This supplement is based on a symposium that took place in New York City on April 20, 2007. Distinguished faculty met to discuss recent advances in orthostatic hypotension and what the future holds.

**Clinical Autonomic Research**

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Update on neurogenic orthostatic hypotension
Pathophysiology, prevalence and treatment
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Neurogenic orthostatic hypotension: New prospects in treatment

Neurogenic orthostatic hypotension is a disorder of noradrenergic neurotransmission. Upon standing, without norepinephrine release from postganglionic sympathetic terminals, vascular resistance does not increase to compensate for the gravitational volume shift and blood pressure falls. This compromises blood supply to vital organs, particularly the brain.

In this supplement of *Clinical Autonomic Research*, five experts from different medical centers in the United States and the United Kingdom discuss recent advances in our understanding and treatment of neurogenic orthostatic hypotension. David Robertson describes the spectrum of blood pressure disorders, and why patients with orthostatic hypotension are so severely impaired, sometimes unable to stand for more than a few seconds without losing consciousness. Phillip Low reviews the prevalence of neurogenic orthostatic hypotension, which increases with age and in neurodegenerative diseases, particularly Parkinson’s disease and multiple system atrophy. A review of the currently available pharmacological therapies for the management of orthostatic hypotension by Roy Freeman makes it clear that more effective therapies are needed. In the next two articles, I review recent phase II studies of the norepinephrine precursor droxidopa conducted in the United States and Christopher Mathias reviews clinical trials conducted across Europe.

Based on the success of the preliminary studies with droxidopa, large multicenter phase III clinical trials have begun recently both in the United States and Europe. The hypothesis that led to the use of this artificial aminoacid is elegant. Replenishing a missing neurotransmitter by a precursor aminoacid has a successful history in neuropharmacology with the treatment of Parkinson’s disease. In the case of droxidopa, the precursor aminoacid is converted in the body into norepinephrine, replenishing the missing neurotransmitter in autonomic failure. The similarities between droxidopa and levodopa are immediately apparent. Droxidopa has one added beta hydroxyl group; otherwise, the molecules are identical. Droxidopa is not a new agent. It is not available in the United States or Europe, but it has been available in Japan for over 25 years and has an excellent safety record. Both the United States and the European trials of droxidopa indicate that the agent is effective with a unique mechanism of action. These are good reasons to be optimistic that the drug will soon be available for patients in the United States and Europe.

Treatment of neurogenic orthostatic hypotension with droxidopa, the precursor of the missing neurotransmitter, is a promising therapeutic approach. If successful, still needed, of course, are means to modulate the autonomic response so that the increase in norepinephrine would occur at the appropriate times. Similar challenges were faced by levodopa in the treatment of Parkinson’s disease. Fortunately, the enzymes involved in catecholamine metabolism are now well known and they have already been the targets of therapeutic strategies in combination with levodopa.

Horacio Kaufmann, MD
Cardiovascular dysregulation

Disorders of cardiovascular dysregulation encompass a broad spectrum all the way from very low pressures to very high pressures. Some of these disorders are depicted in Fig. 1, where the broad middle group includes the great majority of individuals, those with normal blood pressures. On the right, hypertension includes approximately 10% of the population; these patients have blood pressures that are elevated while they are lying, while they are standing and while they are upright. Separating the hypertensive patients from normal are the labile hypertensive patients, who occupy the controversial and ill-defined borderland of pressures ranging from 120/80 to 140/90. Conversely, on the left extreme, are patients with low blood pressure when standing, usually normal blood pressure while seated, and sometimes high blood pressure while lying down. These are individuals with orthostatic hypotension (OH). Between this group and normal subjects are patients with the milder dysautonomias, postural tachycardia syndrome (POTS) and neurally mediated syncope (NMS). POTS patients have orthostatic tachycardia and symptoms of sympathetic activation on standing, while NMS patients usually have normal pressures in all postures, but occasionally have “fainting” associated with a brief, usually less than 1 min, hypotension and/or bradycardia. POTS and NMS patients do not usually have OH, and that is why their disorders are often classified as “milder dysautonomias”; patients with

The pathophysiology and diagnosis of orthostatic hypotension

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Abstract Orthostatic Hypotension (OH) is a common manifestation of blood pressure dysregulation. OH takes a heavy toll on quality of life. It has many potential etiologies, and many effects of aging can increase susceptibility to OH. Neurological disorders are especially likely to cause severe OH. In this brief review, the pathogenesis of OH is considered, particularly in terms of autonomic neuropathy, multiple system atrophy (MSA), pure autonomic failure, baroreflex failure, and dopamine beta hydroxylase deficiency. While OH is difficult to treat, its control greatly enhances the quality of life.

Key words orthostatic hypotension · orthostatic hypertension · autonomic · syncope · fainting
these disorders do not usually consider them mild in a
general sense.

There is one very important difference between
approaches to treatment at the right and left ends of
this spectrum. On the right, the blood pressure per-
turbation usually has no associated symptoms. We do
not treat these patients to make them feel better. We
treat them to try to prevent complications of hyper-
tension perhaps 20 or more years down the line. On
the other hand, people on the left extreme have
symptoms that are often quite devastating. Such
patients need help today. So, our strategy in these
patients is to improve their functional capacity today,
make them feel better, keep them active, and our
focus is one of quality of life today. Many of the same
medicines used to treat OH are also used in an effort
to treat POTS and NMS. Beta blockers have some-
times been used in all categories of cardiovascular
dysregulation depicted in Fig. 1, though the rationale
for their use in NMS and OH is questioned.

**Orthostatic hypotension**

Orthostatic hypotension is defined as a fall of systolic
blood pressure of at least 20 mmHg or a fall of dia-
static blood pressure of at least 10 mmHg within
3 minutes of standing [20]. It is a physical finding and
not a diagnosis; so it may be symptomatic or
asymptomatic. Most people who are symptomatic
from OH have a much greater fall in pressure on
standing. Thus this is a very broad definition, and
perhaps 50% of elderly patients might occasionally
meet these criteria [3]. Evaluation and therapy are
therefore primarily driven by symptoms.

**Physiology of standing**

Why do people get orthostatic hypotension? At one
level the pathophysiology is quite straightforward.

When we stand, there is about 500–1,000 ml of blood
that goes from the upper body to the lower body,
primarily the lower abdomen, buttocks, and legs. In
response to this, there are compensatory effects from
activation of the sympathetic nervous system, the
renin-angiotensin system, and consequent aldoste-
rone release. These come into play to help maintain
cardiac output during the stress of upright posture.
Because upright posture is a relatively late evolu-
tionary development, our mechanisms for mainte-
nance of upright posture may still be under
considerable genetic pressure.

**Orthostatic blood volume shift**

While an individual is lying down, blood volume is
distributed throughout the body as depicted in Fig. 2.
The second frame in the figure shows that same dis-
btribution in a theoretical instantaneously upright
transition. But in the third frame, it can be seen that
by 1 min of upright posture, the shift of perhaps
500 ml of blood to the lower part of the body is well
advanced. The next phenomenon, depicted in the
fourth frame, is perhaps even more important in the
real world of OH management. It illustrates that after
the pooling of blood, there is a period of 20–30 min
during which substantial loss of plasma volume from
the blood into the tissues occurs. This produces at
least as great a challenge to the cardiovascular system
as the more widely appreciated pooling of blood de-
picted in frame 3. Indeed, in healthy subjects, there is
a 14% fall in plasma volume within 20 min after
assumption of the upright posture, most of which
occurs within the first 10 min. That 14% translates
into about 430 ml of blood, close to the amount taken
in a blood donation. Since the cellular component of
the blood remains in the circulation, even the
hematocrit, if you measure it carefully, changes, per-
haps rising from 37 to 41 (Fig. 3). The lower hemato-
crit of the supine posture occasionally puts
otherwise healthy persons into the usually accepted “anemia” range of hematocrit, and has therefore been called “postural pseudoanemia [9]” for that reason. Thus, much of the “noise” in hematocrit measurement in clinical practice is actually not noise but reflective of changes in blood related to patient’s posture in the time leading up to the sampling.

This volume shift is reflected in BP during continuous blood pressure monitoring in a patient with OH. You can see in Fig. 4 that during monitoring after a patient with OH stands for about 20 min, the blood pressure does not so much plummet immediately, but rather transitions downward over a few minutes as the pooling first and then the plasma volume shift become sequentially engaged. It is noteworthy that many patients with chronic OH tolerate degrees of hypotension that are quite low, at least for a few minutes.

