Pathophysiology and Diagnosis of Orthostatic Hypotension
Cardiovascular Dysregulation

- OH
- POTS
- NMS
- Normotension
- Labile HBP
- HBP

Bradycardia/hypotension

Orthostatic tachycardia

Orthostatic hypotension
Cardiovascular Dysregulation

- OH
- POTS
- NMS
- Normotension
- Labile HBP
- HBP

Bradycardia/hypotension
Orthostatic tachycardia
Orthostatic hypotension

asymptomatic

symptomatic
Orthostatic Hypotension: Definition

- American Autonomic Society Criteria:
  - Fall of systolic BP of at least 20 mmHg or of diastolic BP of at least 10 mmHg within 3 min of standing (or 60 degree tilt).
- May be Symptomatic or Asymptomatic
- By AAS definition, 6-50% of elderly have OH

Schatz IJ et al. *Neurology* 1996; 46: 1470
What happens on standing?

- 500–1000 ml of blood pools below diaphragm
- This promotes compensatory changes
- $$$\uparrow \uparrow$$ Sympathetic activation
- $$$\uparrow \uparrow$$ Renin-Angiotensin
- $$$\uparrow \uparrow$$ Aldosterone
- These maintain cardiac output with standing
Postural Hemodynamics

First blood pooling, then plasma loss
Plasma Loss on Standing

Plasma volume falls ~ 14% in healthy subjects

Standing Time (min)

Plasma Volume

%
Plasma Volume Shift and Hematocrit:

The graph shows the plasma volume (PV) in milliliters (ml) under two conditions: supine and upright. The difference between the supine and upright states is indicated as 430 ml.
Plasma Volume Shift and Hematocrit:

- Supine: PV (ml) = 37
- Upright: PV (ml) = 41
- Hematocrit
Orthostatic Hypotension in Autonomic Failure

Female 52 years MSA
Interaction between Brain and Heart
Kinds of Orthostatic Dysfunction

- Initial Orthostatic Hypotension
- Delayed Orthostatic Hypotension
- Orthostatic *Hyper*tension
- Baroreflex Failure
Initial Orthostatic Hypotension

“40/20 mmHg fall within 15 sec of standing”

- Detected by beat-to-beat BP monitoring
- Common cause of syncope on standing (3-10%)
- Symptoms of cerebral hypoperfusion
- Mismatch of cardiac output and vascular resistance
  - Initial increase in venous return
  - Increased right atrial pressure
  - Leg muscle vasodilatation due to act of standing

Delayed Orthostatic Hypotension

Temporal Gradation of OH

• Among 230 patients:
  • 46% had OH within 3 minutes
  • 15% in 3-10 minutes
  • 39% after 10 minutes

• Delayed OH in:
  – Younger patients
  – Smaller phase II fall
  – Greater phase IV rise

Gibbons CH et al. *Neurology* 2006; 67: 28
When Baroreflexes Fail in Orthostatic Hypotension

Orthostatic Hypotension → Signal Amplification → BP↑
Factors Altering BP in Dysautonomia

![Bar chart showing factors altering blood pressure in dysautonomia. The chart includes the following:]
- **Clonidine** with an increase in SBP (±SBP mm Hg) of approximately 40 mm Hg.
- **CO₂** with an increase in SBP of approximately 40 mm Hg.
- **Food** with a decrease in SBP of approximately 40 mm Hg.
- **Terbutaline** with a decrease in SBP of approximately 40 mm Hg.
Oral Water Raises BP

Jordan J Circ 2000
Orthostatic Hypotension: Causes I

• Predisposing Factors
  – Dehydration
  – Deconditioning
  – Nutritional
  – Aging

• Medications
  – Tricyclic antidepressants (chronic)
  – Antihypertensives and diuretics
  – Vasodilators
  – Zanaflex
Tizanidine (Zanaflex®)

- Marketed as muscle relaxant
- Used for fibromyalgia
- $\alpha_2$ agonist (clonidine-like) effect
- May cause episodic orthostatic hypotension
Orthostatic Hypotension: Causes II

• Autonomic Neuropathy
• Pure Autonomic Failure
• Parkinson’s Disease
• Multiple System Atrophy
• Diffuse Lewy Body Disease
• Dopamine β Hydroxylase Deficiency
• Brainstem Lesions
• Spinal Cord Injury
Autoimmune Autonomic Neuropathy

- Onset over days or weeks
- Sympathetic failure:
  - Orthostatic hypotension
  - Anhidrosis
- Parasympathetic failure:
  - Gastrointestinal* (dysmotility, anorexia, pain)
  - Urological* (neurogenic bladder)
  - Pupillary impairment, dry eyes, dry mouth*
- Raised levels of antibody to the α3 subunit of the ganglionic nicotinic receptor in 50%

  Vernino S. *NEJM* 2000; 343: 847
Pure Autonomic Failure

- Severe orthostatic hypotension
- Insidious onset and slow progression
- Modest gastrointestinal/urological impairment
- Marked supine hypertension
- Very Low Plasma NE

- *Am Heart J* 1925; 1:75

Cary Eggleston  Samuel Bradbury
Parkinson’s Disease + Autonomic Failure

- Occurs in some but not all PD patients
- Orthostatic hypotension may be severe
- Cardiac sympathetic degeneration (MIBG)
- Heart may not take up MIBG
- Supine hypertension may be absent

David Goldstein
Diffuse Lewy Body Disease

- Parkinsonism
- Progressive Cognitive Decline
- Visual Hallucinations
- Autonomic Failure
- Rx: Cholinesterase Inhibitors
Multiple System Atrophy

- Hypotension
- Urinary incontinence
- Erectile dysfunction
- Hypohidrosis
- Cerebellar Impairment
- Extrapyramidal Impairment
  - Rigidity
  - Bradykinesia
  - Sometimes tremor
- Sleep Apnea

Milton Shy    Glenn Drager
Dopamine β-Hydroxylase Deficiency

- Orthostatic hypotension
- Exercise intolerance
- Ptosis of eyelids
- $\downarrow$NE  $\uparrow$DA
- Tx: NE restoration with droxidopa
Dopamine β-Hydroxylase Deficiency

• “Lazarus Effect”
• Standing Time:
  – Before Droxidopa: 2 min
  – After Droxidopa: Marathon

Orthostatic Hypotension: Causes III

- Diabetes mellitus
- Amyloidosis
- Paraneoplastic
Investigation of Orthostatic Hypotension

- Hx and PE
- Orthostatic Measures
  - Heart Rate + Blood Pressure
  - Supine + Standing for 1’, 3’, 5’, 10’
  - Plasma Norepinephrine
- Valsalva Maneuver
- CBC (mild anemia)
- Biopsy for amyloid
- MIBG ?
- CXR + Paraneoplastic Panel
Physical Measures

• **Raised Head of Bed**
  8 inch shock blocks; foam wedges, hospital bed

• **Physical Maneuvers**
  Crossed legs, leaning forward, squatting

• **Wet Garment**
  Artificial perspiration for cooling

• **Compression Garments**
  Single vs. two-piece (thigh high + abdominal binders)

• **Other Devices**
  Derby chairs
Vanderbilt Autonomic Dysfunction Center

Italo Biaggioni

www.mc.vanderbilt.edu/gcrc/adc
Epidemiology of Orthostatic Hypotension
Orthostatic hypotension (OH) refers to an excessive and relatively sustained fall in BP on standing up. It is a dynamic entity.

