HHS Public Access

Author manuscript

Auton Neurosci. Author manuscript; available in PMC 2021 December 01.

Published in final edited form as:

Auton Neurosci. 2020 December ; 229: 102721. doi:10.1016/j.autneu.2020.102721.

Pharmacologic treatment of orthostatic hypotension

Jin-Woo Park, MD, PhD[1,3], **Luis E. Okamoto, MD**[1], **Cyndya A. Shibao, MD**[1], **Italo Biaggioni, MD**[1,2]

[1]Division of Clinical Pharmacology, Department of Medicine, Vanderbilt University Medical Center, Nashville, TN

[2]Department of Pharmacology, Vanderbilt University Medical Center, Nashville, TN

[3]Institute for Inflammation Control, Korea University, Seoul, South Korea.

Abstract

Neurogenic orthostatic hypotension (OH) is a disabling disorder caused by impairment of the normal autonomic compensatory mechanisms that maintain upright blood pressure. Nonpharmacologic treatment is always the first step in the management of this condition, but a considerable number of patients will require pharmacologic therapies. Denervation hypersensitivity and impairment of baroreflex buffering makes these patients sensitive to small doses of pressor agents. Understanding the underlying pathophysiology can help in selecting between treatment options. In general, patients with low “sympathetic reserve”, i.e., those with peripheral noradrenergic degeneration (pure autonomic failure, Parkinson’s disease) and low plasma norepinephrine, tend to respond better to “norepinephrine replacers” (midodrine and droxidopa). On the other hand, patients with relatively preserved “sympathetic reserve”, i.e., those with impaired central autonomic pathways but spared peripheral noradrenergic fibers (multiple system atrophy) and normal or slightly reduced plasma norepinephrine, tend to respond better to “norepinephrine enhancers” (pyridostigmine, atomoxetine, and yohimbine). There is, however, a spectrum of responses within these extremes, and treatment should be individualized. Other nonspecific treatments include fludrocortisone and octreotide. The presence of associated clinical conditions, such as supine hypertension, heart failure, and postprandial hypotension, need to be considered in the pharmacologic management of these patients.

Keywords

orthostatic hypotension; pharmacologic treatment

Correspondence to: Italo Biaggioni, MD, Division of Clinical Pharmacology, Departments of Medicine and Pharmacology, 560A RRB, Vanderbilt University, Nashville, TN 37232, 615-936-3420, italo.biaggioni@vumc.org.

1. Introduction

Orthostatic hypotension (OH), defined as a sustained reduction of systolic blood pressure (BP) of at least 20 mmHg, or of diastolic BP of 10 mmHg within 3 minutes of standing or at least 60 degree head up tilt (Freeman et al., 2011), is a disorder particularly prevalent in the elderly population and a cause of significant disability for those affected. Its presence is evidence of a failure of the compensatory autonomic mechanisms that normally maintain upright BP, most often as a consequence of systemic illnesses causing autonomic neuropathies (e.g., diabetes, amyloid, autoimmune or paraneoplastic disorders) or neurodegenerative disorders (pure autonomic failure [PAF], Parkinson's disease [PD], and multiple system atrophy [MSA]) (Arnold et al., 2013b; Robertson, 2008). In all cases, we first need to consider the possibility that OH is precipitated or worsened by reversible factors that overwhelm compensatory autonomic mechanisms already impaired by aging or disease. Hypertension, diabetes mellitus and heart failure are the most common comorbidities associated with OH. Thus, the initial treatment of OH should always be the removal of these aggravating factors. Medications are the most common culprit, in particular alpha-blockers (including tamsulosin, carvedilol), sympatholytics (including clonidine, tizanidine), vasodilators (nitrates, sildenafil citrate), and certain antidepressants (tricyclic antidepressants). This should be followed by educating the patients about conservative countermeasures, such as avoid standing motionless, wearing compression garments (Jordan et al., 2019; Okamoto et al., 2016), and increasing intake of water (1.5–2 L per day) and sodium (6–10 g per day) (Shibao et al., 2012). Water boluses can be effective also (Shannon et al., 2002). Still, these treatments may not be sufficient in a substantial proportion of patients, and additional pharmacological treatments, the focus of this review, may be needed.