**Types of orthostatic hypotension**

The interaction between the brain and the cardiovascular system in blood pressure control is paramount, and this has lead to an expansion of our understanding of the different kinds of abnormalities which occur on standing. First we now recognize that in addition to the OH we commonly recognize between 1 min and 3 min of standing, there is both an earlier form of OH (“initial orthostatic hypotension”, IOH [26] and a later form developing between 5 min and 45 min (“delayed orthostatic hypotension” [5], DOH). IOH occurs immediately upon standing and is detectable only by beat-to-beat blood pressure monitoring [12]. This occurs at a time when many normal subjects, on arising from overnight sleep, may have a transient sense of impaired cerebral blood flow, but this typically goes away in a few seconds. However, falls of 40/20 mmHg in the first 15 s of standing are sometimes seen, and this period is associated fairly commonly with syncope in susceptible individuals. It is due to a mismatch based on an initial increase in venous return, increase in right atrial pressure, and overcompensation, accompanied by the muscle-derived late dilatation in the legs due to the act of standing. Delayed orthostatic hypotension (DOH) has recently been systematically studied by Freeman and his collaborators [6]. They found that among 230 people who ultimately had OH; either on standing or on the tilt table, 46% had OH within 3 min, but another 15% had OH in the 3–10 min interval, and then over the next half hour or so, an additional 39% manifested orthostatic pressures. The latter tended to be younger patients, and many fell into the category of POTS.

**Orthostatic hypertension**

Perhaps surprisingly, some patients have orthostatic increases rather than decreases in blood pressure when they stand. These individuals display orthostatic hypertension [2; 23]. The more severely affected patients have relatively rare disorders such as baroreflex failure [11], mast cell activation disorder (mastocytosis) [22], hyperadrenergic POTS, or pheochromocytoma.

**Signal amplification in dysautonomias**

Patients with OH due to autonomic impairment have a range of remarkable clinical characteristics. Many of these derive from the loss of buffering reflexes. The baroreflex keeps blood pressures from having excessively large excursions; preventing pressure from getting too high when there is a pressor stimulus and preventing pressure from getting too low when there is a depressor stimulus. When the baroreflexes fail,
stimuli that would not do very much in healthy persons may have a big impact on blood pressure in a patient with OH due to autonomic failure. There is thus huge signal amplification in going from normal individuals to individuals with autonomic dysfunction. There are a number of interesting consequences of this. For example; food lowers blood pressure in healthy individuals by only 1 mmHg, but in people with autonomic dysfunction, food may lower blood pressure by 40 mmHg [14; 19], and they may pass out when they try to stand after finishing a meal. Conversely 16 ounces of water can raise blood pressure about 40 mmHg in the hour or so after it is ingested [21]. This effect and that of food can sometimes be harnessed by patients to benefit blood pressure control. Some drugs such as clonidine, which are used to lower blood pressure in hypertension, may display a pressor effect in autonomic failure as there is both hypersensitivity of vascular alpha adrenoreceptors and loss of baroreflex buffering. Likewise, the tachycardic (beta-1) effect of isoproterenol (Isuprel) is 6-fold elevated in the OH of autonomic failure. The depressor (beta-2) effect of isoproterenol is 17-fold elevated in this disorder [18]. Just half of a 5 mg oral terbutaline tablet, such as is used in asthma without notable depressor effect, is capable of reducing supine blood pressure by half in a patient with autonomic failure.

Predisposing factors for orthostatic hypotension

There are a number of predisposing factors for OH, including dehydration, deconditioning, poor nutrition or the bodily changes that occur with aging (Table 1). The latter factors lead to more vulnerability to OH in the aging population. There are drugs administered for other conditions that may concomitantly cause OH. The tricyclic antidepressants in chronic use have long been recognized as a cause of OH, and of course antihypertensive agents and diuretics can do this as well. Vasodilators like nitroglycerin, hydralazine, and calcium channel blockers can also cause OH. A commonly unrecognized cause of OH nowadays is tizanidine (Zanaflex). This problem arises simply because people are not expecting this side effect. Tizanidine is used as a muscle relaxant in fibromyalgia. Patients generally say it helps their condition, but it also is an alpha-2 agonist and therefore has clonidine-like effects, and so may cause episodic OH at the time of the major effects of the drug.

Causes of orthostatic hypotension

Several neurological conditions (Table 2) give rise to OH. Autonomic neuropathy [25] may sometimes occur in relatively pure form, and is recognized by its spectrum of autonomic manifestations (Table 3). It encompasses what used to be called acute pandysautonomia, but also includes many cases of what is termed pure autonomic failure, owing to early conflation of the two pathophysiologies. Typically, it has an onset over days to weeks. There is sympathetic failure with OH and anhidrosis, which may be very severe and then characteristically parasympathetic failure is pronounced. Gastrointestinal, urological, and sicca changes are usually a hint that autonomic neuropathy may be the cause of the patient's OH. Although there probably are many causes for this, some patients have an antibody to a component of nicotinic receptor at the critical ganglion synapse where autonomic function is transduced. It may account for up to 50% of these patients; so assessing that antibody in the paraneoplastic panel identifies these individuals. Pure autonomic failure was described in the classical paper of Bradbury and Eggleston in 1925. It is characterized by severe OH; insidious onset, slow progression, modest gastrointestinal impairment, marked supine hypertension,
and often very low plasma norepinephrine levels [10]. Other neurological systems are not involved. These people have a very good prognosis and often live into their 90s with this. Parkinson’s disease with autonomic failure is associated with sympathetic neuropathy, and OH occurs in some, but not all Parkinson’s disease patients [8]. The hypotension in a few of them can be quite severe and MIBG or PET studies may help detect that, although we do not have good benchmarking for these tests yet. Dementia with Lewy Bodies is important to recognize in individuals with some Parkinsonian features, but progressive cognitive decline in these people may be more dramatic, and include visual hallucinations. The autonomic failure and some of the cognitive aspects can improve with cholinesterase inhibition. Multiple system atrophy (MSA) is a very difficult problem because it involves not only the autonomic but also cerebellar and extrapyramidal systems [17]. MSA has the severest outlook of any dysautonomia. Sleep apnea also occurs commonly in MSA.

Dopamine beta-hydroxylase (DBH) deficiency is an extremely rare but instructive disorder, because it is a notable success story in terms of both diagnosis and therapy. The specific gene defect is in the DBH enzyme which produces norepinephrine from dopamine. Patients with this have severe OH, exercise intolerance, and usually ptosis of the eyelids. Erectile function (primarily parasympathetic) is not prevented but retrograde ejaculation (due to sympathetic failure) occurs. These patients have no norepinephrine in their neurons and instead they have stoichiometric replacement of norepinephrine by its precursor dopamine. DBH deficiency is interesting to us because it is one example where we get almost a “Lazarus” effect in response to droxidopa. Droxidopa is essentially a norepinephrine molecule to which a carboxyl group is attached [7]. This enables it to be absorbed orally, get past the liver and into the circulation where it is a substrate for the norepinephrine transporter and gets pumped into the sympathetic neuron. Within the neuron, and at other sites, droxidopa is decarboxylated to endogenous neurotransmitter norepinephrine, restoring sympathetic function. We reported a DBH deficiency patient in 2005 who, in her early 20s, was only able to stand erect for about 2 min before therapy, but after she was placed on droxidopa she rapidly began to be able to do many more things, and took up running, first tentatively but ultimately in an increasingly athletic fashion. After about a year of training she successfully completed the 26 mile New Orleans Marathon [4]. Completion of this benchmark reflected both the drug and this patient’s determination.

The alien landscape of orthostatic hypotension

Orthostatic regulation of drug levels

Liver blood flow (LBF) in humans is posture dependent. In healthy subjects, LBF is 5% less in the seated posture than in the supine posture, but in patients with OH that LBF decrement is a whopping 30%. A consequence of this is that drugs like lidocaine which are removed from the blood by first pass hepatic clearance will display dramatically posture-dependent plasma levels. When orthostatic hypotensive patients are receiving intravenous lidocaine, levels of the drug are almost twice as high when they are seated as when they are supine. Sitting up can so elevate plasma lidocaine levels that seizures may occasionally be provoked when patients with autonomic failure sit up [1].

Garden hose “therapy” of orthostatic hypotension

In OH due to autonomic failure, hyperventilation reduces blood carbon dioxide and this is attended by rapid fall in blood pressure in subjects with OH, sometimes 40 mHg within 60 s. Since hyperventilation may occur with physical exertion, this effect contributes to the depressor effect of exercise. Conversely, breathing through a dead space increases carbon dioxide concentration in inspired air, and the effect of this is to raise blood pressure 20 mHg or more. Some patients are so sensitive to this effect that they can stand longer while breathing through a short length of garden hose [15].

Afebrile hypotension as presentation of infection

Patients with severe autonomic failure have impaired capacity to manifest a fever in response to infection. Instead they present with an acute fall in blood pressure and a greatly reduced functional capacity. Such infections tend to be in the urinary tract or the lung. When patients note a substantial acute decrement in their functional capacity, they should have urinalysis and a chest examination to rule out infection [16].

Wet shirt therapy in hot weather

When the hypohidrosis in autonomic failure is severe, the inability to perspire can lead to temperature elevation in patients exposed to hot weather (>90° F). This increase in temperature leads to a fall in blood
pressure and the patient feels greatly fatigued, and may only be able to tolerate this temperature for a few minutes. Providing “artificial perspiration” in the form of a wet shirt will help speed heat dissipation and allow more tolerance of hot weather with maintenance of a higher blood pressure. Usually the wet shirt will provide benefit for about an hour before it must be re-wetted [16].