Prevalence of OH varies with:
- Definition (30 mm Hg vs 20 mm Hg SBP)
- Population (healthy vs select groups)
- Age
- Medications
- Associated health status
- Orthostatic stress
Orthostatic Hypotension: Definition

- Sustained orthostatic fall in SBP $\geq 20$ mm Hg or DBP $\geq 10$ mm Hg within 3 minutes of standing up (Schatz et al 1996)

- Population-based normative database (Low et al 1997)
  - 270 normal subjects
  - Recommended 30/15 fall
  - 5% OH if 20/10 used
  - 1% OH if 30/15 used
Prevalence of OH

- True prevalence defines the frequency of OH in a defined population.

- Useful information is also provided by “prevalence” in defined patient groups or patients seen in defined settings. It provides information on how common OH is in settings such as:
  - Outpatients clinics
  - Nursing homes
What is the Prevalence of OH?

- Cross-sectional prevalence of OH in unselected elders aged 65 years or older has been reported - 5% to 30% (Lipsitz 1989; Mader et al 1987; Caird et al 1973; Johnson et al 1965; Rutan et al 1992; Masaki et al 1998; Tilvis et al 1996)

- Greater in institutionalized populations
  - (10-33%) (Palmer et al 1983; Aronow et al 1988; Lock et al 1997)
Prevalence of OH: Healthy Elderly

- Cardiovascular Health Study, a multicenter, observational, longitudinal study (Rutan et al 1992)
- 5,201 men and women aged 65 years and older at initial examination
- OH ≥20 mm Hg decrease in SBP or ≥10 mm Hg decrease in DBP
## Prevalence of OH (Rutan et al 1992)

<table>
<thead>
<tr>
<th>Condition</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic OH</td>
<td>799</td>
<td>16.2</td>
</tr>
<tr>
<td>Systolic BP decrease $\geq 20$ mm Hg only</td>
<td>391</td>
<td>7.9</td>
</tr>
<tr>
<td>Diastolic BP decrease $\geq 10$ mm Hg only</td>
<td>253</td>
<td>5.1</td>
</tr>
<tr>
<td>Both systolic and diastolic BP decreases</td>
<td>155</td>
<td>3.1</td>
</tr>
<tr>
<td>Symptomatic OH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness upon standing; BP measurement aborted</td>
<td>98</td>
<td>2.0</td>
</tr>
<tr>
<td>Total</td>
<td>897</td>
<td>18.2</td>
</tr>
</tbody>
</table>

Total sample $N=4,931$. OH, orthostatic hypotension; BP, blood pressure.
**Prevalence of OH (Rutan et al 1992)**

<table>
<thead>
<tr>
<th>Age</th>
<th>Total in age group (n)</th>
<th>Systolic BP (decrease ≥20 mm Hg)</th>
<th>Diastolic BP (decrease ≥10 mm Hg)</th>
<th>Symptomatic OH</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>65–69</td>
<td>1,725</td>
<td>159</td>
<td>9.4</td>
<td>109</td>
<td>6.5</td>
</tr>
<tr>
<td>70–74</td>
<td>1,543</td>
<td>188</td>
<td>12.4</td>
<td>141</td>
<td>9.4</td>
</tr>
<tr>
<td>75–79</td>
<td>1,017</td>
<td>125</td>
<td>12.7</td>
<td>89</td>
<td>9.1</td>
</tr>
<tr>
<td>80–84</td>
<td>465</td>
<td>50</td>
<td>11.2</td>
<td>49</td>
<td>11.2</td>
</tr>
<tr>
<td>85+</td>
<td>181</td>
<td>24</td>
<td>14.1</td>
<td>20</td>
<td>12.0</td>
</tr>
<tr>
<td>Total*</td>
<td>4,931</td>
<td>546</td>
<td>11.4</td>
<td>408</td>
<td>8.6</td>
</tr>
</tbody>
</table>

*p Value 0.02 0.001 0.008 0.00004

Total sample N=4,931. OH, orthostatic hypotension (for complete criteria, refer to text); BP, blood pressure.

*Seventy-seven women and 78 men had OH by more than one criterion; therefore, row totals are not additive.

**OH increases with age**

**Symptomatic OH increase with age**
Prevalence of OH is Increased with:
(Rutan et al 1992)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio</th>
<th>CI (95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>difficulty walking</td>
<td>1.23</td>
<td>1.02, 1.46</td>
</tr>
<tr>
<td>frequent falls</td>
<td>1.52</td>
<td>1.04, 2.22</td>
</tr>
<tr>
<td>history of MI</td>
<td>1.24</td>
<td>1.02, 1.30</td>
</tr>
<tr>
<td>TIA</td>
<td>1.68</td>
<td>1.12, 2.51</td>
</tr>
<tr>
<td>Systolic HT</td>
<td>1.35</td>
<td>1.09, 1.68</td>
</tr>
<tr>
<td>Major ECG abnorm</td>
<td>1.21</td>
<td>1.03, 1.42</td>
</tr>
<tr>
<td>Carotid stenosis</td>
<td>1.67</td>
<td>1.23, 2.26</td>
</tr>
</tbody>
</table>
Honolulu Heart Study (Masaki et al 1998)

- Population based study of 3522 Japanese American men 71 to 93 years old
- OH = BP fall ≥20 mm Hg SBP or DBP ≥ 10 mm Hg.
- Prevalence of OH was 6.9%
- OH increased with age
- 4 year age-adjusted MR rates in those with and without OH were 56.6 and 38.6 per 1000 person-years
**Honolulu Heart Study** (Masaki et al 1998)

- With Cox proportional hazards models, after adjustment for risk factors, OH was a significant independent predictor of 4-year all-cause mortality.
- Relative risk 1.64 (95% CI 1.19 to 2.26)
- Significant linear association between change in SBP fall and 4-year MR (P<0.001), suggesting a dose-response relation.
<table>
<thead>
<tr>
<th></th>
<th>Orthostatic Hypotension</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of participants</td>
<td>Absent: 3279, Present: 243</td>
<td></td>
</tr>
<tr>
<td>Total no. of deaths</td>
<td>Absent: 421, Present: 52</td>
<td></td>
</tr>
<tr>
<td>Average follow-up period to death, y</td>
<td>Absent: 3.37, Present: 3.19</td>
<td></td>
</tr>
<tr>
<td>Unadjusted mortality rate, per 1000 person-years</td>
<td>Absent: 38.2, Present: 67.2</td>
<td></td>
</tr>
<tr>
<td>Age-adjusted mortality rate, per 1000 person-years</td>
<td>Absent: 38.6, Present: 56.6</td>
<td></td>
</tr>
</tbody>
</table>
Prevalence of OH Increases with Increasing Age (Masaki et al 1998)
OH Increases Mortality Rate

