THERAPY IN PRACTICE

Drug-Related Orthostatic Hypotension: Beyond Anti-Hypertensive Medications

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Abstract

Orthostatic hypotension (OH) is an abnormal blood pressure response to standing, which is associated with an increased risk of adverse outcomes such as syncope, falls, cognitive impairment, and mortality. Medical therapy is one the most common causes of OH, since numerous cardiovascular and psychoactive medications may interfere with the blood pressure response to standing, leading to drug-related OH. Additionally, hypotensive medications frequently overlap with other OH risk factors (e.g., advanced age, neurogenic autonomic dysfunction, and comorbidities), thus increasing the risk of symptoms and complications. Consequently, a medication review is recommended as a first-line approach in the diagnostic and therapeutic work-up of OH, with a view to minimizing the risk of drug-related orthostatic blood pressure impairment. If symptoms persist after the review of hypotensive medications, despite adherence to non-pharmacological interventions, specific drug treatment for OH can be considered. In this narrative review we present an overview of drugs acting on the cardiovascular and central nervous system that may potentially impair the orthostatic blood pressure response and we provide practical suggestions that may be helpful to guide medical therapy optimization in patients with OH. In addition, we summarize the available strategies for drug treatment of OH in patients with persistent symptoms despite non-pharmacological interventions.

Key Points

Several cardiovascular and psychoactive medications may alter the blood pressure response to standing, leading to drug-related orthostatic hypotension.

This narrative review provides an overview on cardiovascular and non-cardiovascular medications potentially impairing orthostatic blood pressure.

This review may be helpful to guide medical therapy optimization in patients with an abnormal orthostatic blood pressure response, to minimize the risk of drug-related orthostatic hypotension.

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1 Introduction

Orthostatic hypotension (OH) is an impaired blood pressure (BP) response to the upright position which is defined by a systolic BP drop $\geq$ 20 mmHg or by an absolute systolic BP value $\leq$ 90 mmHg and/or a diastolic BP drop $\geq$ 10 mmHg within 3 minutes of standing [1, 2]. It is a recognized risk factor for adverse outcomes such as syncope and falls, cardiovascular events (including coronary events, heart failure hospitalization, and stroke), cognitive impairment, and mortality [3–6]. Therefore, OH diagnostic assessment and treatment play a relevant role in patients' health care and prognosis.

OH is usually classified according to its etiopathogenesis into neurogenic and non-neurogenic forms. Neurogenic OH is determined by structural lesions of autonomic pathways, due to disorders affecting central or peripheral autonomic structures (e.g., Parkinson disease, multiple system atrophy, diabetes mellitus, advanced renal failure). By contrast, non-neurogenic OH forms are attributable to functional causes of autonomic nervous system failure. Among the latter, medications are the most common, particularly in older patients.

With standing, the force of gravity rapidly displaces approximately 10% of the circulating blood volume (300–800 mL) to the lower body, particularly to the lower

extremities and splanchnic venous capacitance vessels [1, 7]. As a consequence, venous return and cardiac output are reduced and an ensemble of compensatory responses is activated to prevent a BP fall. The latter usually include an increase in sympathetic outflow and a decrease in vagal nerve activity, leading to an increase in peripheral vascular resistance, heart rate, and cardiac contractility aimed to preserve organ perfusion. Additionally, contractions of lower body muscles (the so-called 'muscle pump') prevent excessive blood pooling in venous vessels and favor venous return to the heart. OH derives from a failure of the aforementioned compensatory responses, which determines a fall in cardiac output and/or inadequate vasoconstriction. A significant BP fall may also occur in the posture change from a supine to a sitting position. Therefore, measuring sitting BP may be an alternative to standing BP, if the latter is not feasible (e.g., in bedridden patients). Yet, measurements in the sitting position may reduce sensitivity [8] and standing BP should be preferred, whenever possible.

Some medications may interfere with compensatory reflex responses to standing (e.g., sympathetic-mediated vasoconstriction and increased heart rate response and inotropism), while others may increase venous pooling (e.g., vasodilators) and/or induce volume depletion (e.g., diuretics), thus favoring OH.

OH accounts for 1.3% of drug adverse reactions and its incidence increases with advancing age [9]. Indeed, age-related pharmacokinetic changes usually occur that may alter the bioavailability and distribution of medications [10]. Additionally, older adults have a higher susceptibility to OH due to the frequent coexistence of multiple predisposing factors, such as comorbidities, polypharmacy, and deconditioning. Therefore, drug-related OH may overlap with other neurogenic and non-neurogenic causes of OH [9], thus worsening patients' symptoms and the risk of complications. Given all of the above, medical therapy review and optimization should be routinely included in the diagnostic and therapeutic work-up of OH, along with patient's education on lifestyle measures to counteract orthostatic symptoms (e.g., hydration, physical conditioning, use of abdominal binders).