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References


Orthostatic hypotension (OH) is a dynamic state and not a disease in itself or necessarily a pathologic entity. Cross-sectional prevalences primarily reflect the influence of age (Fig. 1), but to some degree also reflect the effects of medications, the degree of orthostatic stress, and the presence of abnormalities of the autonomic nervous system. This review considers the prevalence of OH in particular settings (such as long-term care facilities and outpatient clinics), and the prevalence of OH in patients with autonomic disorders associated with OH.

### OH in the normal aging population

The cross-sectional prevalence of OH in unselected elders, aged 65 years or older, has been reported to be between 5 and 30% [9, 13, 15, 22, 27]. The difference in these estimates varies due to a number of factors, such as the definition of OH, the segment of the population studied (age range, institutions), the composition of the population (healthy population versus select groups), the influence of medications and the level of orthostatic stress. The prevalence appears to be similar in North America [9], in Japanese in Hawaii [15] and in Finns in Finland [27]. In all of these studies the prevalence of OH increased with age.

Orthostatic hypotension (OH) is defined as a fall in blood pressure of at least 20 mmHg systolic or 10 mmHg diastolic when standing or during head-up tilt testing. The prevalence of OH increases with age, with disorders that affect autonomic nerve transmission, and with increasingly severe orthostatic stress. In normal elderly subjects, the prevalence of OH is reported to be between 5 and 30%. The actual prevalence depends on the conditions during diagnostic testing, such as the frequency of blood pressure recordings, the time of day and the degree of orthostatic stress. Elderly subjects are often taking medications, such as antihypertensives and diuretics that can cause or aggravate OH. Neurological diseases such as diabetic neuropathy, Parkinson’s disease, multiple system atrophy and the autonomic neuropathies further increase the likelihood of OH. The development of OH in normal subjects is associated with an increased mortality rate. OH in diabetes is also associated with a significant increase in mortality rate.

### Key words

orthostatic hypotension · aging · neuropathy · mortality · prevalence · autonomic nervous system
or older at their initial examination, the prevalence of asymptomatic OH (defined as a minimum fall in systolic BP by 20 mmHg or in diastolic BP by 10 mmHg within 3 min of standing) was 16.2%. When the criteria for defining OH also included those in whom the procedure was aborted due to dizziness upon standing, this prevalence increased to 18.2%. The prevalence of symptomatic OH increased from 14.8% in subjects aged 65–69 years to 26% in subjects 85 years and older, clearly demonstrating the association between OH and aging [22].

### OH and mortality rate

In a population-based study of 3,522 Japanese Americans in Hawaii aged between 71 and 92 years, Masaki et al. [15] reported that the prevalence of OH was 6.9%, and again that the prevalence increased with age (Fig. 1). They also found that the 4-year age-adjusted mortality rate was higher in those with OH than in those without (56.6 versus 38.6 per 1,000 person-years). With Cox proportional hazards models, after adjusting for other risk factors, OH was a significant independent predictor of 4-year all-cause mortality, with a relative risk of 1.64 (95% CI 1.19 to 2.26). Furthermore, there was a significant linear association between the change in systolic BP fall and 4-year mortality rate \( (P < 0.001) \), suggesting a dose-response relationship [15].

Rose et al. [21] studied the association between OH and a 13-year mortality among middle-aged black and white men and women from the Atherosclerosis Risk in Communities Study (from the year 1987 to 1989). At baseline, 674 participants (5%) had OH. All-cause mortality was higher among those with (13.7%) than without (4.2%) OH (see Fig. 2). This association was only partly explained by “traditional” risk factors [21].

### OH in defined groups

Although not true prevalences, the presence of OH in settings such as in nursing homes or outpatient clinics is of interest. If the OH associated with aging is included, the “prevalence” is quite high in subjects older than 70 years of age. Table 1 lists seven prevalences (as percentage of the affected group with OH) in particular settings, taken from studies carried out with similar criteria in subjects who were otherwise generally healthy. These are perhaps the best estimates of the prevalence of OH based on current data. Therefore, a reasonable estimate of prevalence in
ambulant older subjects, diagnosed during testing with simple BP recordings, is between 10 and 30%.

**OH and increasing orthostatic stress**

When testing is done repeatedly and under conditions of increased orthostatic stress, the percentage of subjects with OH increases. For instance, Ooi et al. [17] evaluated 991 long stay residents 60 years of age and older who were able to stand and took four sets of supine and standing BP recordings before and after breakfast and before and after lunch. They found that 13.3% of subjects had persistent OH, consistent with the values reported in Table 1. However, they reported that 51.5% of subjects had OH at least once and that OH was most common first thing in the morning [17].

**OH and medications**

Another variable that impacts upon the prevalence of OH in elderly subjects is the effect of medications. In a Veteran Administration study of 342 veterans 75 years or older, 55% (189/342) had OH, of whom 33% and symptoms of orthostatic intolerance, and 52 patients had falls [19]. There was a significant relationship between the presence OH and the number of medications: with no drug 35% had OH; with one drug 58% had OH; with two drugs 60% had OH; with three drugs 65% had OH. The antihypertensives Hydrochlorothiazide (65% OH) and Lisinopril (60% OH), the diuretic Furosemide (56% OH), the antidepressant Trazodone (58% OH), and the alpha-blocker Terazosin (54% OH) had the greatest propensity to cause OH.

**OH and neurological disorders**

Neurological disorders that affect the release of noradrenaline can cause OH. The prevalence of OH in autonomic disorders is summarized in Table 2.

### Table 1 Estimated “Prevalence” of OH in certain settings

<table>
<thead>
<tr>
<th>Setting</th>
<th>n</th>
<th>Age (years)</th>
<th>“Prevalence” (%)</th>
<th>Study reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nursing home</td>
<td>250</td>
<td>61–91</td>
<td>11</td>
<td>Rodstein and Zeman [20]</td>
</tr>
<tr>
<td>Medical outpatient</td>
<td>494</td>
<td>≥65</td>
<td>24</td>
<td>Caird et al. [3]</td>
</tr>
<tr>
<td>VA Geriatric unit</td>
<td>319</td>
<td>50–99</td>
<td>10.7</td>
<td>Myers et al. [16]</td>
</tr>
<tr>
<td>Medical outpatients</td>
<td>186</td>
<td>≥65</td>
<td>22</td>
<td>MacLennan et al. [12]</td>
</tr>
<tr>
<td>Geriatric unit</td>
<td>272</td>
<td>83*</td>
<td>10</td>
<td>Lennox and Williams [8]</td>
</tr>
<tr>
<td>Geriatric unit</td>
<td>247</td>
<td>≥60</td>
<td>33</td>
<td>Palmer et al. [18]</td>
</tr>
<tr>
<td>Medical outpatient</td>
<td>300</td>
<td>70*</td>
<td>6.4</td>
<td>Mader et al. [14]</td>
</tr>
</tbody>
</table>

Data taken from seven studies carried out with similar criteria in elderly subjects who were otherwise generally healthy. From this we can conclude that “prevalence” is between 10 and 30%. * mean value; n, number of subjects.

### Table 2 Estimated prevalence of OH in different autonomic disorders

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Prevalence</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aging</td>
<td>10–30%</td>
<td>Table 2</td>
</tr>
<tr>
<td>Diabetes</td>
<td>10%*</td>
<td></td>
</tr>
<tr>
<td>Diabetics-Type 1</td>
<td>8.4%</td>
<td>Low et al. [10]</td>
</tr>
<tr>
<td>Diabetics-Type 2</td>
<td>7.4%</td>
<td>Low et al. [10]</td>
</tr>
<tr>
<td>Parkinson’s disease</td>
<td>47%</td>
<td>Alcock et al. [1]</td>
</tr>
<tr>
<td>Parkinson’s disease</td>
<td>48%; 37%</td>
<td>Wood et al. [29]</td>
</tr>
<tr>
<td>Parkinson’s disease</td>
<td>58%</td>
<td>Senard et al. [25]</td>
</tr>
<tr>
<td>Other autonomic neuropathies</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 Diabetic Cohort for 1997 (PI: PJ Dyck)

### Diabetes and OH

In a cohort of adult diabetic patients (insulin-dependent diabetes mellitus and non-insulin-dependent diabetes mellitus) evaluated at the Mayo Clinic (Rochester, Minnesota) from 1987 to 1997 (mean age over this decade 60 ± 12 years) 10% had OH. To investigate the association between autonomic function and symptoms of OH a population-based study in 148 diabetic patients (83 with Type 1 diabetes) and 246 healthy controls was conducted. OH symptoms (assessed using the “Autonomic Symptom Profile”—a validated self-reporting instrument), standardized autonomic function tests (cardiovagal, adrenergic, sudomotor function), and a Composite Autonomic Severity Score (CASS, which corrects for the effects of age and gender [11]) were evaluated. A CASS score of 1–3 was used for either sudomotor and cardiovagal functional deficits and 0–4 for adrenergic deficits. Autonomic neuropathy (defined as a CASS score of 1 in at least 2 domains or ≥2 in one domain) was found in 54% of Type 1 diabetes and 73% of Type 2 diabetes. Despite the high prevalence of autonomic dysfunction, OH was found in only 8.4% (Type 1) and 7.4% (Type 2) of diabetic patients.