Masaki, et al. 1998

The graph shows the survival distribution function over years of follow-up, comparing two groups labeled "OH -" and "OH +." The solid line represents the group labeled "OH -," and the dashed line represents the group labeled "OH +." The graph indicates that the "OH +" group has a higher mortality rate compared to the "OH -" group throughout the follow-up period.
Dose-response relation of mortality and orthostatic changes in SBP and DBP

<table>
<thead>
<tr>
<th>Variable</th>
<th>Model 1</th>
<th></th>
<th>Model 2</th>
<th></th>
<th>Model 3</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR</td>
<td>95% CI</td>
<td>RR</td>
<td>95% CI</td>
<td>RR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Orthostatic hypotension (yes/no)</td>
<td>1.56</td>
<td>1.17–2.09</td>
<td>1.61</td>
<td>1.17–2.22</td>
<td>1.64</td>
<td>1.19–2.26</td>
</tr>
<tr>
<td>Age (4.5 years)</td>
<td>1.73</td>
<td>1.61–1.87</td>
<td>1.51</td>
<td>1.37–1.66</td>
<td>1.51</td>
<td>1.37–1.66</td>
</tr>
<tr>
<td>Current smoking (yes/no)</td>
<td>2.43</td>
<td>1.70–3.49</td>
<td>2.42</td>
<td>1.69–3.46</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Past smoking (yes/no)</td>
<td>1.63</td>
<td>1.30–2.05</td>
<td>1.57</td>
<td>1.25–1.97</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus (yes/no)</td>
<td>1.39</td>
<td>1.12–1.71</td>
<td>1.32</td>
<td>1.06–1.63</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI (3.1 kg/m²)</td>
<td>0.80</td>
<td>0.71–0.89</td>
<td>0.79</td>
<td>0.71–0.88</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical activity index (4.6 U)</td>
<td>0.64</td>
<td>0.56–0.73</td>
<td>0.65</td>
<td>0.57–0.75</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seated SBP (23.3 mm Hg)</td>
<td>1.01</td>
<td>0.97–1.05</td>
<td>1.02</td>
<td>0.97–1.06</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antihypertensive medications (yes/no)</td>
<td>1.17</td>
<td>0.95–1.44</td>
<td>1.11</td>
<td>0.90–1.37</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematocrit (4.3%)</td>
<td>0.79</td>
<td>0.71–0.87</td>
<td>0.81</td>
<td>0.73–0.89</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol intake (40 oz/mo)</td>
<td>1.11</td>
<td>1.04–1.18</td>
<td>1.10</td>
<td>1.03–1.17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prevalent coronary heart disease (yes/no)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.43</td>
<td>1.10–1.87</td>
</tr>
<tr>
<td>Prevalent stroke (yes/no)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.58</td>
<td>0.99–2.53</td>
</tr>
<tr>
<td>Prevalent cancer (yes/no)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.63</td>
<td>1.27–2.09</td>
</tr>
</tbody>
</table>

*All relative risks for continuous variables represent a difference of 1 SD.

Model 1 (n=3522): Orthostatic hypotension, age.
Model 2 (n=3218): Orthostatic hypotension, age, current and past smoking (relative to never smoking), diabetes mellitus, BMI, physical activity index, SBP, antihypertensive medications, hematocrit, and alcohol intake.
Model 3 (n=3218): Same variables as model 2 plus prevalent coronary heart disease, stroke, and cancer.
Influence of OH on CHD and Mortality
(Schatz et al 2002)

Both coronary heart disease and MR increased by OH.
What is the “Prevalence” of Orthostatic Hypotension in Select Groups of Patients
# Prevalence of OH In Elderly

(Mader et al 1989)

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Age</th>
<th>“Prevalence”</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rodstein and Zeman (1957)</td>
<td>250</td>
<td>61-91</td>
<td>11%</td>
<td>Nursing home</td>
</tr>
<tr>
<td>Johnson et al (1965)</td>
<td>100</td>
<td>&gt;70</td>
<td>17%</td>
<td>Geriatric unit</td>
</tr>
<tr>
<td>Caird et al (1973)</td>
<td>494</td>
<td>&gt;65</td>
<td>24%</td>
<td>Medical outpatients</td>
</tr>
<tr>
<td>Myers et al (1978)</td>
<td>319</td>
<td>50-99</td>
<td>10.7%</td>
<td>VA Geriatrics unit</td>
</tr>
<tr>
<td>MacLennon et al (1980)</td>
<td>186</td>
<td>&gt;65</td>
<td>22%</td>
<td>Medical outpatients</td>
</tr>
<tr>
<td>Lennox and Williams (1980)</td>
<td>272</td>
<td>83 mean</td>
<td>10%</td>
<td>Inpatient geriatric unit</td>
</tr>
<tr>
<td>Palmer (1983)</td>
<td>247</td>
<td>&gt;60</td>
<td>33%</td>
<td>Inpatient geriatric unit</td>
</tr>
<tr>
<td>Mader et al (1987)</td>
<td>300</td>
<td>70 mean</td>
<td>6.4%</td>
<td>Outpatient</td>
</tr>
</tbody>
</table>
OH in Elderly Nursing Home (Lock et al JAMA 1997)

- 991 subjects, long stay residents
  - ≥60 years
  - Able to stand
- 4 sets of recordings
  - Before and after breakfast
  - Before and after lunch
- 51.5% had OH at least once
  - Most common first thing in the morning
  - 13.3% had persistent OH
Prevalence in OH: Prognostic Significance (Davis et al 1987)

- 10,940 identified hypertensive individuals men and women 30 to 69 years old recruited from 14 communities in the United States
- Segregated into 4 groups
- Group 1 had OH
- Groups 2-4 had progressively smaller orthostatic fall in BP
Distribution of Orthostatic BP Change

Davis et al. 1987
Effect of Age on OH (Davis et al 1987)

Percentage of Participants in Given Age Group with ΔSBP ≤ 20 mm Hg:

- 30-39: 2.15% (34/1578)
- 40-49: 2.37% (72/3031)
- 50-59: 3.56% (130/3650)
- 60-69: 4.98% (113/2271)

AGE GROUP
Influence of OH on Mortality (Davis et al 1987)

<table>
<thead>
<tr>
<th>Subgroups</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>349</td>
<td>4036</td>
<td>5572</td>
<td>579</td>
</tr>
<tr>
<td>Deaths</td>
<td>42</td>
<td>275</td>
<td>353</td>
<td>50</td>
</tr>
<tr>
<td>Rate</td>
<td>12.07</td>
<td>6.83</td>
<td>6.35</td>
<td>8.64</td>
</tr>
<tr>
<td>Age-adjusted rate</td>
<td>10.21</td>
<td>6.70</td>
<td>6.56</td>
<td>7.70</td>
</tr>
</tbody>
</table>

- Adjusted by age, using total HDFP population as the standard.
- Rate significantly different at p < .005.
- Rate significantly different at p < .04.