2. Basic autonomic concepts that influence the selection of pharmacological treatment

There is little empirical evidence on which to base guidelines regarding the selection of the optimal pharmacologic treatment in a given patient, and this is left mostly to the clinician's experience and preference (Biaggioni, 2017). Nonetheless, understanding the basic concepts of the underlying pathophysiology of the patient's condition, and the clinical pharmacology of available therapies, is valuable in the management of these patients (Biaggioni, 2017). We will discuss the disease characteristics that affect the response to pharmacological treatment, followed by a discussion of the clinical pharmacology of individual medications.

2.1. Denervation hypersensitivity

Patients with autonomic impairment have an exaggerated response to both pressor and depressor stimuli because of denervation hypersensitivity. This explains the profound drop in BP in response to venous pooling induced by standing (orthostatic hypotension) or digestion (postprandial hypotension), but also the dramatic increase in BP observed after seemingly trivial stimuli (e.g., the water pressor reflex (Shannon et al., 2002)). Denervation hypersensitivity can also contribute to supine hypertension commonly seen in these patients (Arnold et al., 2012).

Two mechanisms can account for this hyperresponsiveness. First, and perhaps the most important, is the loss of baroreflex buffering that normally counteracts any change in BP. The second is upregulation of adrenergic receptors in response to the decreased exposure to norepinephrine (NE) resulting from the loss of noradrenergic nerve fibers (classical denervation hypersensitivity) (Benarroch, 2020; Jacob et al., 1999). Accordingly, intravenous administration of very low doses of alpha- or beta-adrenoreceptor agonists triggers exaggerated increases in BP and heart rate (HR), respectively (Nakamura et al., 2011; Niimi et al., 1999). This denervation hypersensitivity is easily explained in patients with peripheral neurodegeneration (i.e., PAF and PD), characterized by loss of postganglionic noradrenergic fibers and low plasma NE. However, it is also observed in patients with central neurodegeneration (i.e., MSA) and relatively preserved postganglionic fibers and plasma NE (Coon et al., 2018). The patient's hyperresponsiveness to pressor stimuli can be used to their advantage when developing treatments.

2.2. Residual sympathetic function ("sympathetic reserve")

Ultimately, OH is due to the inability of sympathetic nerves to release sufficient NE required to maintain upright BP. This is caused either by a loss of peripheral noradrenergic fibers (PAF and PD) or by impairment of central pathways that normally trigger sympathetic activation on standing (MSA). The former is characterized by low plasma NE (low sympathetic reserve) and the latter by normal or only slightly reduced plasma NE (residual sympathetic reserve). The functional relevance of these differences is evidenced by the observation that the ganglionic blocker trimethaphan, which interrupts the pathways that release NE in the peripheral nervous system, resulting in a profound decrease in of BP in MSA patients (Jordan et al., 2015). On the other hand, the ganglionic blockade has little if any effect in patients with severe peripheral postganglionic denervation (e.g., PAF) (Jordan et al., 2015; Shannon et al., 1997). In clinical practice, most patients with OH are in the middle of this spectrum of responses and have some degree of sympathetic reserve.

Understanding these concepts can help us in the selection of medications. The logical treatment for patients with impaired sympathetic reserve (PAF) would be to restore low plasma NE with "norepinephrine replacers" (direct adrenergic agonists such as midodrine and droxidopa). On the other hand, in patients with impaired central autonomic pathways (MSA), we can harness their preserved sympathetic reserve with "norepinephrine enhancers" ("indirect sympathomimetics") either by facilitating cholinergic ganglionic transmission with the cholinesterase inhibitor pyridostigmine (Singer et al., 2006), or increasing synaptic NE with the NE transporter blocker atomoxetine (Shibao et al., 2007c). It is important to consider that denervation hypersensitivity will magnify the effect of even small increases in synaptic NE, resulting in significant increases in BP.