### Autonomic failure and OH

Alcock et al. [1] estimated the prevalence of OH in Parkinson’s disease in a population of 237,564 in the county of Durham (UK). They identified 270 patients with Parkinson’s disease of whom 104 (38.5%) agreed to participate. They reported that 47% had OH [1], a remarkably high incidence. Other reports in Parkinson’s disease outpatient cohorts have estimated the prevalence of OH to be between 16 and 58% [25, 29]. OH is an integral feature of the autonomic neuropathies, pure autonomic failure (PAF), and multiple...
The causes of neurogenic OH are shown in Table 3. The diseases with the highest prevalence of neurogenic OH, are MSA, PAF, diabetic autonomic neuropathy, autoimmune autonomic neuropathy and paraneoplastic autonomic neuropathies. In specialist spinal cord injury practices, tetraplegia is a common cause of OH.

In a prospective study of 90 consecutive patients referred with suspected OH, evaluated at the Mayo Autonomic Laboratory, and confirmed to have OH, the diagnoses were:

<table>
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<th>Disease</th>
<th>Prevalence</th>
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<td>Pure autonomic failure (PAF)</td>
<td>33%</td>
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<tr>
<td>Multiple system atrophy (MSA)</td>
<td>26%</td>
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<tr>
<td>Guillain-Barre syndrome</td>
<td>17%</td>
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<tr>
<td>Autonomic dysautonomia clinically important</td>
<td>14%</td>
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<tr>
<td>Botulism</td>
<td>8%</td>
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<td>Paraneoplastic autonomic neuropathy</td>
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Information on the clinical features, progression and outcome in PAF is somewhat limited. Some patients with PAF have continued relatively symptom free for many years, with standing blood pressures as low as 80 mmHg. The natural history of PAF is that of a slow progression taking place over some 10–15 years [2]. However, we should take into account the difficulties in diagnosing PAF. About 10% patients originally thought to have PAF turn out to have autoimmune autonomic ganglionopathy with A3 acetylcholine receptor antibodies. The development of OH worsens the prognosis of patients with diabetic neuropathy. Ewing et al. [4] reported a mortality rate of 50% at 2½ years in patients with symptomatic diabetic autonomic neuropathy. However, these patients had long-standing
clinical autonomic neuropathy and died of renal failure. Subsequent studies suggest that autonomic failure worsens prognosis, but less dismally than was originally thought [5]. The clinical and laboratory features of 229 patients with primary systemic amyloidosis seen at the Mayo Clinic reported that median survival from the time of diagnosis for patients with peripheral neuropathy, carpal tunnel syndrome, OH and cardiac failure was 60, 45, 9.5, and 6.5 months, respectively [7].

We have reviewed the Mayo Clinic experience with idiopathic autoimmune autonomic neuropathy. Patients seem to improve substantially over the first year followed by a slower rate of improvement over the subsequent 4 years [26]. Overall, approximately 1 in 3 patients makes a good functional recovery. However, the majority of patients are left with a chronic debilitating illness with significant residual deficits.

For patients with OH associated with aging, the coexistence of OH is associated with a worse prognosis [15].

Concluding thoughts

OH is a dynamic entity, it is frequent, and increases with age. Indeed, it is likely to be present in most of the elderly under circumstances of increased orthostatic stress. Its prevalence is further increased in certain neurologic disorders. The presence of OH worsens prognosis and increases mortality.

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References


Current pharmacologic treatment for orthostatic hypotension

Roy Freeman

Introduction

Orthostatic hypotension is the most incapacitating symptom of autonomic failure. Fortunately, with the help of non-pharmacological and pharmacological interventions, most patients’ quality of life can be improved substantially. The therapeutic interventions to treat patients with orthostatic hypotension should be implemented in stages and depend, in large part, on the severity of symptoms. Some patients may be markedly improved by education, counseling, removal of hypotensive medications and other non-pharmacological interventions, while more severely afflicted patients require pharmacological interventions [9].

Non-pharmacological measures

Patient education is the cornerstone of the management of orthostatic hypotension. Throughout the day, patients are subject to a number of orthostatic demands for which there are simple but effective countermeasures. The time spent with patients emphasizing these practical management principles is of inestimable value. These include moving from a supine to standing position in gradual stages; avoiding orthostatic stress in the morning when orthostatic tolerance is lowest [24]; minimizing straining and isometric exercise; should be discouraged; and avoiding deconditioning. Frequent small meals are preferable as food ingestion often exacerbates orthostatic hypotension [19, 32].

Physical counter-maneuvers such as leg-crossing and squatting may be used to facilitate cerebral perfusion by increasing central blood volume and cardiac filling pressures [39]. The use of custom fitted elastic stockings may also be used to provide a graded pressure to the lower extremity and abdomen. Medications such as diuretics, anti-hypertensive agents, anti-anginal agents, anti-depressants and alpha adrenoreceptor antagonists should be tapered as these can cause or exacerbate orthostatic hypotension.

Abstract

Orthostatic hypotension is treated effectively with the combined use of non-pharmacological and pharmacological interventions. Patients should be counseled as to the nature of the underlying disorder and reversible causes of orthostatic hypotension should be removed. Should symptoms persist, pharmacological treatment is implemented. First line pharmacotherapeutic interventions include volume repletion in combination with alpha-adrenoceptor agonists. If unsuccessful there are several supplementary agents with different mechanisms of action that may provide an additive effect.

Key words

orthostatic hypotension Æ syncope Æ autonomic failure Æ sympathetic nervous system
Volume expansion

Administration of fluid and sodium chloride

Plasma volume expansion is essential to improve orthostatic tolerance. The high nocturnal blood pressure causes a pressure natriuresis and results in nocturnal volume and sodium chloride depletion. Several measures are available for maintaining and repleting plasma volume (See Table 1). Patients should have a daily dietary intake of at least 10 g (185 mmol) of sodium per day accompanied by an increase in fluid intake of 2–2.5 l (in adults) per day. An early morning body weight gain of about 1–2 kg usually implies adequate extra-cellular fluid volume expansion [38].

Ingestion of approximately 500 cc of tap water elicits a marked pressor response and improvement in symptoms in patients with autonomic failure. The pressor response, a systolic blood pressure increase of over 30 mmHg in some patients, is evident within 5 minutes after the water ingestion [14].

9-α-Fluorohydrocortisone

9-α-Fluorohydrocortisone (fludrocortisone acetate), a synthetic mineralocorticoid, may be used if patients are unable to increase plasma volume effectively with fluid and salt [3, 11, 18]. This agent has a long duration of action and is well-tolerated by most patients. Fludrocortisone increases the blood volume and enhances the sensitivity of blood vessels to circulating catecholamines [7, 11]. Other potential modes of action include enhancing norepinephrine release from sympathetic neurons and increasing vascular fluid content [34].

Treatment is initiated with a 0.1 mg tablet and can be increased to 0.3–0.5 mg daily [38]. Treatment may unfortunately be limited by supine hypertension due to an increase in the peripheral vascular resistance [4]. Other side effects include ankle edema, hypokalemia, headache and rarely congestive heart failure. Potassium supplementation is usually required, particularly when higher doses are used.

Vasopressin analogs

The vasopressin analogs may be used to supplement volume expansion. Arginine-vasopressin has a circadian rhythm that peaks during the night. Thus, the increase in nocturnal urinary excretion in patients with autonomic failure, which is in part due to the increase in supine blood pressures, is also due to loss of vasopressin neurons in the suprachiasmatic nucleus of the hypothalamus and the ensuing loss of the normal AVP circadian rhythm [27].

The potent, synthetic vasopressin analog desmopressin acetate (DDAVP) acts on the V2 receptors in the collecting ducts of the renal tubules and prevents nocturia, weight loss and reduces the morning postural fall in blood pressure. DDAVP is usually administered as a nasal spray (5–40 μg) or orally (100–800 μg). Adverse events include water intoxication and hyponatremia [21]. Low doses of intranasal desmopressin (5 μg) may be sufficient to attenuate the nocturnal diuresis without placing the patient at risk for hyponatremia [33].

Sympathomimetic agents

The administration of sympathomimetic agents is central to the management of patients with cardiovascular autonomic failure. Thus, if symptoms of orthostatic intolerance persist once intravascular volume is replenished the direct or indirect adrenergic agonists and antagonists should be administered (See Table 2). The pressor response of these agents is due to the reduction in venous capacity and the constriction of the resistance vessels.

The available ɑ1-adrenoreceptor agonists include those with direct and indirect effects (ephedrine, pseudoephedrine), those with direct effects (midodrine and phenylephrine) and those with only indirect effects (methylphenidate and dextroamphetamine sulphate).