- Group 1 (OH group) had significantly increased MR
Influence of Drugs on OH (Poon et al 2005)

- 342 VA veterans ≥75 years
- 55% had OH (189/342)
  - 33% of OH patients were symptomatic
  - 52 patients had falls
- Relationship to medications
  - 0 drug 35% OH
  - 1 drug 58% OH
  - 2 drugs 60% OH
  - 3 drugs 65% OH
  - Hydrochlorothiazide (65%) > Lisinopril (60%) > Trazodone (58%) > furosemide (56%) > terazosin (54%)
What is the “Prevalence” of Orthostatic Hypotension in Patients with Neurologic Disorders
Prevalence of OH in Parkinson’s Disease (Allcock et al 2004)

- Population of 237,564
- 270 patients identified
  - 104 (38.5%) agreed to participate
  - 89 patients met the UKPDS criteria
- OH in **47%** (other studies lower, but OH likely does occur commonly in situations of increased orthostatic stress).

No relationship to duration or severity of PD
<table>
<thead>
<tr>
<th>Disorder</th>
<th>Prevalence</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aging</td>
<td>10 - 30%</td>
<td>Low 1997</td>
</tr>
<tr>
<td>Diabetes</td>
<td>10 -15%*</td>
<td></td>
</tr>
<tr>
<td>Other AN</td>
<td>10 -50 per 100,000</td>
<td></td>
</tr>
<tr>
<td>MSA</td>
<td>5 - 15 per 100,000</td>
<td></td>
</tr>
<tr>
<td>PAF</td>
<td>10 -30 per 100,000</td>
<td></td>
</tr>
</tbody>
</table>

*, Prevalence for adult combined IDDM and NIDDM for the Rochester
Diabetes and Orthostatic Hypotension
Size of the Problem

- Leading cause of neuropathy in developed countries
- Affects 18.2 million in USA
- Projected to affect 39 million by 2050
- Neuropathy affects 50% of diabetics within 25 years
- Symptomatic neuropathy develops in 15% of patients within 25 years
Rochester Diabetic Study

- PI: Dr Peter Dyck
- Population based: Cross-sectional followed by longitudinal study
- >15 years
- High ascertainment
- Minimal criteria (motor, sensory, autonomic) and staged and continuous measure of severity
- Endpoints as percentiles of population-based normative database
Rochester Diabetic Study

- 1.3% of Rochester subjects had diabetes
- 47.6% had diabetic polyneuropathy
- 13% had Sx
- 10% of symptomatic diabetic neuropathy had diabetic autonomic neuropathy
- Motor impairment less
- High association of neuropathy with:
  - retinopathy, P<0.001
  - nephropathy, P=0.003
Rochester Diabetic Study

- Study of AFTs (cardiovagal, adrenergic, sudomotor) and symptoms using validated instrument (autonomic symptom profile) (Low et al. 2004)
- 148 diabetic patients (Type 1, n=83)
- 246 healthy controls
- Autonomic neuropathy (CASS score of 1 in at least 2 domains or ≥2 in one domain)
- 54% of type 1; 73% of type 2
- OH in 8.4% (Type 1) and 7.4% (Type 2)
Diabetic OH and Vascular MR
(Luukinen et al 2005)
Orthostatic Hypotension: Experience in Mayo
Autonomic Reflex Laboratory
Orthostatic hypotension (OH) occurs in a heterogeneous group of patients with differences in etiology, degree of autonomic impairment, and symptoms.

We reviewed an unselected group of patients evaluated in an uniform manner at the Mayo Autonomic Reflex Laboratory to determine:

- the cause and characteristics
- complications
All patients undergoing autonomic reflex testing at Mayo Clinic Rochester in 1998, whose BP dropped by ≥ 20mmHg during 70 degree head-up tilt were included.

Patients were asked to complete an extensive symptom questionnaire evaluating type, duration, frequency and other characteristics of orthostatic symptoms.

Autonomic function was quantified using CASS.

Review of clinical notes, lab results, EKG, and ECHO.
• 127 patients with OH were included
• 70 male, 57 female, mean-age 65.8±14.0 years
• CASS_total 5.6±2.2 ▼ moderate autonomic failure
• Distribution of primary disorders
  • Multiple System Atrophy (MSA): 34%
  • Diabetic Neuropathy (DN): 18%
  • Neurogenic OH (unspecified): 15%
  • Parkinson’s Disease (PD): 10%
  • Pure Autonomic Failure (PAF): 8%
  • Idiopathic Autonomic Neuropathy (IAN): 6%
  • Other disorders: 5%
  • Neurogenic POTS: 3%
Frequency of complications

- Renal end-organ damage (Crea/Proteinuria): 65%
- Supine hypertension (BP>160/95): 49%
- History of syncope: 42%
- Anemia: 39% (84% normocytic)
- Left ventricular hypertrophy (EKG/ECHO): 9%

Significant correlations between

- supine BP and orthostatic BP drop
- supine BP and CASS
- Creatinine and orthostatic BP drop
- Creatinine and CASS
- Creatinine and duration of disease
$R^2 = 0.24$

$p < 0.001$
Orthostatic symptoms reported in 94%

- dizziness/lightheadedness: 89%
- generalized weakness: 79%
- blurred vision: 45%
- cognitive impairment: 45%
- spinning sensation: 44%

Symptom characteristics:

- no circadian changes: 62%
- worst in early morning: 32%
- aggravating factors:
  - activity/exercise: 54%
  - after meal: 18%
  - menstrual cycle: 4%
  - prolonged standing: 51%
  - heat stress: 17%
Distinct differences between patient groups

- **CASS**, orthostatic BP-drop, frequency of supine hypertension and renal impairment were highest in PAF and lowest in neuropathic POTS
- Anemia was most frequently seen in MSA and DN

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>%</th>
<th>Age (years)</th>
<th>CASS total</th>
<th>CASS adren</th>
<th>BP-drop (mmHg)</th>
<th>Supine BP (mmHg)</th>
<th>Hypertension (%)</th>
<th>Anemia (%)</th>
<th>Renal Damage (%)</th>
<th>Cardiac Damage (%)</th>
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<tbody>
<tr>
<td>MSA</td>
<td>34</td>
<td>69.0±9.6</td>
<td>5.9±2.0</td>
<td>2.8±1.0</td>
<td>43.3±24.4</td>
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<td>150.2±22.5</td>
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<td>7.1±1.1</td>
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<td>71.1±27.1</td>
<td>179.4±26.8</td>
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<td>42.4±34.1</td>
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<td>5.6±2.2</td>
<td>2.6±0.9</td>
<td>42.7±25.2</td>
<td>156.0±28.6</td>
<td>49</td>
<td>39</td>
<td>65</td>
<td>9</td>
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</tbody>
</table>
Final Thoughts

- OH is common in the elderly, affecting 5-10% (in the better studies)
- OH increases with increasing age
- OH is mostly asymptomatic in the elderly
- Medications especially diuretics will increase the frequency of OH
- OH is associated with increased mortality
- OH is more common in certain communities such as retirement homes
- Neurologic disease such as diabetes and Parkinson’s disease increases OH
- OH is associated with significant organ damage
Current Pharmacologic Treatment for Orthostatic Hypotension
TREATMENT OVERVIEW

- Non-pharmacological
  - Education
  - Prevention
- Pharmacological
  - Increase central blood volume
  - Enhance vasoconstriction
Increase central blood volume

- Increase fluid ingestion
- Sodium chloride
- Fludrocortisone acetate
- DDAVP
- Acute water ingestion
Fludrocortisone acetate