2.3. Estimation of sympathetic reserve

There are indirect and noninvasive clinical indicators that can help us estimate individual sympathetic reserve (Biaggioni, 2014; Biaggioni, 2017). The magnitude of the compensatory orthostatic tachycardia is one of them. Patients with neurogenic OH are unable to appropriately increase HR in response to the drop in BP, so that on average, for every two mmHg drop in BP, patients with autonomic failure only increase their HR by one

beat per minute (Norcliffe-Kaufmann et al., 2018). A greater orthostatic tachycardia implies either intact cardiovagal function or relative preserved sympathetic reserve. Of greater practical importance, it can alert the physician of the presence of factors that trigger or worsen OH such as medications. The BP response to the Valsalva maneuver can also provide an estimate of the severity of sympathetic impairment (Low et al., 2013). Autonomic failure is characterized by an exaggerated and sustained decrease in BP during strain (phase 2) and the absence of overshoot after release (phase 4). The time it takes for BP to return to baseline during phase 4 can be an indicator of disease severity (Vogel et al., 2005). However, this method requires continuous BP monitoring which is not always available in general practice. Measurement of plasma NE is arguably a more direct method to assess sympathetic reserve of peripheral postganglionic neurons; plasma NE is normal or only slightly low in OH patients with central nervous lesions, whereas patients with diffuse peripheral nervous lesions typically show reduced or very low plasma NE levels. In a research setting, samples are drawn after patients rest supine for at least 10 minutes to avoid any unintentional stimulation of NE (Grouzmann et al., 2013), but even when measured in these carefully-controlled conditions, there is a substantial overlap between patients with central or peripheral disease. Nonetheless, in clinical practice even measuring random seated NE in a regular clinical laboratory may provide useful information.

3. Pharmacologic treatments of OH

3.1 Physiologic targets to increase blood pressure

The activation of sympathetic pathways and thereby stimulating autonomic effectors (e.g., smooth and cardiac muscles) via alpha or beta receptor activation is the major mechanism to increase the blood pressure either by contraction of the blood vessel (i.e., increasing total peripheral resistance), or increasing the heart rate and contractility (i.e., increasing cardiac output). As discussed above, NE plays the most essential role in this mechanism. Therefore, the major pharmacologic treatments targets to replace or enhance NE which is mostly deficient in OH patients (Figure 1). These treatments will eventually be attributed to direct alpha-receptor activation (NE replacement) or more physiologically enhance the remaining potential NE function by stimulating the secretion, or preventing the degradation of NE (NE enhancement).

3.2 Norepinephrine replacers

3.2.1 Midodrine—Midodrine is an oral prodrug that is metabolized to the alpha 1-adrenoreceptor agonist desglymidodrine. Midodrine activates alpha 1A and 1B receptors to trigger peripheral arterial and venous constriction, thus increasing peripheral vascular resistance and elevating BP without increasing HR. The active metabolite of midodrine rapidly reaches peak blood concentrations (C_{max}) in 1–2 hours (i.e., t_{max}), and has an elimination half-life of approximately 3–4 hours (Lamarre-Cliche et al., 2008). The initial dose is 2.5 mg, three times daily, and can be escalated up to 10 mg (Gibbons et al., 2017; Palma et al., 2020a). Standing systolic BP can increase by 10 to 30 mmHg after a 10 mg dose of midodrine within an hour, and the effect persists for another 2–3 hours (Palma et al., 2017; Zachariah et al., 1986). The short-term efficacy of midodrine has been proven in several clinical research studies (Byun et al., 2017; Low et al., 1997; Singer et al., 2014). In

a randomized, double-blind multicenter clinical trial for neurogenic OH, midodrine was safe and effective both in improving upright BP and orthostatic symptoms during a 6-week study period (10 mg, three times per day) (Low et al., 1997). However, there is still uncertainty about its long-term efficacy. The major adverse effects using midodrine include urinary symptoms (retention, hesitation, urgency), goosebumps and piloerection ("itchy scalp") and, importantly, worsening of supine hypertension (Wright et al., 1998).