The peripheral selective direct, ɑ1-adrenoreceptor agonist midodrine is the only agent approved by the FDA for the treatment of orthostatic hypotension [20]. Its efficacy has been demonstrated in double-blind placebo controlled studies [15, 20, 42]. Midodrine, the prodrug is activated to desglymidodrine, the active ɑ-adrenoreceptor agonist. Midodrine has an elimination half life of 0.5 hours and is undetectable in plasma 2 hours after an oral dose. The agent undergoes enzymatic hydrolysis (deglycination) in the systemic circulation to form the active agent, desglymidodrine. Desglymidodrine is 15 times more potent than midodrine and is primarily responsible for the therapeutic effect. The elimination half-life of

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<td>Fluid and sodium chloride</td>
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<td>9-α-Fluorohydrocortisone</td>
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<td>Vasopressin analogs</td>
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<td>Acute water ingestion</td>
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<th>Table 2 Sympathomimetic agonists</th>
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<tr>
<td>Midodrine</td>
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<td>Ephedrine</td>
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<td>Pseudoephedrine</td>
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<td>Methylphenidate</td>
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<td>Dextroamphetamine</td>
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Desglymidodrine is 2–4 hours. Desglymidodrine is predominantly excreted by the kidneys. Patient sensitivity to this agent varies and the dose should be titrated from 2.5 mg to 10 mg three times a day. The peak effect of this agent occurs 1 hour after ingestion [42]. Potential side effects of midodrine include pilomotor reactions, pruritus, supine hypertension, gastrointestinal complaints, and urinary retention. Central nervous system side-effects occur infrequently.

The mixed α-adrenoreceptor agonists—which act directly on the α-adrenoreceptor and release norepinephrine from the post-ganglionic sympathetic neuron—include ephedrine, pseudoephedrine. There are structural, pharmacological and therapeutic differences between these agents and midodrine. Ephedrine is an agonist of α, β1 and β2 receptors. The β2 vasodilatory effects may attenuate the pressor effect of this drug. Pseudoephedrine, a stereoisomer of ephedrine has similar pharmacological and therapeutic properties [13]. Typical doses of the agents are ephedrine: 25–50 mg three times a day; and pseudoephedrine: 30–60 mg three times a day. Because the effectiveness of these agents is at least in part due to the release of norepinephrine from the post-ganglionic neuron, these medications are in theory most likely to benefit patients with partial or incomplete lesions [1, 6, 10]. The indirect agonists, methylphenidate and dextroamphetamine, that release norepinephrine from post-ganglionic neurons are infrequently used to treat orthostatic hypotension. In a small head-to-head trial midodrine (mean dose 8.4 mg tid) improved standing blood pressure and orthostatic tolerance more than ephedrine (22.3 mg tid) [8]. In another trial, phenylpropanolamine (12.5 mg) and yohimbine (5.4 mg) produced equivalent increases in standing systolic blood pressure while methylphenidate failed to increase standing systolic blood pressure significantly [13].

The use of the sympathomimetic agents (with the possible exception of midodrine) may be complicated by tachyphylaxis, although efficacy may be regained after a short drug holiday. The central sympathomimetic side-effects such anxiety, tremulousness and tachycardia that invariably accompany the use of these agents are frequently intolerable to patients. Midodrine, which does not cross the blood brain barrier in significant amounts, does not have these central sympathomimetic side-effects. There is evidence that phenylpropanolamine increases the risk of hemorrhagic stroke in women [16] and the FDA has suggested that phenylpropanolamine be removed from all drug products.

Severe hypertension is an important adverse-effect of all sympathomimetic agents. Patients should not take these medications for 4 hours prior to recumbency. Patients taking midodrine report piloerection, pruritus and tingling. These are most likely peripheral sympathomimetic effects of the drug.

### Supplementary therapy

There are rare patients who do not respond to first line interventions and require additional agents to treat their symptoms. These supplementary agents may provide an additive therapeutic effect to the first-line therapies (see Table 3).

### Acetylcholinesterase inhibition

The acetylcholinesterase inhibitor, pyridostigmine, (60 mg) administered orally increased head-up tilt blood pressure and reduced orthostatic hypotension in patients with neurogenic orthostatic hypotension. The associated increase in supine blood pressure may not be as great as that seen with other pressors. Twenty percent of patients report cholinergic side-effects. The rationale for the use of this agent is that inhibition of acetylcholinesterase enhance sympathetic ganglionic neurotransmission and that the effect is maximal while upright, when sympathetic nerve traffic is greatest [35].

### Caffeine

The methylxanthine caffeine has a well-established, although modest, pressor effect that is in part due to blockade of vasodilating adenosine receptors. The pressor effect is subject to tachyphylaxis. Typical caffeine doses are 100–250 mg three times a day, either as tablets or caffeinated beverages (one cup of coffee contains approximately 85 mg of caffeine and one cup tea contains 50 mg of caffeine) [25].

### Erythropoietin

Erythropoietin increases standing blood pressure and improves orthostatic tolerance in patients with orthostatic hypotension [12, 28]. This agent corrects the normochromic normocytic anemia that frequently accompanies autonomic failure [2, 41] and diabetic autonomic neuropathy [40].
Recombinant human erythropoietin, erythropoietin alpha, is administered subcutaneously or intravenously at doses between 25 and 75 U per kg three times a week until a hematocrit that approaches normal is attained. Lower maintenance doses (approximately 25 U per kg three times a week) may then be used. Iron supplementation is usually required, particularly during the period when the hematocrit is increasing. Erythropoietin increases red cell mass and central blood volume although the precise mechanism of action of this agent is not resolved. There is evidence that the effect of erythropoietin is related to vascular tone regulation mediated by the interaction between hemoglobin and the vasodilator nitric oxide [29]. Supine hypertension may accompany the use of erythropoietin [12, 28].

β-Blockers

Nonselective β-blockers, particularly those with intrinsic sympathomimetic activity such as pindolol and xamoterol, may have a limited place in the treatment of orthostatic hypotension despite the well-acknowledged negative chronotropy and inotropy associated with these medications [5, 22, 23, 37]. The suggested mechanism of action of these medications is the blockade of vasodilating β-2 receptors allowing unopposed α-adrenoreceptor mediated vasoconstrictor effects to dominate. The pressor effect of these agents has not been demonstrated consistently in clinical trials [17].

Clonidine

Clonidine is an α2 agonist that usually produces a central, sympatholytic effect and a consequent decrease in blood pressure. In patients with autonomic failure, who have little central sympathetic efferent activity, the effect of this agent on post synaptic α2 adrenoreceptors may predominate. The use of clonidine (0.1–0.6 mg per day) could therefore result in an increase in venous return without a significant increase in peripheral vascular resistance although mechanism of action is still not clearly defined [36]. The use of this agent, at least theoretically, is limited to patients with severe central autonomic dysfunction in whom there is no ostensible effect of further sympatholysis and the peripheral effect may dominate [30, 31]. Clonidine should be used cautiously as exacerbation of hypotension may occur. Side-effects include somnolence, xerostomia and constipation.

Yohimbine

Yohimbine is a centrally and peripherally active selective α2 adrenoreceptor antagonist that increases sympathetic nervous system efferent output by antagonizing central or presynaptic α2-adrenoreceptors or both. This agent, theoretically, should be more effective in patients that have some residual sympathetic nervous system output, although this has not always been borne out in clinical studies. Side effects of yohimbine include anxiety, tremor, palpitations, diarrhea and supine hypertension [13, 26].

Conclusion

With the help of non-pharmacological and pharmacological interventions, most patients' quality of life can be improved substantially. Treatment should be initiated in stages. First, patients should be counseled as to the nature of the underlying disorder and reversible causes of orthostatic hypotension should be removed. If symptoms persist, pharmacological treatment is implemented. Many patients will be adequately treated by education, counseling, removal of hypertensive medications and other non-pharmacological interventions while more severely afflicted patients require pharmacological interventions.

Disclosure

Dr. Freeman has served as a consultant for Chelsea Therapeutics.

References

L-dihydroxyphenylserine (Droxidopa): a new therapy for neurogenic orthostatic hypotension
The US experience

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Abstract Neurogenic orthostatic hypotension results from failure to release norepinephrine, the neurotransmitter of sympathetic postganglionic neurons, appropriately upon standing. In double blind, cross over, placebo controlled trials, administration of droxidopa, a synthetic amino acid that is decarboxylated to norepinephrine by the enzyme L-aromatic amino acid decarboxylase increases standing blood pressure, ameliorates symptoms of orthostatic hypotension and improves standing ability in patients with neurogenic orthostatic hypotension due to degenerative autonomic disorders. The pressor effect results from conversion of droxidopa to norepinephrine outside the central nervous system both in neural and non-neural tissue. This mechanism of action makes droxidopa effective in patients with central and peripheral autonomic disorders.

Key words autonomic failure · orthostatic hypotension · DOPS · droxidopa · multiple system atrophy · pure autonomic failure · Parkinson’s disease · norepinephrine · blood pressure · autonomic nervous system

Horacio Kaufmann

Autonomic failure, like Parkinson’s disease, is a neurotransmitter disorder. While Parkinson’s disease is a disorder of dopamine neurotransmission, autonomic failure is a disorder of norepinephrine neurotransmission. The idea that deficient dopamine neurotransmission in Parkinson’s disease could be overcome by treatment with oral levodopa, the amino acid precursor of dopamine, led to the most successful therapeutic intervention in 20th century neurology.

Although levodopa is the amino acid precursor of both dopamine and norepinephrine, treatment with levodopa leads to an increase in dopamine but not to a significant increase in norepinephrine levels. Norepinephrine is synthesized from levodopa in two steps (Fig. 1). The first step is the decarboxylation of levodopa to dopamine by the enzyme L-aromatic amino acid decarboxylase. The second step, catalyzed by the enzyme dopamine beta hydroxylase, is the hydroxylation of dopamine to norepinephrine.
Dopamine beta hydroxylase is the rate-limiting enzyme and it creates a "bottle neck" like effect, so that taking levodopa orally results in an increase in dopamine levels but not to a significant increase in norepinephrine levels.