- Increases central blood volume
- Enhances blood vessel sensitivity to catecholamines
- Enhances NE release from SNS neurons
- Increases blood vessel wall fluid content
Fludrocortisone acetate

- Dosage: 0.05- 0.5 mg
- Long duration of action
- Side Effects:
  - Supine hypertension
  - Edema and congestive heart failure
  - Hypokalemia
  - Headache
Vasopressin analogues

- V2 receptor agonists
  - Desmopressin (DDAVP)
  - Dosage: 5-40 ug nasal spray
  - Prevents nocturnal polyuria
  - SE: hyponatremia
Ingestion of ~ 500cc of tap water
SBP increase of > 30 mmHg in some patients within 5 minutes
The peak effect occurs after 20-30 minutes
Effect lasts for up to 1 hour.
There is some inter-patient variability
The mechanism is not established

TREATMENT OVERVIEW

• Non-pharmacological
  – Education
  – Prevention

• Pharmacological
  – Increase central blood volume
  – Enhance vasoconstriction
Sympathomimetic agents

- **Direct $\alpha_1$ adrenoreceptor agonists**
  - Midodrine (2.5 - 10 mg qid)
- **Mixed $\alpha_1$ adrenoreceptor agonists**
  - Ephedrine (25 - 50 mg qid)
  - Pseudoephedrine (30 - 60 mg qid)
Sympathomimetic agents

- Direct $\alpha_1$ adrenoreceptor agonists
  - Midodrine
- Mixed $\alpha_1$ adrenoreceptor agonists
  - Ephedrine
  - Pseudoephedrine
Midodrine hydrochloride

- Arteriolar and venous constrictor
- Does not cross blood brain barrier
- Peak plasma concn: 20-40 min
- Prodrug converted to desglymidodrine
- Dosage: 2.5-10 mg tid
- SE: Piloerection, pruritis, supine hypertension, urinary retention, bradycardia
Phase III Midodrine study

- Midodrine 10 mg tid
- 171 patients in 25 centres
- 139 completed the trial
- Primary endpoints
  - Improvement in standing SBP
  - Improvement in symptoms of lightheadedness

Midodrine

- Bioavailability following oral administration - 93%
- Minimal protein binding
- Undergoes enzymatic hydrolysis (deglycination) in the systemic circulation.
- Elimination Half-Life: 0.5 hour
- Undetectable in plasma 2 hours after an oral dose
Desglymidodrine

- Minimal protein binding
- Primarily responsible for therapeutic activity
- ~ 15 times as potent as midodrine
- Predominantly excreted renally (~ 40-75%)
- Elimination Half-Life: 2-4 hours
- Dialyzable: Yes
Improvement in Standing SBP (mm Hg)

Visit 1 Visit 2 Visit 3 Visit 4 Visit 5 Visit 6

Dose response trial

Side effects
- Goosebumps, tingling scalp, pruritis
- 4 patients taking 10 mg dose had supine BP > 200mmHg
- Mean for study population < 170mm Hg 2 hours post-dose
- Adverse effects dose related

**Sympathomimetic agents**

- **Mixed $\alpha_1$ adrenoreceptor agonists**
  - Ephedrine (25 - 50 mg qid)
  - Pseudoephedrine (30 - 60 mg qid)

- **SE**
  - Anxiety and tremulousness
  - Vasculitis
  - Intracerebral haemorrhage
Supplementary Agents

- Caffeine
- Erythropoietin
- Pyridostigmine
- β adrenoreceptor antagonists
- Dihydroergotamine
- MAOI with tyramine
- α₂-adrenoreceptor agonists
- α₂-adrenoreceptor antagonists
- Somatostatin analogue
Supplementary Agents

- Caffeine
- Erythropoietin
- Pyridostigmine
Caffeine

- Supplemental therapy
- Blocks vasodilating adenosine receptors
- Dose: 200 mg tid
- Caffeinated beverages
  - Coffee 85 mg per cup
  - Tea 50 mg per cup
- Tachyphylaxis
Erythropoietin

- Increases BP
- Corrects the normochromic normocytic anemia of autonomic failure
- Dosage: 25-75 U/kg 3X per week sc or iv
- Maintenance: 25 U/kg 3X per week
- Iron supplementation
- Mechanism of action unresolved
- SE: Supine hypertension
Acetylcholinesterase inhibition

• Rationale:
  – Preganglionic cholinergic neuron
  – Low ganglionic nerve traffic in the supine position
  – Facilitation of sympathetic ganglionic neurotransmission in the upright position
  – Minimize supine hypertension

Open label trial

Pyridostigmine (60 mg)

Significant increase in tilted BP

Modest increase in supine BP

Cholinergic SE in 20%


TREATMENT OVERVIEW

- Non-pharmacological
  - Education
  - Prevention
- Pharmacological
  - Increase central blood volume
  - Enhance vasoconstriction
  - Supplementary agents
A New Therapeutic Option: l-dihydroxyphenylserine (droxidopa)

US Experience
Could treatment with DOPS do for autonomic failure what DOPA did for Parkinson’s disease?

Horacio Kaufmann, MD
Parkinson’s disease is a disorder of dopaminergic neurotransmission.
Aromatic amino acids and modification of parkinsonism
Cotzias GC, Van Woert MH, Schiffer LM.
N Engl J Med 1967
Neurotransmitter disorders

Parkinson’s disease is a disorder of dopaminergic neurotransmission.

Autonomic failure is a disorder of noradrenergic neurotransmission.
TYROSINE  
\[ \text{tyrosine-3-monooxygenase (tyrosine hydroxylase)} \]

DOPA  
\[ \text{aromatic L-amino acid decarboxylase} \]

DOPAMINE  
\[ \text{dopamine } \beta\text{-hydroxylase} \]

NOREPINEPHRINE
L-dopa

L-dops
Br J Pharmacol. 1950
**The formation of noradrenaline from dihydroxyphenylserine.**
Blaschko H, Burn JH, Langemann H.

Br J Pharmacol. 1951
**The formation in vivo of noradrenaline from 3:4-dihydroxyphenylserine.**
Schmiterlow CG.
L-DOPA

DOPAMINE

NOREPINEPHRIN
L-DOPA

\[
\begin{align*}
\text{HOHO} & \text{N} \\
\text{OH} & \text{N} \\
\text{OH} & \text{N} \\
\text{OH} & \text{N} \\
\end{align*}
\]

\[\text{L-DAAD} \rightarrow \text{N} \]

\[
\begin{align*}
\text{HOHO} & \text{N} \\
\text{OH} & \text{N} \\
\text{OH} & \text{N} \\
\text{HO} & \text{N} \\
\end{align*}
\]

DOPAMINE

L-DOPS

\[
\begin{align*}
\text{HOHO} & \text{N} \\
\text{OH} & \text{N} \\
\text{OH} & \text{N} \\
\text{OH} & \text{N} \\
\end{align*}
\]

\[\text{L-DAAD} \rightarrow \text{N} \]

NOREPINEPHRIN

Bypass

\[\text{DBH} \rightarrow \text{N} \]
Dopamine beta hydroxylase deficiency

dcongenital DBH deficiency
Droxidopa in dopamine beta hydroxylase deficiency

Endogenous restoration of noradrenaline by precursor therapy in dopamine-beta-hydroxylase deficiency.
Biaggioni I, Robertson D.
Lancet 1987