3.2.2 Droxidopa—Droxidopa (L-threo-3,4-dihydroxyphenylserine, L-DOPS) is an oral synthetic NE prodrug approved by the FDA in 2014 for the treatment OH. It is converted to NE by L-aromatic-amino-acid decarboxylase (AAAD), the same enzyme that converts levodopa to dopamine, which is widely expressed in most organs (Berry et al., 1996). Droxidopa can penetrate the blood-brain barrier (BBB) but its pressor effect is due to its peripheral actions because it is blocked by high-dose carbidopa (an inhibitor of AAAD that does not cross the BBB) (Kaufmann et al., 2003). An integrated analysis of three randomized double-blinded clinical trials that included a total of 460 patients demonstrated an improvement in OH symptoms compared to placebo (Biaggioni et al., 2017). Open-label observations suggest durability of efficacy after 6-month use, with improvement of symptoms, functionality, and quality of life, including a reduction in falls (Francois et al., 2019). The t_{max} of droxidopa is 2 hours, and its elimination half-life is around 2.5 hours. The dose should be titrated from 100 to 600 mg three times during the daytime with the last dose given earlier to avoid supine hypertension (8 am, noon, and 4 pm) (Chen et al., 2018; Kaufmann et al., 2003). A potential consideration is the use of droxidopa in patients with PD taking carbidopa in combination with levodopa. Whereas high-doses of carbidopa can reduce the conversion of droxidopa to NE (Kaufmann et al., 2003), in clinical practice, dose titration of droxidopa seems to overcome this limitation, and thus droxidopa can be effective in PD patients with OH (Biaggioni et al., 2017). The main adverse effects of using droxidopa include headache, dizziness, nausea, and supine hypertension (Palma et al., 2020a), but in general, it seems to have a better side effect profile than midodrine. In particular, urinary retention has not been reported, and the incidence of supine hypertension seems to be lower. The integrated analysis of the pivotal clinical trials of this drug suggested that droxidopa is not as effective in controlling OH symptoms in MSA compared to PAF and PD patients (Biaggioni et al., 2017), in agreement with our concept that "norepinephrine replacers" will be more effective in patients with low sympathetic reserve. This phenomenon likely contributes to the interindividual variability in response to droxidopa observed in NOH.

3.3 Norepinephrine enhancers

3.3.1 Pyridostigmine—Pyridostigmine is an orally active inhibitor of cholinesterase, the enzyme that hydrolyzes acetylcholine in the synaptic cleft, thus terminating its action. The use of this medication for the treatment of OH is based on the concept that it facilitates cholinergic neurotransmission in autonomic ganglia thereby increasing sympathetic drive. It has the theoretical advantage that this effect will be greater during the standing position when neurotransmission at sympathetic autonomic ganglia is increased, thus preferentially increasing upright BP without worsening supine hypertension (Singer et al., 2003). Based on this mechanism of action, pyridostigmine may be more effective in patients with

sympathetic reserve. In patients with severe OH the effect tends to be modest (Singer et al., 2003; Singer et al., 2006). The suggested dosage for pyridostigmine is 30 to 60 mg, 2 to 3 times per day (t_{max}: 1.5 hours, elimination half-life: 3 to 4 hours) (Agarwal et al., 2007; Palma et al., 2020a; Singer et al., 2006). Currently, this medication is used “off-label” and not specifically approved for the treatment of OH. Dose-limiting side effects are mostly gastrointestinal, including abdominal cramps, nausea, and diarrhea (Palma et al., 2020a).

3.3.2 Atomoxetine—Atomoxetine is an oral NE transporter (NET) blocker. NET is a monoamine transporter located presynaptically in postganglionic sympathetic nerves. By reuptaking NE from the synapse, it terminates its actions and restores intracellular NE (Hahn, 2004). Inhibition of NET increases NE concentrations in the synaptic cleft leading to a pressor response. Among patients with severe autonomic failure, atomoxetine has been shown to be effective in those with preserved peripheral sympathetic fibers function (i.e., MSA) but not in those with low sympathetic reserve (i.e., PAF) (Biaggioni, 2017). In patients with milder forms of peripheral autonomic impairment, however, atomoxetine can be effective likely due to denervation hypersensitivity (Shibao et al., 2007c).

Although the use of atomoxetine for OH is not yet approved by the FDA, several clinical trials suggested the efficacy and safety of this approach (Byun et al., 2020; Okamoto et al., 2019; Palma et al., 2020a; Ramirez et al., 2014). The drug is effective at pediatric doses of 10 to 18 mg twice per day, underscoring the hypersensitivity of these patients. A comparative study found atomoxetine superior to midodrine in improving orthostatic symptoms (Ramirez et al., 2014). Finally, there is a synergistic interaction between atomoxetine and pyridostigmine so that even patients with a low sympathetic reserve who do not respond to either drug alone, may respond to the combination (Okamoto et al., 2019). Atomoxetine reaches a t_{max} in 1 to 2 hours and has an elimination half-life of 5 hours (Simpson et al., 2004). Side effects of dry mouth, insomnia, loss of appetite, supine hypertension, suicidal ideation have been reported (Palma et al., 2020a).

