hypertension, and blood pressure should be measured in this position. If supine hypertension cannot be managed by elevation of the head of the bed, reduce or discontinue NORTHERA® (droxidopa).

CONTRAINDICATIONS

- None

WARNINGS AND PRECAUTIONS

- **Supine Hypertension:** NORTHERA therapy may cause or exacerbate supine hypertension in patients with NOH, which may increase cardiovascular risk if not well-managed

NOH, neurogenic orthostatic hypotension.

NORTHERA [package insert]. Deerfield, IL: Lundbeck; August 2014.

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Important Safety Information (Cont'd)

WARNINGS AND PRECAUTIONS

- **Hyperpyrexia and Confusion:** Postmarketing cases of a symptom complex resembling neuroleptic malignant syndrome (NMS) have been reported in Japan with NORTHERA® (droxidopa) use. Observe patients carefully when the dosage of NORTHERA is changed or when concomitant levodopa is reduced abruptly or discontinued, especially if the patient is receiving neuroleptics. NMS is an uncommon but life-threatening syndrome characterized by fever or hyperthermia, muscle rigidity, involuntary movements, altered consciousness, and mental status changes. The early diagnosis of this condition is important for the appropriate management of these patients
- **Ischemic Heart Disease, Arrhythmias, and Congestive Heart Failure:** NORTHERA therapy may exacerbate symptoms in patients with existing ischemic heart disease, arrhythmias, and congestive heart failure
- **Allergic Reactions:** This product contains FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons. Although the overall incidence of FD&C Yellow No. 5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity

NORTHERA [package insert]. Deerfield, IL: Lundbeck; August 2014.

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Important Safety Information (Cont'd)

ADVERSE REACTIONS

- The most common adverse reactions (greater than 5%) were headache, dizziness, nausea, hypertension, and fatigue

DRUG INTERACTIONS

- Administering NORTHERA® (droxidopa) in combination with other agents that increase blood pressure (e.g., norepinephrine, ephedrine, midodrine, and triptans) would be expected to increase the risk for supine hypertension. DOPA-decarboxylase inhibitors may require dose adjustments for NORTHERA

USE IN SPECIFIC POPULATIONS

- Clinical experience with NORTHERA in patients with severe renal function impairment (GFR less than 30 mL/min) is limited. There are no adequate and well-controlled trials of NORTHERA in pregnant women. Women who are nursing should choose nursing or NORTHERA. The safety and effectiveness of NORTHERA in pediatric patients have not been established. No overall differences in safety or effectiveness were observed between subjects aged 75 years and older and younger subjects in clinical trials, but greater sensitivity of some older individuals cannot be ruled out

GFR, glomerular filtration rate.

NORTHERA [package insert]. Deerfield, IL: Lundbeck; August 2014.

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UNC REX HEALTHCARE

NORTHERA® (droxidopa) Experience in Geriatric Patients or Patients With Renal Impairment

GERIATRIC USE

- 197 patients ≥75 years of age with symptomatic NOH were included in the NORTHERA clinical program
- No overall differences in safety or effectiveness were observed between these and younger patients, although greater sensitivity of some older patients cannot be ruled out

PATIENTS WITH RENAL IMPAIRMENT

- Patients with mild/moderate renal impairment (GFR ≥30 mL/min) were included in clinical trials and did not have a higher frequency of adverse reactions
- Clinical experience with NORTHERA in patients with severe renal function impairment (GFR <30 mL/min) is limited

NOH, neurogenic orthostatic hypotension; GFR, glomerular filtration rate.
NORTHERA [package insert]. Deerfield, IL: Lundbeck; August 2014.

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UNC REX HEALTHCARE

Concomitant Use

- NORTHERA® (droxidopa) has no contraindications
- NORTHERA has been used concomitantly in clinical trials with levodopa/carbidopa, dopamine agonists, monoamine oxidase B (MAO-B) inhibitors, catechol-O-methyltransferase (COMT) inhibitors, and other medications used to treat Parkinson's disease
- Administering NORTHERA in combination with other agents that increase blood pressure (eg, norepinephrine, ephedrine, midodrine, and triptans) would be expected to increase the risk for supine hypertension. DOPA-decarboxylase inhibitors may require dose adjustments for NORTHERA
- Dopamine agonists, amantadine derivatives, and MAO-B inhibitors do not appear to affect NORTHERA clearance, and no dose adjustments are required

NORTHERA [package insert]. Deerfield, IL: Lundbeck; August 2014.

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UNC REX HEALTHCARE

NORTHERA® (droxidopa) DOSING AND ADMINISTRATION

Northera (droxidopa) capsules

UNC REX HEALTHCARE

In Clinical Trials, NORTHERA® (droxidopa) Was Taken TID

- The recommended starting dose of NORTHERA is 100 mg, taken orally TID
  - Upon rising in the morning
  - At midday
  - In the late afternoon at least 3 hours prior to bedtime (to reduce the potential for supine hypertension during sleep)

NORTHERA is supplied in 3 dosage strengths: 100, 200, and 300 mg to facilitate customized dosing

Capsules are not actual size.

TID, 3 times daily.

NORTHERA [package insert]. Deerfield, IL: Lundbeck; August 2014.

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Additional Dosing Considerations

- Take NORTHERA® (droxidopa) whole, the same way each time, either with food or without food
- If a dose is missed, the next dose should be taken at the regularly scheduled time. The patient should not double the next dose
- Use of or change in dose of dopamine decarboxylase inhibitors (such as carbidopa) may require dose adjustments for NORTHERA

NORTHERA [package insert]. Deerfield, IL: Lundbeck; August 2014.

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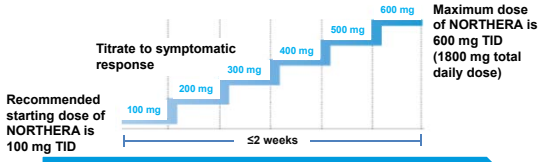
In Clinical Trials, NORTHERA® (droxidopa) Was Titrated Every 24-48 Hours

- Titrate in increments of 100 mg TID every 24-48 hours



Monitor supine blood pressure prior to initiating NORTHERA and after increasing the dose. Elevating the head lowers the risk of high blood pressure while lying down

TID, 3 times daily.

NORTHERA [package insert]. Deerfield, IL: Lundbeck; August 2014.

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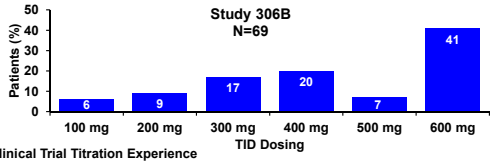
In Clinical Trials, Titration Was to Tolerability and Symptomatic Response



Clinical Trial Titration Experience

- NORTHERA® (droxidopa) was shown to be safe and well tolerated in total daily doses from 300 to 1800 mg
- ~70% of patients received a dose of 400-600 mg NORTHERA TID
- Titration phase lasted a maximum of 14 days

TID, 3 times daily.
Data on file. Deerfield, IL: Lundbeck; 2014.

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UNC REX HEALTHCARE

Case Study: RW, a 74-Year-Old Man With Worsening Lightheadedness (Cont'd)

Treatment

NORTHERA® (droxidopa) Treatment

- Patient is started on NORTHERA 100 mg TID
- He is instructed to take his blood pressure lying down daily before and after increasing NORTHERA dose and to record his results and symptoms in a diary
- NORTHERA dose is increased by 100 mg TID every 48 hours
- Patient reaches dose of 400 mg TID, symptoms of lightheadedness persist

TID, 3 times daily.

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Discussion

How would you continue to manage this patient?

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