Effect of unnatural noradrenaline precursor on sympathetic control and orthostatic hypotension in dopamine-beta-hydroxylase deficiency.
Man in ‘t Veld AJ, et al
Lancet 1987
Causes of autonomic failure
Causes of autonomic failure

MSA

DBH deficiency

DA $^{DBH}$ NE
Causes of autonomic failure

- MSA
- DBH deficiency
- Lewy body disorders
- Peripheral neuropathies

DA $\xrightarrow{DBH}$ NE
Causes of autonomic failure

- MSA
- AAN atb ganglionic NiAchR
- DBH deficiency
- Lewy body disorders
- Peripheral neuropathies
Causes of autonomic failure

- DA
- NE
- AAN atb ganglionic NiAchR
- DBH deficiency
- MSA
- Lewy body disorders
- Peripheral neuropathies
**Orthostatic hypotension in familial amyloid polyneuropathy: treatment with DL-threo-3,4-dihydroxyphenylserine.**
Suzuki T, Higa S, Sakoda S, Hayashi A, Yamamura Y, Takaba Y, Nakajima A.

J Neural Transm. 1983
**DL-3,4-threo-DOPS in Parkinson's disease: effects on orthostatic hypotension and dizziness.**
Birkmayer W, Birkmayer G, Lechner H, Riederer P.

**DL-Threo-3,4-dihydroxyphenylserine does not exert a pressor effect in orthostatic hypotension.**
Hoeldtke RD, Cilmi KM, Mattis-Graves K.
Norepinephrine Precursor Therapy in Neurogenic Orthostatic Hypotension

Horacio Kaufmann, MD; Daniela Saadia, MD; Andrei Voustanionouk, PhD; David S. Goldstein, MD, PhD; Courtney Holmes, CMT; Melvin D. Yahr, MD; Rachel Nardin, MD; Roy Freeman, MD

Background—In patients with neurogenic orthostatic hypotension (NOH), the availability of the sympathetic neurotransmitter norepinephrine (NE) in the synaptic cleft is insufficient to maintain blood pressure while in the standing posture.

Methods and Results—We determined the effect of oral administration of the synthetic amino acid L-threo-3,4-dihydroxyphenylserine (L-DOPS), which is decarboxylated to NE by the enzyme L–aromatic amino acid decarboxylase (L-AADC) in neural and nonneural tissue, on blood pressure and orthostatic tolerance in 19 patients with severe NOH (8 with pure autonomic failure and 11 with multiple-system atrophy). A single-blind dose-titration study determined the most appropriate dose for each patient. Patients were then enrolled in a double-blind, placebo-controlled, crossover trial. L-DOPS significantly raised mean blood pressure both supine (from 1014 to 1415 mm Hg) and standing (from 604 to 1006 mm Hg) for several hours and improved orthostatic tolerance in all patients. After L-DOPS, blood pressure increases were closely associated with increases in plasma NE levels. Oral administration of carbidopa, which inhibits L-AADC outside the blood-brain barrier, blunted both the increase in plasma NE and the pressor response to L-DOPS in all patients.

Conclusions—Acute administration of L-DOPS increases blood pressure and improves orthostatic tolerance in patients with NOH. The pressor effect results from conversion of L-DOPS to NE outside the central nervous system.

Key Words: autonomic nervous system, blood pressure, vasoconstriction, norepinephrine, alpha adrenergic receptors

19 patients with severe symptomatic orthostatic hypotension
   11 MSA
   8  PAF

64 ± 2 years old

4 females
15 males
US Droxidopa Studies

Admission to Clinical Research Center

**Dose-ranging study**

Incremental doses of Droxidopa
200 mg at 7 am
400, 1000, 1600, and 2000 at 7 am on subsequent days
or until
Fall in orthostatic BP < 20 mmHg
Supine SBP > 200 mmHg or DBP > 110 mmHg
Maximal dose of 2000 mg.

**Double blind, placebo-controlled, crossover study**

On days 1 and 3 either Droxidopa or placebo. Day 2 washout day.
Dose of Droxidopa as determined in the dose ranging study
## Dose ranging phase - US Droxidopa Studies

<table>
<thead>
<tr>
<th>Patient #</th>
<th>Age</th>
<th>Gender</th>
<th>Diagnosis</th>
<th>DOPS dose (mg)</th>
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<tbody>
<tr>
<td>1</td>
<td>74</td>
<td>M</td>
<td>MSA</td>
<td>1000</td>
</tr>
<tr>
<td>2</td>
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<td>19</td>
<td>77</td>
<td>F</td>
<td>PAF</td>
<td>1000</td>
</tr>
</tbody>
</table>

Mean dose: 1137 mg
200 to 2000 mg

US Droxidopa Studies

Placebo

Standing MAP (mmHg)

Time (hours)

n = 19; data are mean±SE

Circulation. 2003;108:724-728
US Droxidopa Studies

**Standing MAP (mmHg)**

- Placebo
- Droxidopa

-2 0 2 4 6 8 10 12

Time (hours)

n = 19; data are mean ±SE
<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Droxidopa dose (mg)</th>
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<tbody>
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<td>MSA</td>
<td>1327 ± 875</td>
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<tr>
<td>PAF</td>
<td>441 ± 650</td>
</tr>
</tbody>
</table>
US Droxidopa Studies

**Graph:**
- **Y-axis:** Standing MBP (mmHg)
- **X-axis:** Time (hours)
- **Legend:**
  - **Line with dots:** Droxidopa
  - **Line with circles:** Placebo

**Data Points:**
- At Time 0:
  - Droxidopa: 40 mmHg
  - Placebo: 65 mmHg
- At Time 12:
  - Droxidopa: 115 mmHg
  - Placebo: 90 mmHg

**Significance:**
- Asterisks (*) indicate significant differences between Droxidopa and Placebo groups.
- The graph shows an increase in MBP for both groups, with Droxidopa peaking at Time 6 and Placebo at Time 8.

**Note:**
- The graph indicates that Droxidopa may have a more rapid and pronounced effect on MBP compared to Placebo.
US Droxidopa Studies

**MSA**

- **Droxidopa**
- **Placebo**

The graph shows the change in Standing MBP (mmHg) over time (hours) for Droxidopa and Placebo treatments. The data points are marked with stars (*) indicating statistical significance. The graph includes error bars representing the variability in the measurements.
Adverse Events

1 patient had hyponatremia which reversed after saline infusion

1 patient had transient anginal pain with ST-segment depression on ECG but no elevation of cardiac enzymes
Droxidopa increased blood pressure and improved orthostatic tolerance in all patients
What is the mechanism of action of droxidopa?