3.3.3 Yohimbine—Yohimbine is an oral alpha-2 adrenergic antagonist (Tam et al., 2001). It is the pharmacological opposite to the alpha-2 agonist clonidine; in the CNS it increases central sympathetic outflow and in peripheral noradrenergic nerves it potentiates the release of NE. Given this mechanism of action, yohimbine should be more effective in the treatment of OH patients with preserved sympathetic function, but empirically it is also helpful in patients with peripheral disease. Efficacy data is limited; a clinical study showed short-term efficacy and safety with the administration of 5.4 mg oral dose, up to three times per day (Shibao et al., 2010). Another study showed a synergistic pressor effect between yohimbine and atomoxetine in patients with low sympathetic reserve who do not respond to either drug alone, suggesting that increasing residual sympathetic outflow with yohimbine can potentiate the pressor effect of atomoxetine (Okamoto et al., 2012). Both t_{max} and elimination half-life are less than one hour, but the duration of action is longer. Side effects of yohimbine include sweating, insomnia, palpitation, suicidal ideation, and supine hypertension (Tam et al., 2001). Yohimbine is no longer available as a commercial pharmaceutical but can be compounded in specialty pharmacies.

3.4 Nonspecific treatments

3.4.1 Fludrocortisone—Fludrocortisone acetate is an oral synthetic corticosteroid with potent mineralocorticoid effects and comparatively weak glucocorticoid activity. It has been clinically used in the treatment of OH by over 40 years, based on its role as an interstitial volume expander by promoting sodium reabsorption in the kidney. The increase in plasma volume, however, is transient and the sustained increase in BP in patients with OH is possibly due to potentiation of the pressor effects of endogenous NE and angiotensin II (Hickler et al., 1959; Ten Harkel et al., 1992). The observation that mineralocorticoid receptor blockade acutely lowers BP in OH patients, independent from volume regulation, also suggests off-target actions (Arnold et al., 2016). Its t_{max} is 2 hours with an elimination half-life of 4 to 6 hours (Ribot et al., 2013). Usual doses are 0.1–0.2 mg once daily (Palma et al., 2020a). Evidence of efficacy is largely based on clinical experience; there are only a series of case reports for the efficacy of fludrocortisone in the treatment of OH in the 1970s (Campbell et al., 1976; Hoehn, 1975). A recent efficacy study of fludrocortisone in 13 Parkinson's patients with OH showed that fludrocortisone (0.2 mg per day) was beneficial in reducing the orthostatic fall in diastolic BP and improving standing mean BP (Schreglmann et al., 2017). Hypokalemia and hypomagnesemia occurs in a significant percentage of patients (Robertson, 2004). Other potential adverse effects include headache, edema, and supine hypertension (Robertson, 2004). Adrenal suppression can occur if higher doses (>0.3 mg a day) are used. Compared with midodrine, fludrocortisone has been shown to increase all-cause hospitalization in patients with OH (Grijalva et al., 2017). This medication should not be used in patients with hypertension or congestive heart failure.

3.4.2 Octreotide—Octreotide is a stable somatostatin analog that inhibits the release of a number of gastrointestinal vasodilating peptides, increasing cardiac output by acting as a splanchnic vasoconstrictor. Its effect was found to be comparable to midodrine and was particularly effective for the prevention of postprandial hypotension (Hoeldtke et al., 1998). The recommended doses are 12.5 to 25 μg subcutaneously (t_{max}: 30 minutes, elimination half-life: 2 hours) (Harris, 1994; Hoeldtke et al., 1998) prior to meals. Adverse effects include nausea, abdominal cramps, diarrhea, flatulence, and fat malabsorption (Lamberts et al., 1996). In our experience, octreotide is particularly useful in patients that are refractory to other treatments.

4. Pharmacologic treatment in specific clinical conditions associated with OH

4.1 Supine hypertension

Supine hypertension is present in the majority of OH patients, even in those with no previous history of essential hypertension. Thus, supine hypertension and OH may be a hemodynamically opposite manifestation of the same disease as the baroreflex is not able to counteract either one. Its presence complicates the management of OH, and the argument has been made that the treatment of OH should take precedence over that of supine hypertension (Espay et al., 2016). However, supine hypertension is associated with end-organ damage and renal impairment (Garland et al., 2009; Vagaonescu et al., 2000).