Fortunately, the possibility of overcoming this limitation and realizing another therapeutic breakthrough using a precursor amino acid to replace a deficient catecholamine neurotransmitter, in this case norepinephrine, was made possible by the discovery, in the 1950's, that an artificial amino acid, 3,4-threo-dihydroxyphenylserine, identical to levodopa but with an added beta hydroxyl group (Fig. 2) was converted to norepinephrine in a single step by L-aromatic amino acid decarboxylase, thus bypassing the need for dopamine beta hydroxylase and its bottle neck effect [3, 15].

Droxidopa was first used successfully to treat one particular form of autonomic failure: congenital deficiency of the enzyme dopamine beta hydroxylase. Robertson and Biaggioni and Man in’t Veld et al. showed that after oral administration, droxidopa was taken up by post-ganglionic sympathetic neurons, decarboxylated to NE, stored and released appropriately when standing up [2, 12]. Droxidopa has now been used to treat orthostatic hypotension in several autonomic disorders, including familial amyloid polyneuropathy [16], autoimmune autonomic neuropathy [5], pure autonomic failure (PAF), Parkinson’s disease and multiple system atrophy [MSA; 4, 10, 11, 13].

3,4-Threo-dihydroxyphenylserine has four stereoisomers [1]. Early studies used a racemic mixture that contained both the D and L isoforms of 3,4-threo-dihydroxyphenylserine but only the L-isoform is converted to biologically active L-norepinephrine. Furthermore, the D-stereoisomer of 3,4-threo-dihydroxyphenylserine might competitively inhibit the decarboxylation of the L stereoisomer to L-norepinephrine [8]. Thus, the pure L isoform of 3,4-threo-dihydroxyphenylserine (droxidopa) is the preferred formulation for treatment.

Here I will review the most recent studies conducted in the United States using droxidopa in the treatment of orthostatic hypotension in patients with degenerative autonomic disorders, including PAF and MSA.

**Studies of droxidopa in the United States**

We conducted a comprehensive study of droxidopa in patients with severe symptomatic orthostatic hypotension due to MSA or PAF [11]. We examined the effect of droxidopa on standing blood pressure and orthostatic tolerance, as well as its pharmacokinetics and its mechanism of action.
Dose titration study

Because patients with autonomic failure have different degrees of adrenergic denervation supersensitivity, we individualized the dose of droxidopa for each patient in a single blind dose-ranging study.

Patients received progressively higher dosages of droxidopa, beginning with 200 mg followed by 400, 1,000, 1,600, and 2,000 mg on successive days. The dose ranging study was terminated when the orthostatic fall in systolic blood pressure after 3 min of standing was consistently < 20 mm Hg, or the patient had a sustained supine systolic blood pressure of > 200 mm Hg or diastolic pressure of > 110 mm Hg; or when a maximum dose of 2,000 mg of droxidopa was reached. The optimal dose of droxidopa varied between 200 mg and 2,000 mg (mean dose ± SE was 1,137 ± 131 mg).

Double blind, crossover, placebo controlled study

Once the individual dose of droxidopa was determined, patients were enrolled in a double blind crossover study lasting 3 days. On days 1 and 3 either droxidopa (at the dose previously determined in the dose ranging study) or placebo was given at 7:00 am. Day 2 was a washout day. As shown in Fig. 3 administration of droxidopa significantly increased blood pressure in all patients (P < 0.05 vs. placebo). All data are mean ± SEM, (n = 19). Data from Kaufmann et al. [11]

Adverse events

Droxidopa was well tolerated by all patients and there were no significant side effects. The frequency of supine hypertension (systolic pressure > 180, diastolic > 110 mmHg or both) was higher on droxidopa than on placebo (45% vs. 23% of blood pressure measurements, P < 0.00001). After receiving droxidopa, the frequency of supine systolic and diastolic hypertension was similar in MSA and PAF patients. However, on placebo, diastolic, but not systolic, supine hypertension was more common in MSA patients than in PAF (25% vs. 3%, P < 0.05). One patient had hyponatremia, which reversed after saline infusion. Another patient had transitory chest pain with electrocardiographic ST segment depression, but cardiac enzymes were normal.

Mechanism and site of action of droxidopa

Droxidopa could exert its pressor effect in three different ways [9] (Fig. 4):

1. As a central stimulator of sympathetic activity. Because droxidopa crosses the blood brain barrier, it could, at least theoretically, act as a central stimulator of sympathetic outflow. It could be converted to epinephrine and activate sympathetic preganglionic neurons in the spinal cord.

2. As a peripheral sympathetic neurotransmitter. As it had been shown in patients with dopamine beta hydroxylase (DBH) deficiency [2, 12] droxidopa could be taken up by post ganglionic peripheral sympathetic neurons, transformed to norepinephrine intraneuronally, and released when sympathetic neurons are activated, i.e., act as a physiologic sympathetic neurotransmitter in peripheral sympathetic neurons.
3. As a *circulating hormone*. Norepinephrine synthesized from droxidopa could also act as a circulating hormone. The enzyme aromatic aminoacid decarboxylase is widely expressed throughout the body, in the stomach, kidney and liver. Thus, droxidopa could be converted to norepinephrine outside neurons, and then released into the blood stream where it would exert a pressor effect as a circulating hormone.

### Decarboxylase inhibitor study

To determine whether the pressor action of droxidopa was due to its metabolism to norepinephrine inside or outside the central nervous system we used carbidopa as a pharmacological probe [11]. Carbidopa is an inhibitor of L-aromatic-amino-acid decarboxylase that does not cross the blood-brain barrier. Therefore, carbidopa's inhibition of L-aromatic-amino-acid decarboxylase and its blockade of norepinephrine synthesis from droxidopa is confined to tissues outside the brain and it does not affect the decarboxylation of droxidopa to norepinephrine within the central nervous system.

If the mechanism of action of droxidopa is in the central nervous system, a large dose of carbidopa taken before droxidopa should not prevent its pressor effect. Indeed, it may even increase its pressor effect, similarly to the enhanced anti parkinsonian effect of levodopa when it is administered with carbidopa. Conversely, if the mechanism of action of droxidopa is through its conversion to norepinephrine outside the central nervous system, either in neural or non-neural tissue, then concomitant administration of carbidopa will block the pressor effect of droxidopa.

In a double-blind placebo controlled study, six patients [11] sequentially received droxidopa alone on day 1, 200 mg of carbidopa alone on day 2, and 200 mg of carbidopa combined with droxidopa on day 3. As expected, droxidopa taken alone increased standing blood pressure in all patients. Carbidopa taken alone had no effect on blood pressure. However, when carbidopa was administered together with droxidopa the increase in blood pressure previously seen with droxidopa alone was completely abolished (Fig. 5). From this study we concluded that the pressor effect of droxidopa was due to its conversion into norepinephrine outside the brain, either in neuronal or non-neuronal tissues.

After carbidopa administration plasma levels of droxidopa were higher than when droxidopa was administered without carbidopa (4,556 ± 1,011 ng/ml, \( P < 0.01 \), versus droxidopa alone). In addition, carbidopa markedly attenuated the increase in plasma norepinephrine levels. Six hours after concomitant carbidopa and droxidopa administration, the venous plasma norepinephrine level had only increased from 216 ± 125 to 407 ± 271 pg/ml (\( P < 0.05 \), versus droxidopa alone).

### Droxidopa in patients with PD taking levodopa and a decarboxylase inhibitor

Levodopa/carbidopa therapy is a mainstay in the treatment of Parkinson disease. Because carbidopa inhibits the conversion of droxidopa to norepinephrine, droxidopa may be ineffective in the treatment of
orthostatic hypotension in patients with Parkinson disease treated with levodopa/carbidopa. However, to block the pressor effect of droxidopa it is necessary to completely inhibit the enzyme aromatic aminoacid decarboxylase. To achieve complete inhibition of aromatic aminoacid decarboxylase a high dose of carbidopa (200 mg) is required. Lower dosages of carbidopa, such as those commonly used to treat Parkinson disease, should not abolish the pressor effect of droxidopa. Indeed, studies of droxidopa in Europe included patients with PD who were also taking benzeraside, an aromatic aminoacid decarboxylase inhibitor, at a low dose, together with levodopa (i.e., Madopar, see Mathias, this supplement). Because benzerazide at a low dose does not completely inhibit the enzyme aromatic aminoacid decarboxylase, patients with PD still experienced the desired pressor effect of droxidopa.

Therapeutic implications

A peripheral mechanism of action makes droxidopa an exciting new treatment option in both central and peripheral autonomic disorders. In patients with destruction of peripheral autonomic neurons (i.e., in the Lewy body disorders), droxidopa can be converted to norepinephrine in non-neuronal tissues, released to the blood stream and act as a circulating vasoconstrictor hormone. In patients with central autonomic disorders and preserved peripheral autonomic neurons (i.e., MSA), droxidopa is converted to norepinephrine outside the central nervous system, both in neuronal and non-neuronal tissue. In these patients, droxidopa-derived norepinephrine acts as a neurotransmitter and a circulating hormone.