1. Peripheral sympathetic neurotransmitter?

2. Circulating hormone?

3. Central stimulator of sympathetic outflow?
Peripheral sympathetic neurotransmitter
Circulating hormone

Peripheral sympathetic neurotransmitter

DOPS → AAD
NE → PNMT
E → +

DOPS → AAD → NE

stomach
kidney
liver
Central stimulator of sympathetic outflow

Circulating hormone

Peripheral sympathetic neurotransmitter

DOPS  ↓  AAD  NE

E  ↓  PNMT

DOPS  ↓  AAD  NE

stomach  kidney  liver
AAD inhibition with carbidopa

Central stimulator of sympathetic outflow

Circulating hormone

Peripheral sympathetic neurotransmitter

DOPS ↘ AAD

[DOPS ↘ AAD](DOPS ↘ AAD)

NE ↘ PNMT

E ↘

AAD inhibition with carbidopa

Peripheral sympathetic neurotransmitter
Carbidopa does not cross the BBB, it inhibits the synthesis of NE from DOPS only outside the CNS.
If DOPS is a central stimulator of sympathetic outflow, coadministration of carbidopa will not affect the increase in blood pressure.
If the pressor effect of DOPS is through NE synthesis in the periphery, both in neuronal and nonneuronal tissue, coadministration of carbidopa should block the increase in blood pressure.
Decarboxylase inhibition (DCI) study

- Double blind, placebo controlled study (n=6)
  - Placebo
  - Droxidopa
  - Carbidopa (200 mg)
  - Droxidopa+Carbidopa
Droxidopa+DCI study

Kaufmann et al. Circ 2003
Droxidopa+DCI study

Kaufmann et al Circ 2003
Droxidopa+DCI study

Kaufmann et al Circ 2003
Droxidopa+DCI study

Standing MAP (mmHg)

-2 0 2 4 6 8 10 12

Time (hours)

Placebo  Droxidopa  Carbidopa  Droxidopa + Carbidopa

* * * *

Kaufmann et al Circ 2003
Pressor effect of droxidopa is due to its conversion to norepinephrine outside the brain, both in neuronal and non neuronal tissue.
Droxidopa is effective in patients with central and peripheral autonomic disorders.

In patients with peripheral autonomic disorders and degeneration of sympathetic neurons (e.g. PAF), droxidopa is converted to NE in non neuronal tissue.

In patients with central autonomic degeneration and preserved peripheral sympathetic neurons (e.g. MSA), droxidopa is converted to NE in neuronal and non neuronal tissue.
200 mg of carbidopa achieves complete inhibition of the enzyme dopa decarboxylase and blocks the pressor effect of DOPS.

Lower doses of carbidopa, regularly used in PD, may not block the pressor effect of DOPS.
Pharmacokinetic study
US Droxidopa Studies
US Droxidopa Studies

![Graph showing the concentration of L-DOPS and Norepinephrine over time. The graph indicates a peak at around 10 hours for both substances, followed by a decrease.](image-url)
US Droxidopa Studies

\( r^2 = 0.914, \ p < 0.005 \)
L-DOPS significantly increases blood pressure and improves orthostatic tolerance in patients with autonomic failure due to PAF or MSA.

The pressor effect results from conversion of L-DOPS to NE outside the central nervous system, both in sympathetic neurons and non neural tissues.
THE END
A New Therapeutic Option: 1-dihydroxyphenylserine (droxidopa) - European Experience
Goals

- Ensure appropriate mobility/function
- Prevent falls and injuries
- Maintain quality of life

General measures

- Eliminate hypotensive agents, if safe
- Increase salt intake; expand blood volume
- Support stockings

Drugs that increase BP
Droxidopa

Synthetic amino acid precursor of the neurotransmitter norepinephrine (NE)

- European development
  - Phase IIa at 10 centers: France 5, Germany 3, UK 2
    
    Principal Investigator: Christopher J. Mathias  DPhil, DSc, FRCP, FMedSci
  - Phase IIb at 30 centers: Germany 10, France 7, Italy 7, UK 6
    
    Principal Investigator: Christopher J. Mathias  DPhil, DSc, FRCP, FMedSci
  - Application for Orphan Medicinal Product status for PD, MSA, and PAF

Mechanism of action not fully elucidated

- Metabolized to NE
  - Direct stimulation of alpha (and beta) receptors
  - Replenishment of NE intraneuronally
Two European Phase II Studies of Droxidopa

Two Phase II studies of droxidopa completed in Europe

1. Dose-escalating, open-label Phase IIa study
   • multiple system atrophy and pure autonomic failure*

2. Dose-ranging placebo-controlled Phase IIb study
   • multiple system atrophy and Parkinson’s disease

* Mathias et al. Clinical Autonomic Research 2001
Objective
• Evaluate the efficacy and safety of increasing doses of droxidopa
• Patients with symptomatic orthostatic hypotension associated with pure autonomic failure (PAF) or multiple system atrophy (MSA)

Study design
• Multinational: UK, Germany and France
• Incremental dose: 100, 200, and 300 mg droxidopa b.i.d.
• Final dosage maintained for 6 to 10 weeks
• Primary efficacy variable
  • Decrease in orthostatic fall in SBP
All patients (32) received droxidopa 100 mg b.i.d.
- 25 were titrated to 200 mg b.i.d.
- 18 were titrated to 300 mg b.i.d.

Mean reduction of fall in SBP:
- 22.2 mm Hg (baseline fall: 54.3 mm Hg)
- 25/32 (78%) patients improved
- 14/32 (43%) no longer had orthostatic hypotension

Reduction in orthostatic fall in SBP
- 100 mg b.i.d. 22% (7/32)
- 200 mg b.i.d. 24% (6/25)
- 300 mg b.i.d. 61% (11/18)
Phase IIa Study of Droxidopa

Efficacy comparable between PAF and MSA groups

Efficacy comparable between patients receiving L-dopa and dopa decarboxylase inhibitor (DCI) and those not receiving these medications

• 16 patients were receiving L-dopa + DCI
• 16 patients were not receiving L-dopa + DCI
Phase IIa Study of Droxidopa

Symptoms of orthostatic hypotension improved
- light-headedness/dizziness (p = 0.0125)
- blurred vision (p = 0.0290)

No reports of supine hypertension

Mean supine BP at final visit
- 118.9 ± 28.2 mm Hg systolic
- 70.9 ± 15.2 mm Hg diastolic
CONCLUSIONS

Droxidopa effective and well tolerated when used to control symptomatic orthostatic hypotension in MSA and PAF patients

300 mg b.i.d. most effective of three tested doses

Droxidopa efficacy not affected by concomitant DCI
Phase IIb Study of Droxidopa

Droxidopa in the treatment of orthostatic hypotension in patients with multiple system atrophy or Parkinson’s disease
Phase IIb Study of Droxidopa

Objective

- Determine minimum effective dose of droxidopa that safely produces significant reduction in the fall in orthostatic systolic blood pressure compared with placebo
- Patients with symptomatic orthostatic hypotension associated with multiple system atrophy or Parkinson’s disease

Study design

- Randomized, double-blind, double-dummy
- Multinational, 30 centers: Germany 10, France 7, Italy 7, UK 6
- Droxidopa 100, 200, or 300 mg t.i.d., or placebo
- Screening period: 2 to 7 days
- Treatment period: 28 days
Phase IIb Study of Droxidopa

First-day Clinically Relevant Reduction in Orthostatic Fall in SBP

Mean reduction in orthostatic fall in SBP, mm Hg

- 100 mg t.i.d. Droxidopa
- 200 mg t.i.d. Droxidopa
- 300 mg t.i.d. Droxidopa
- Placebo
Phase IIb Study of Droxidopa