Furthermore, supine hypertension induces pressure diuresis, a normal renal compensatory mechanism aimed at normalizing BP. Thus, nocturnal supine hypertension begets early morning OH by causing nighttime volume depletion.

Attempts should be made, therefore, to manage supine hypertension without worsening OH. One approach is to use short-acting antihypertensives at bedtime to reduce daytime carryover effects. OH patients are sensitive to the vasodilatory effects of nitric oxide (NO) (Gamboa et al., 2012) and several treatment options related to NO mechanisms are effective in controlling supine hypertension, including nitroglycerine patch (0.1 mg per hour) (Shibao et al., 2006), nebivolol (Okamoto et al., 2014), and sildenafil (Okamoto et al., 2014). Targeting the angiotensin-aldosterone system with losartan (Arnold et al., 2013a) and eplerenone (Arnold et al., 2016) can also be effective. The efficacy of these treatments, however, has only been assessed in acute trials under controlled conditions.

4.2 Heart failure

Heart failure is one of the most common comorbidities associated with OH (Ricci et al., 2015; Shibao et al., 2007b), and one that requires a distinct approach. In general, fludrocortisone should be avoided in this patient population; fludrocortisone increases the risk of hospitalizations not only for heart failure but for all causes (Grijalva et al., 2017). Midodrine is often used in the treatment of OH because of its short duration of action (Arnold et al., 2013b), but concerns have been raised because of supine hypertension (Olshansky et al., 2020). We prefer droxidopa for the treatment of OH in heart failure patients. In a small cohort of patients, we found droxidopa to be well-tolerated, and the persistence on medication was more than 60% at 6 months (McDonell et al., 2019). Beta-blockers can be combined with droxidopa if indicated for cardioprotection, because they do not lower BP significantly in autonomic failure patients (Okamoto et al., 2014). However, vasodilating beta-blockers with alpha-blocking actions (e.g., carvedilol) should be avoided if possible.

4.3 Postprandial hypotension

Postprandial hypotension is defined as a fall in systolic BP greater than 20 mmHg within 2 hours after meals (Jansen et al., 1995). It likely represents normal splanchnic venous pooling, and a small effect can be demonstrated in healthy individuals, but hypotension is made evident by autonomic impairment (Luciano et al., 2010). Postprandial hypotension can increase the risk of syncope and falls. Pharmacological treatments include octreotide and caffeine (Hoeldtke et al., 1998; Onrot et al., 1985) based on their possible roles in antagonizing vasodilatory peptide release, and adenosine antagonist effect, respectively. The alpha-glucosidase inhibitor acarbose has been shown the be effective in attenuating postprandial hypotension and we consider it the preferred initial therapy. Doses are 25–50 mg, given 10 minutes prior to meals. Contraindications include co-morbid conditions such as inflammatory bowel diseases. The mechanism of action is the decrease in absorption of simple carbohydrates that triggers the release of GUT peptide (Shibao et al., 2007a; Zhang et al., 2017).

4.4 Parkinson's disease

OH is one of the premotor symptoms of the PD, which may manifest with or prior to classic PD symptoms such as tremor, bradycardia, and rigidity. The prevalence of OH in PD is very frequent. In an investigation of over 7 years from the time of diagnosis, more than 65% of patients experienced OH during this period (Hiorth et al., 2019). A substantial portion of these patients also suffered supine hypertension (41.3%). Clinicians should also aware that such medications used to treat PD can cause OH (e.g., dopamine agonists). Therefore, it is important to speculate and investigate the underlying OH symptoms in PD patients and provide adequate treatment options based on this. As discussed above, PD patients are more likely to benefit by use of NE replacers considering their loss of function in postganglionic neurons. However, there are still some portion of patients who are non-neurogenic orthostatic hypotension (Palma et al., 2020b). In these patients, the sympathetic reserve is relatively preserved with normal or enhanced NE level upon standing, and should be more benefited from non-pharmacologic treatment and volume expanders.