Pharmacokinetic study

We investigated the pharmacokinetics of droxidopa and the generated norepinephrine and determined the relationship between the pressor response and venous plasma norepinephrine levels [6, 11]. The peak droxidopa level of 1,942 ± 224 ng/ml was attained 3 h after its ingestion (P < 0.001). Plasma norepinephrine increased from the baseline level of 294 ± 80 pg/ml to 806 ± 235 pg/ml (P < 0.05) 2 h after droxidopa administration. Norepinephrine peaked at 1,250 ± 208 pg/ml 6 h after droxidopa ingestion (P < 0.005, see Fig. 6). Plasma levels of norepinephrine remained significantly elevated for at least 46 h. The levels of norepinephrine associated with an increase in blood pressure were above 700 pg/ml (see Fig. 7), similar to the norepinephrine levels necessary to increase blood pressure when norepinephrine is infused.

Fig. 5 Droxidopa plus decarboxylase inhibitor study. The effect of droxidopa, decarboxylase inhibitor (DCI), droxidopa and DCI, and placebo on mean arterial pressure (MAP) after 3 min standing. Time 0 (arrow) represents the time of drug administration (7 am). Meals were served at −1 (6 am) and 6 h (1 pm). *P < 0.05 (versus placebo). All data are mean ± SEM, (n = 6). Data from Kaufmann et al. [11]

Fig. 6 Plasma levels of droxidopa and norepinephrine. Venous plasma levels of droxidopa and norepinephrine after droxidopa administration (Time 0, 7 am). Meals were served at −1 (6 am) and 6 h (1 pm). All data are mean ± SEM, (n = 8). Data from Kaufmann et al. [11]

Fig. 7 Relationship between blood pressure and norepinephrine levels after droxidopa administration. Changes in systolic blood pressure (SBP) versus plasma concentration of norepinephrine after droxidopa administration. Solid curve represents the line of best fit. All data are mean ± SEM, (n = 8). Data from Kaufmann et al. [11]
Responses in patients with MSA and patients with PAF

Prior to droxidopa ingestion, MSA and PAF patients had similar blood pressures and similar heart rates, both while supine and while standing. The mean dose of droxidopa in the MSA group was $1,327 \pm 441$ mg (mean ± SD) for a mean weight of $77 \pm 21$ kg. Following droxidopa administration, systolic blood pressure in the supine position increased more in patients with PAF than in patients with MSA ($P < 0.05$). There was a trend towards higher systolic blood pressure in patients with PAF after 1 min in the standing position but this did not reach statistical significance. The finding that the pressor response to droxidopa in supine patients with PAF was more pronounced than in patients with MSA indicate a peripheral mechanism of action. Indeed, because of their widespread loss of sympathetic terminals, patients with PAF have markedly exaggerated pressor responses to circulating norepinephrine [7, 14].

In summary, Droxidopa effectively raises standing blood pressure and ameliorates symptoms of orthostatic hypotension in patients with central and peripheral autonomic disorders. The pressor effect of droxidopa is due to its conversion to norepinephrine outside the brain, both in neuronal and non neuronal tissues. In patients with peripheral autonomic disorders and degeneration of sympathetic neurons (e.g. PAF), droxidopa is converted to norepinephrine in non neuronal tissue. In patients with central autonomic degeneration and preserved peripheral sympathetic neurons (e.g. MSA), droxidopa is converted to norepinephrine in neuronal and non neuronal tissue.

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References

L-dihydroxyphenylserine (Droxidopa) in the treatment of orthostatic hypotension
The European experience

Abstract

Neurogenic orthostatic hypotension is a cardinal feature of generalised autonomic failure and commonly is the presenting sign in patients with primary autonomic failure. Orthostatic hypotension can result in considerable morbidity and even mortality and is a major management problem in disorders such as pure autonomic failure, multiple system atrophy and also in Parkinson’s disease. Treatment is ideally two pronged, using non-pharmacological and pharmacological measures.

Drug treatment ideally is aimed at restoring adequate amounts of the neurotransmitter noradrenaline. This often is not achievable because of damage to sympathetic nerve terminals, to autonomic ganglia or to central autonomic networks. An alternative is the use of sympathomimetics (that mimic the effects of noradrenaline, but are not identical to noradrenaline), in addition to other agents that target physiological mechanisms that contribute to blood pressure control.

L-threo-dihydroxyphenylserine (Droxidopa) is a pro-drug which has a structure similar to noradrenaline, but with a carboxyl group. It has no pressor effects in this form. It can be administered orally, unlike noradrenaline, and after absorption is converted by the enzyme dopa decarboxylase into noradrenaline thus increasing levels of the neurotransmitter which is identical to endogenous noradrenaline. Experience in Caucasians and in Europe is limited mainly to patients with dopamine beta hydroxylase deficiency. This review focuses on two studies performed in Europe, and provides information on its efficacy, tolerability and safety in patients with pure autonomic failure, multiple system atrophy and Parkinson’s disease. It also addresses the issue of whether addition of dopa decarboxylase inhibitors, when combined with l-dopa in the treatment of the motor deficit in Parkinson’s disease, impairs the pressor efficacy of Droxidopa.

Key words

L-dihydroxyphenylserine · orthostatic hypotension · autonomic failure · noradrenaline · multiple system atrophy · Parkinson’s disease
Introduction

Orthostatic (or postural) hypotension (OH) is a cardinal manifestation of generalised autonomic failure and often is the presenting feature in patients with primary autonomic failure due to pure autonomic failure (PAF) and multiple system atrophy (MSA) [9]. It is increasingly recognised also in Parkinson’s disease [11]. It results in a number of symptoms, mainly as a result of hypoperfusion of organs, including the skeletal musculature. Organs above the level of the heart, such as the brain, are particularly susceptible to hypoperfusion; this can result in dizziness, visual disturbances, cognitive deficits and loss of consciousness [1, 6]. Orthostatic hypotension can reduce mobility, result in falls, and may cause death. The symptomatic consequences of OH, taken together can substantially reduce a patient’s quality of life.

There are many causes of OH that can be considered under the mechanisms responsible - neurogenic, non-neurogenic and drug induced [12]. Non-neurogenic OH is rectified more readily than neurogenic OH, which often is difficult to treat, with management dependent on a combination of non-pharmacological measures and drugs [3, 10]. A key factor in neurogenic OH is reduction in sympathetic nerve activity, and thus a reduction of the neurotransmitter, noradrenaline at the synaptic cleft. To replace this deficiency, a variety of drugs that mimic noradrenaline have been used, that include ephedrine and midodrine, which are of partial benefit and have limitations to their use because of adverse effects. The ideal approach would be replacement of noradrenaline itself.

L-threo-dihydroxyphenylserine (Droxidopa) has a structure which is similar to noradrenaline but with a carboxyl group. It can be administered orally, and is acted upon by the ubiquitous enzyme L-aromatic amino acid decarboxylase (dopa decarboxylase), which is found all over the body. It is converted directly to noradrenaline. It is likely to have both neuronal and extra neuronal effects, with a direct effect through noradrenaline on target organs. Droxidopa has been highly successful in replacing deficient or absent noradrenaline in patients with dopamine beta hydroxylase deficiency [4, 5, 15]. In Japan, it has been approved since 1989 use for in the treatment of neurogenic OH due to various disorders, that include familial amyloid polyneuropathy, haemodialysis induced hypotension, and MSA and PD [8, 14, 16, 17, 18]. Experience with Droxidopa, especially in primary autonomic failure and PD in Caucasians is limited. Because of its potential value in the management of symptomatic orthostatic hypotension, two Phase II studies were performed in Europe. These were multicentre, multinational studies. An escalating dose of Droxidopa was used in the first study in patients with PAF and MSA. In the second a randomised double blind placebo controlled study was performed using three doses of Droxidopa in patients with MSA or PD.

This review will describe key components from each of these studies, and will focus on whether inhibition of the enzyme dopa decarboxylase, which converts Droxidopa to noradrenaline, can influence its ability to reduce orthostatic hypotension.

Droxidopa in pure autonomic failure and multiple system atrophy

This study was performed in 6 PAF and 26 MSA patients with symptomatic orthostatic hypotension [7]. It was an open dose ranging study with a one week run in period, following which three doses of Droxidopa, 100, 200 and 300 mg were administered twice daily. The incremental dose adjustment was dependent on the blood pressure response and an improvement in symptoms. When optimum dosage was reached the dosage was maintained for a 6 week period. The study therefore determined both the efficacy and the tolerability of increasing doses of Droxidopa in treating symptomatic orthostatic hypotension in PAF and MSA. This dose escalating trial was performed in ten centres within three countries in Europe. A key primary variable was to determine the extent of decrease in orthostatic fall in systolic blood pressure.

Table 1 provides details of the response to Droxidopa. The effects of Droxidopa persisted even at the last individual visit, with orthostatic systolic blood pressure reductions of 20, 29 and 23 mmHg respectively. In 25 patients (78%) OH had improved, and in 14 (44%) OH was not measurable. Importantly the mean supine systolic BP levels were not elevated (Table 1). Thus Droxidopa, particularly in the highest doses, was efficacious in reducing OH (Fig. 1).