Magnitude of success

- For reductions of $\geq 10$, $\geq 15$, and $\geq 20$ mm Hg in orthostatic fall in SBP, all droxidopa groups had better results than the placebo group
- For reductions of $\geq 25$ mm Hg, the 100 and 300 mg t.i.d. groups had better results than the placebo group
- Reductions $\geq 20$ mm Hg: 21% of 300 mg t.i.d. group

No significant association between baseline SBP fall and magnitude of treatment success achieved
Phase IIb Study of Droxidopa

Baseline: Patients’ classification of symptoms similar for all the treatment groups

- Majority of patients:
  - mild to moderate dizziness
  - mild to severe tiredness
  - mild or no visual disturbances
  - no episodes of loss of consciousness or falls
- Overall trend toward improvement in symptoms in all droxidopa groups and placebo group

No significant association between change in symptoms and change in orthostatic SBP fall by Day 28

- Longer study may show significant improvement in symptoms as did Phase IIa study which lasted 6–10 weeks
Heart Rate Unaffected by Droxidopa

- Cardiovascular system monitored because of droxidopa’s mechanism of action: increasing NE activity
- No notable difference found in heart rate when measured at Day 0 and Day 28 between any of the treatment groups
- No significant association found between change in heart rate and change in orthostatic SBP fall by Day 28
Phase IIb Study of Droxidopa

<table>
<thead>
<tr>
<th></th>
<th>Mean Heart Rate - Beats per Minute (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>100 mg t.i.d. n=33</td>
</tr>
<tr>
<td><strong>Day 0</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pre-dose 10 min supine</td>
</tr>
<tr>
<td></td>
<td>Pre-dose 6 min head-up tilt</td>
</tr>
<tr>
<td></td>
<td>Post-dose 10 min supine</td>
</tr>
<tr>
<td></td>
<td>Post-dose 6 min head-up tilt</td>
</tr>
<tr>
<td><strong>Day 28</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>10 min supine</td>
</tr>
<tr>
<td></td>
<td>6 min head-up tilt</td>
</tr>
</tbody>
</table>
Phase IIb Study of Droxidopa

Effect of Droxidopa on Plasma Norepinephrine

- Statistically significant change in post-tilt plasma NE concentration from Day 0 to Day 28 for the droxidopa 300 mg t.i.d. group ($p = 0.022$)

- 38 MSA patients:
  - mean increase in plasma NE of statistical significance only for the droxidopa 300 mg t.i.d. group ($p = 0.003$)

- 66 Parkinson’s disease patients:
  - Increase in mean plasma NE concentration for all groups

- NE and primary efficacy data suggest that MSA and PD populations may respond differently to droxidopa

- Higher droxidopa doses may produce significantly higher NE levels
## Phase IIb Study of Droxidopa

### Mean Noradrenaline Plasma Concentrations (SD)

<table>
<thead>
<tr>
<th>Day</th>
<th>100 mg t.i.d. n=33</th>
<th>200 mg t.i.d. n=27</th>
<th>300 mg t.i.d. n=31</th>
<th>Placebo n=30</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Day 0</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pre-dose 10 min supine</td>
<td>0.30 (0.20)</td>
<td>0.30 (0.24)</td>
<td>0.23 (0.17)</td>
</tr>
<tr>
<td></td>
<td>Pre-dose 6 min head-up tilt</td>
<td>0.34 (0.19)</td>
<td>0.43 (0.39)</td>
<td>0.31 (0.21)</td>
</tr>
<tr>
<td></td>
<td>Post-dose 10 min supine</td>
<td>0.36 (0.26)</td>
<td>0.56 (0.65)</td>
<td>0.36 (0.29)</td>
</tr>
<tr>
<td></td>
<td>Post-dose 6 min head-up tilt</td>
<td>0.42 (0.26)</td>
<td>0.65 (0.74)</td>
<td>0.41 (0.29)</td>
</tr>
<tr>
<td><strong>Day 28</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>10 min supine</td>
<td>0.54 (0.74)</td>
<td>0.41 (0.25)</td>
<td>0.50 (0.39)</td>
</tr>
<tr>
<td></td>
<td>6 min head-up tilt</td>
<td>0.54 (0.31)</td>
<td>0.53 (0.37)</td>
<td>0.61 (0.47)</td>
</tr>
</tbody>
</table>
Phase IIb Study of Droxidopa

- The number of Adverse Events (AEs) was similar in all treatment groups
- Most frequently reported AEs were neurological (15%)
  - dizziness (4%), headache (3.2%), loss of consciousness (2.4%), somnolence (2.4%)
- The majority of AEs were of mild or moderate severity
- 18 severe events in 12 patients
- 1 patient withdrawn due to severe supine hypertension considered related to droxidopa (200 mg t.i.d. group)
- Only 1 of 3 serious AEs possibly related to droxidopa
- No clinically significant patterns of change in laboratory parameters
## Similar Incidences of AEs with Droxidopa and Placebo

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of AEs (No. of patients reporting AEs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (32)</td>
<td>18 (13)</td>
</tr>
<tr>
<td>100 mg t.i.d. droxidopa (34)</td>
<td>24 (13)</td>
</tr>
<tr>
<td>200 mg t.i.d. droxidopa (27)</td>
<td>16 (9)</td>
</tr>
<tr>
<td>300 mg t.i.d. droxidopa (32)</td>
<td>23 (12)</td>
</tr>
<tr>
<td>Total (125)</td>
<td>81 (47)</td>
</tr>
</tbody>
</table>
DCIs Do Not Blunt Droxidopa BP Effect in PD Patients

- >80% of PD patients were treated with an oral DOPA decarboxylase inhibitor (DCI)
  - Oral DOPA DCIs benefit PD patients by inhibiting conversion of L-DOPA to dopamine in the periphery, improving levels of L-DOPA reaching the brain
- The possibility existed that DOPA DCIs may also block the conversion of droxidopa to norepinephrine in the periphery and influence droxidopa treatment outcome
- DOPA DCIs did not block the effect of droxidopa on blood pressure in PD patients
  - Difference between reduction in orthostatic fall in SBP between droxidopa 300 mg t.i.d. and placebo:
    - patients taking DCI 13.8 mm Hg
    - all patients 11.6 mm Hg
Phase IIb Study of Droxidopa

Clinically Relevant Reduction in Orthostatic Fall in SBP, Day 0 to Day 28

Mean reduction in orthostatic fall
in SBP, mm Hg

Overall
Parkinson's disease
MSA*

Droxidopa 100 mg t.i.d.
Droxidopa 200 mg t.i.d.
Droxidopa 300 mg t.i.d.
Placebo

*MSA, multiple system atrophy
CONCLUSIONS
Droxidopa Effective, Safe, Well Tolerated in PD and MSA Patients

- Droxidopa may be more effective for PD patients than for MSA patients
- The effect of droxidopa is apparent with its first dose
- The effect of droxidopa persists for $\geq 28$ days
- 300 mg t.i.d. is more effective than 100 or 200 mg t.i.d.
An Update on the Diagnosis, Epidemiology and Treatment of Orthostatic Hypotension

Moderated Panel: Faculty Q&A