4.5. Multiple system atrophy

MSA is a progressive neurodegenerative disorder and central autonomic failure is one of the hallmarks of MSA in addition to motor symptoms which results in severe neurogenic OH. More than 50% of patients are known to manifest orthostatic hypotension without profound impairment of sympathetic reserve. Pathologically, peripheral sympathetic fibers are relatively spared and sympathetic reserve can be harnessed in these patients as discussed above (Jordan et al., 2015). Therefore, ideally, NE enhancers can be used as a treatment of choice to start with, if non-pharmacologic treatment are not sufficient. We have shown a greater pressor effect of atomoxetine in MSA patients compared to patients with peripheral autonomic failure (Shibao et al., 2012). However, the clinical diagnosis of MSA is challenging in the early stages of disease; therefore, estimation of sympathetic reserve can be useful to select a proper initial treatment. Denervation hypersensitivity and supine hypertension in these patients should be carefully monitored before pharmacologic treatment. It has been reported that 37% of patients with MSA possesses supine hypertension and there is a loss of nocturnal dipping in up to 75% of patients (Fanciulli et al., 2018).

4.6 Diabetes

Autonomic neuropathy is a common complication in both type 1 and type 2 diabetes mellitus (DM). In the 10 years of the follow-up study, OH was present in 31.7 of patients with type 1 DM and 32.3% with type 2 DM, and prevalence was correlated with other DM associated complications (Gaspar et al., 2016). Because cardiovascular autonomic neuropathy and the presence of OH is known to be an independent risk factor for mortality in OH, the early diagnosis of these complications is important (Soedamah-Muthu et al., 2008). The immediately optimized blood glucose control and lifestyle modification is the first step to prevent worsening of OH symptoms and disease progression (Pop-Busui et al., 2017), especially in type 1 DM. Certain medications such as tricyclic antidepressants, diuretics, and alpha-adrenoreceptor antagonists, which are commonly used in diabetic

patients for various purposes should be carefully removed based on risk-benefit considerations before starting pharmacologic treatment (Fisher et al., 2017).

5. Conclusion

It is important to emphasize that nonpharmacologic treatment is always the first step in the management of OH. However, many patients will require pharmacological support. The pharmacologic treatment of OH may seem daunting, but understanding the underlying pathophysiology, and the basic clinical pharmacology of available therapies, can guide us to individualized optimal treatments.

Acknowledgements

Funded in part by HL122847, HL149386, HL144568 and DK11175 from the National Institutes of Health, FD0004778 from the Food and Drug Administration, and by a KNA-20-Neuro Frontier Fellowship Award from the Korean Neurological Association.

Disclosures

IB and CAS have received consultant fees and research support from Lundbeck and Theravance Biopharma, Inc. IB and LO are patent holders for the use of an automated binder in the treatment of orthostatic hypotension.

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Highlights

- Nonpharmacologic countermeasures are always the first step in the management of OH, and pharmacologic treatments are then added to the management of OH.
- Treatment selection should consider the underlying pathophysiology. Patients with degeneration of peripheral noradrenergic neurons and low plasma norepinephrine (pure autonomic failure, Parkinson disease) tend to respond better to “norepinephrine replacers” (midodrine, droxidopa).
- Patients with relatively spared sympathetic reserve and normal or mildly reduced plasma norepinephrine (multiple system atrophy) tend to respond better to “norepinephrine enhancers” (pyridostigmine, atomoxetine, yohimbine).
- Associated clinical conditions such as supine hypertension, heart failure, and postprandial hypotension need to be considered in the pharmacological management of these patients.