In this study, symptoms associated with orthostatic hypotension, that included light headedness, dizziness and blurred vision were assessed while on and when off Droxidopa drug. These were evaluated using bi-polar scales with ten point numeric objectivity. They showed an improvement in both objective and subjective evaluations of benefit (Fig. 2).

Droxidopa was well tolerated. There were two serious adverse events; laryngeal dyspnoea and syncope. The first was on 100mg twice daily and the second on 300 mg twice daily. Both could be attributed to the disease itself rather than to the drug. Supine hypertension was not reported.
In summary, Droxidopa was an effective drug which reduced the orthostatic fall in blood pressure in patients with PAF and MSA. It improved symptoms of OH and was well tolerated. It did not result in supine hypertension. The most effective of the three tested doses was 300 mg twice daily.

### Table 1 Dose effects of L-threo-DOPS (Droxidopa) expressed as change from baseline, in multiple system and pure autonomic failure patients.

<table>
<thead>
<tr>
<th>L-threo-DOPS dose</th>
<th>100 mg twice daily</th>
<th>200 mg twice daily</th>
<th>300 mg twice daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>Last individual visit per dose*</td>
<td>n = 32*</td>
<td>n = 25*</td>
<td>n = 17*</td>
</tr>
<tr>
<td>Baseline orthostatic SBP decrease</td>
<td>54.3 ± 27.7</td>
<td>55.8 ± 24.6</td>
<td>60.6 ± 24.9</td>
</tr>
<tr>
<td>Final visit supine SBP</td>
<td>120.9 ± 31.6</td>
<td>118.9 ± 30.3</td>
<td>117.2 ± 31.9</td>
</tr>
<tr>
<td>Reduction in orthostatic SBP decrease</td>
<td>−23.2 ± 28.0</td>
<td>−28.4 ± 54.4</td>
<td>−22.7 ± 36.4</td>
</tr>
<tr>
<td>Reduction in orthostatic DBP decrease</td>
<td>−9.4 ± 17.0</td>
<td>−10.9 ± 31.0</td>
<td>−11.5 ± 22.6</td>
</tr>
<tr>
<td>Noradrenaline while supine</td>
<td>562.5 ± 1,024.2 (n = 30)</td>
<td>779.5 ± 1,214.1 (n = 23)</td>
<td>966.1 ± 969.3 (n = 14)</td>
</tr>
<tr>
<td>Noradrenaline at end of standing period†</td>
<td>1,096.8 ± 1,228.8</td>
<td>1,350.1 ± 1,612.4</td>
<td>1,361.9 ± 864.3 (n = 16)</td>
</tr>
<tr>
<td>Last individual visit*</td>
<td>n = 7*</td>
<td>n = 8*</td>
<td>n = 17*</td>
</tr>
<tr>
<td>Baseline orthostatic SBP decrease</td>
<td>48.7 ± 38.8</td>
<td>45.6 ± 22.0</td>
<td>60.6 ± 24.9</td>
</tr>
<tr>
<td>Final visit supine SBP</td>
<td>129.3 ± 28.4</td>
<td>114.1 ± 24.6</td>
<td>117.1 ± 31.9</td>
</tr>
<tr>
<td>Reduction in orthostatic SBP decrease</td>
<td>−19.7 ± 13.9</td>
<td>−28.5 ± 22.2</td>
<td>−22.7 ± 36.4</td>
</tr>
<tr>
<td>Reduction in orthostatic DBP decrease</td>
<td>−9.2 ± 8.8</td>
<td>−5.1 ± 8.6</td>
<td>−11.5 ± 22.6</td>
</tr>
<tr>
<td>Noradrenaline while supine</td>
<td>472.1 ± 341.7</td>
<td>379.6 ± 394.9 (n = 7)</td>
<td>966.1 ± 969.3 (n = 14)</td>
</tr>
<tr>
<td>Noradrenaline at end of standing period†</td>
<td>1,304.6 ± 1,077.5</td>
<td>1,303.5 ± 1,659.8</td>
<td>1,361.9 ± 864.3 (n = 16)</td>
</tr>
</tbody>
</table>

Analysis used all available data, with n values as shown in asterisked (*) rows unless otherwise specified against mean values. Orthostatic blood pressure decrease data were obtained after 5 min standing and are measured in mm Hg. Noradrenaline plasma concentration are pg/ml

† Data for noradrenaline at end of standing time represent actual values and are not presented as change from baseline

SBP = systolic blood pressure; DBP = diastolic blood pressure


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**Fig. 1** Orthostatic systolic blood pressure decrease at baseline and at individual last visit. Individual orthostatic blood pressure decrease (mm Hg) after 5 minutes' standing at last visit is plotted against decrease at baseline (all 32 “efficacy-evaluable” patients). Each point below the line represents a patient whose condition improved between baseline and last visit, and every point above this line a patient whose condition deteriorated. From: Mathias CJ, Senard J-M, Braune S, Watson L, Aragishi A, Keeling J, Taylor M. L-threo-dihydroxypheynlserine (L-threo-DOPS; droxidopa) in the management of neurogenic orthostatic hypotension: a multi-national, multi-centre, dose-ranging study in multiple system atrophy and pure autonomic failure. Clin Aut Res 2001, 11; 235–242.

**Droxidopa in multiple system atrophy and in Parkinson’s disease**

This study was designed to determine the minimum effective dose of Droxidopa that safely reduced the orthostatic fall in systolic blood pressure in comparison with placebo. After screening and evaluation a total of 121 patients with either MSA or PD were randomized and received doses of 100, 200, 300 mg of Droxidopa or matching placebo. The drug was administered three times daily, as was placebo. It was conducted in 30 centres within 4 European countries. The screening period was between two seven days and the treatment continued for 28 days. Data was obtained in 55 patients with MSA and in 66 with Parkinson’s disease. A preliminary report recently has been presented [13].

Droxidopa treatment resulted in a reduction in the orthostatic fall in blood pressure with each of the Droxidopa doses, unlike with placebo. It was noted that in the previous study the same patient had escalating doses with individual comparisons, unlike this second study with different individuals on different doses of drugs. There was no clear dose response improvement but the 300 mg dose was the
most effective in reducing OH. Even with this dose mean levels of supine blood pressure were not elevated after acute or chronic dosage. The drug remained efficacious 28 days of treatment.

In this study up to 900mg of Droxidopa was used each day, and adverse effects on heart rate were analysed. There was neither bradycardia nor tachycardia with any of the doses, at day 0 or after 28 days of treatment.

The majority of patients in this study had mild to moderate symptoms of dizziness, tiredness and visual disturbance. There was no loss of consciousness before or after drug or placebo treatment. There was an overall trend towards improvement in symptoms but this did not reach statistical significance. The reasons for the apparent dissociation between objective improvement in OH and subjective reduction in symptoms remains unclear. It may reflect the different individual characteristics of each group, or insensitivity of the symptom scales used.

Droxidopa was well tolerated, with similar adverse effects in each of the treatment groups when compared with placebo. Most of the symptoms were mild. One patient had supine hypertension.

In summary, therefore, 300 mg tid of Droxidopa was more effective than either 100 or 200 mg in the majority of patients with MSA or PD. It was well tolerated and with few side effects.

**Droxidopa in patients on dopa decarboxylase inhibitors**

Dopa decarboxylase is essential for the conversion of Droxidopa into noradrenaline and would be expected noradrenaline to reduce the formation of a dopa decarboxylase inhibitor and thus the prodrugs pressor effect. In each of the studies described there were patients treated with a combination of L-dopa and dopa decarboxylase inhibitors. In the first study these included MSA patients, and in the second both MSA and PD patients.

There were no obvious differences in the beneficial response of Droxidopa in the first study with patients on a dopa decarboxylase inhibitor. Similar observations were made in the second study, where over 80% of the PD patients were on a dopa decarboxylase inhibitor. In a previous study in 4 PAF and 2 MSA patients, pre-treatment with 200mg of the dopa decarboxylase inhibitor Carbidopa, prior to Droxidopa, blunted the pressor effects of Droxidopa [2]. Plasma noradrenaline levels rose from 294 ± 80 to 806 ± 235 pg/mL in Droxidopa treated patients compared to 216 ± 125 to 407 ± 271 after Droxidopa treated patients had been pretreated with Carbidopa, which thus attenuated, but did not abolish, the rise in levels of plasma noradrenaline. It is important to note that the dose of carbidopa used in this study [2] was substantially higher than the dose used in clinical preparations when combined with l-dopa, these usually being 25mg for 100mg of l-dopa. In each of the European studies reported there was a beneficial pressor effect of Droxidopa despite the presence of a dopa decarboxylase inhibitor; this may reflect incomplete inhibition of dopa decarboxylase with the clinical preparations used to treat the motor deficits. The pressor effect may even have been higher without an inhibitor.

**Conclusions**

Treatment with Droxidopa, which results in the formation of noradrenaline, has been demonstrated
in two pan European studies to be effective, well tolerated and safe when used to treat orthostatic hypotension in patients with pure autonomic failure, multiple system atrophy, and Parkinson’s disease.

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Disclosure

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