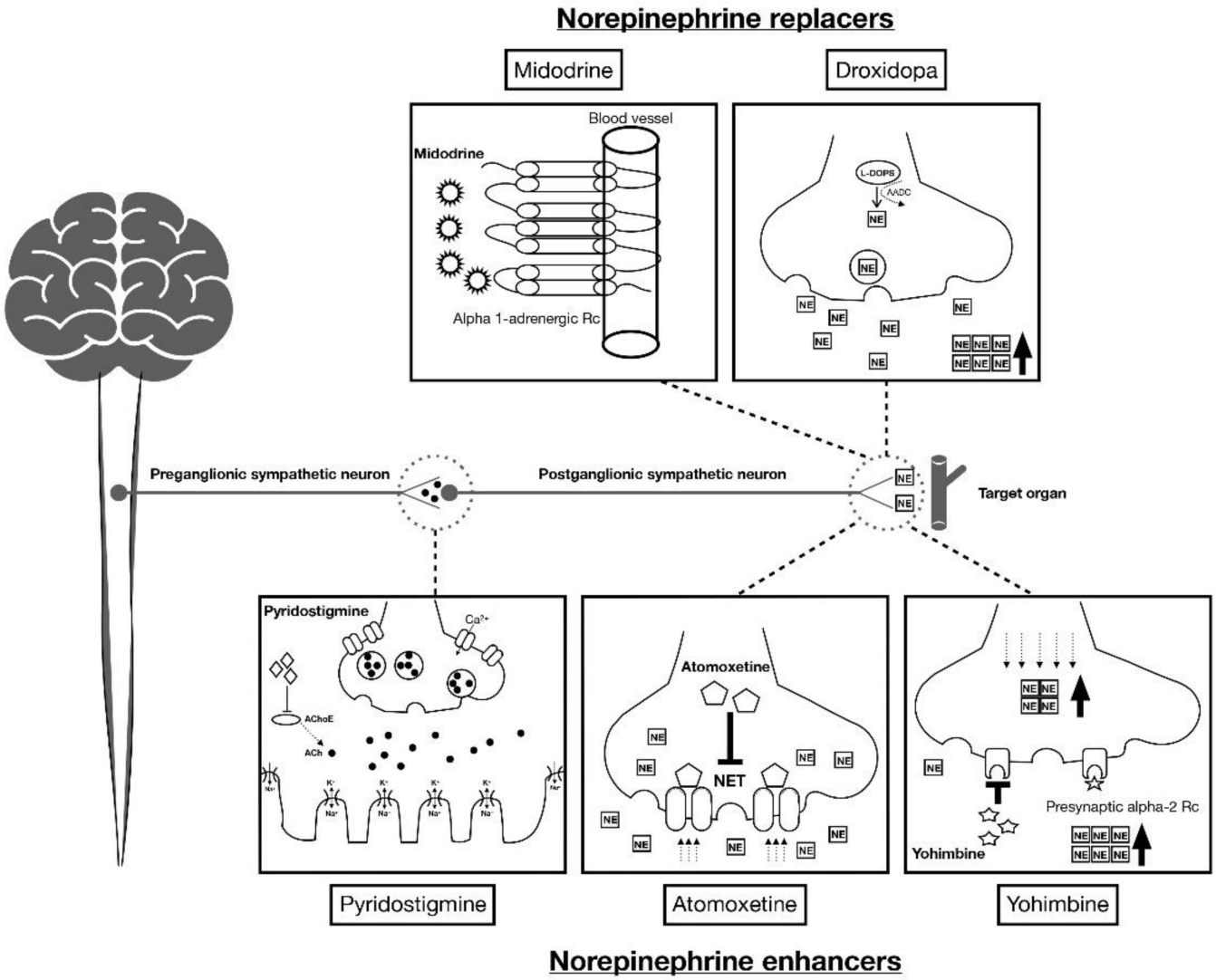

Figure 1.
Schematic mechanism of action in norepinephrine replacers and enhancers.

Table 1.

Current pharmacologic treatment options for orthostatic hypotension.

Treatment	Mechanism of action	Dosage recommendation	Administration	Adverse effects
Norepinephrine replacers				
Midodrine	Alpha-1 adrenoceptor agonist	Start with a 2.5 to 5 mg dose, increase up to 10 mg, up to 3 times/day	orally	Urinary retention, piloerection, supine hypertension
Droxidopa	Prodrug, converted to norepinephrine	100 to 600 mg, 3 times/day	orally	Headache, nausea, supine hypertension
Norepinephrine enhancers				
Pyridostigmine	Cholinesterase inhibitor	30 to 60 mg, up to 3 times/day	orally	Abdominal discomfort, diarrhea, nausea, urinary frequency
Atomoxetine	NE transporter (NET) inhibitor	10 to 18 mg, 3 times/day	orally	Dry mouth, insomnia, loss of appetite, supine hypertension, suicidal ideation
Yohimbine	Alpha-2 adrenoreceptor antagonist	5.4 mg, up to 3 times/day (available through compounding pharmacies only)	orally	Sweating, insomnia, palpitation, suicidal ideation, supine hypertension
Nonspecific treatments				
Fludrocortisone	Increasing renal sodium reabsorption and alpha-1 adrenoceptor sensitization	0.05 to 0.2 mg/day	orally	Hypokalemia, headache, edema, adrenal suppression, supine hypertension
Octreotide	Somatostatin analogue	12.5–25 μg, up to 1–3 times/day	subcutaneously	Nausea, abdominal cramps, diarrhea, flatulence, fat malabsorption