It is well known that many cardiovascular medications may predispose to OH, and it has been shown that withdrawal of antihypertensive medications can decrease BP drop associated with postural change [11]. Yet, potentially hypotensive medications also include psychoactive drugs [12] and opioids [13], which are frequently prescribed in older adults (Fig. 1). In patients with OH, the medication review should be aimed at identifying all the medications potentially impairing orthostatic BP and reassessing their indications and benefits, in order to evaluate withdrawal or dose reduction. In this context, the knowledge of medications potentially influencing orthostatic BP is essential for appropriate management of OH. If symptoms persist despite the reduction of hypotensive medications and adherence to non-pharmacological interventions, specific drug treatment for OH can be considered, even if evidence-based data are limited.

This narrative review presents an overview on cardiovascular and non-cardiovascular medications potentially causing OH, which may be helpful to optimize medical therapy in patients with an impaired orthostatic BP response. In addition, we summarize the available strategies for drug treatment of OH in patients with persistent symptoms despite non-pharmacological interventions.

Fig. 1 Medications acting on cardiovascular system (white) and central nervous system (dark grey) potentially responsible for drug-related orthostatic hypotension. *BDZs* benzodiazepines
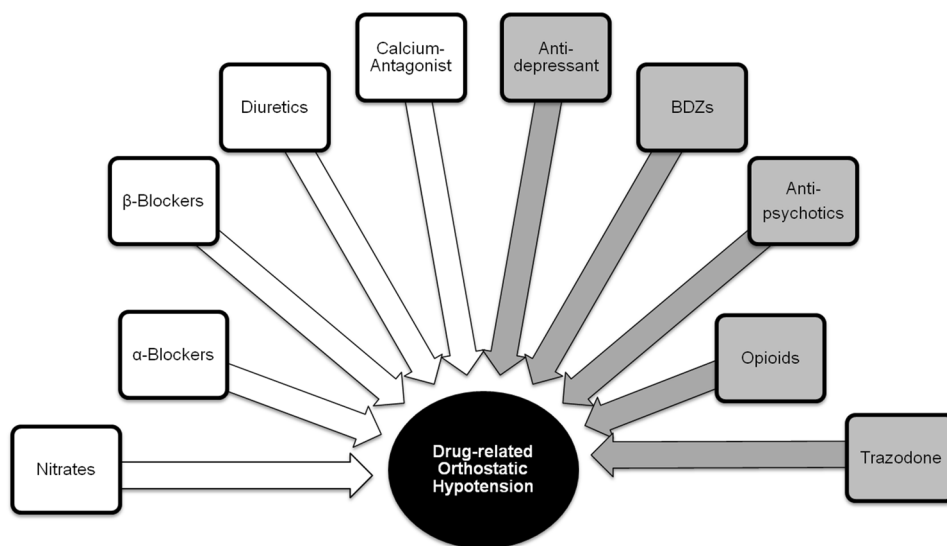
2 Antihypertensive Medications and Other Cardiovascular Drugs Predisposing to Orthostatic Hypotension (OH)

2.1 Diuretics

Diuretics are considered to be one of the main determinants of drug-related OH. Indeed, diuretics increase urinary sodium excretion and predispose to volume depletion and OH, particularly in older adults. Loop diuretics also increase venous capacitance, thus reducing venous return and cardiac output.

A significant association with OH (OR 10.44, 95% CI 1.22–89.08 for loop diuretics [14]; OR 1.25, 95% CI 1.02–1.53 for thiazide diuretics [15]) and orthostatic syncope (OR 3.73, 95% CI 1.23–11.28 [16]) is reported by several studies, irrespective of drug dosage [4, 14–17], while this was not confirmed by other population studies [18–23]. Hypokalemia and hyponatremia, which may develop during diuretic therapy, have been reported to be associated with OH [24, 25] and may confound this association. Loop diuretics seem to be more prone than thiazide diuretics to cause volume depletion and should probably be avoided as treatment of hypertension in frailer and older patients, unless specifically indicated (e.g., glomerular filtration rate < 30 mL/min) [26]. Diuretics can generally be safely discontinued in patients with chronic conditions, although a follow-up is necessary to exclude the appearance of heart failure signs [27]. Available data mainly refer to loop and thiazide diuretics, whereas data on potassium-sparing molecules are scarce. In particular, an association between spironolactone and OH is only reported by Fedorowski et al. [28] (14% vs 7% in patients with and without OH, respectively, $p = 0.04$).

2.2 α-Receptor Blockers

α-Receptor blockers are a known risk factor for OH, which mainly derives from reduced vascular resistance [29–31]. Indeed, α-blockers act through a selective blockade of vascular α1-adrenergic receptors, which inhibits the vasoconstrictor effect of catecholamines. α1-Adrenergic receptors are also located in the prostate and bladder neck, where they mediate the tension of smooth muscle. Consequently, α-receptor blockers facilitate bladder emptying and improve urinary flow in patients with bladder outflow obstruction, mainly older males with benign prostatic hyperplasia. Three different α1-adrenergic receptors subtypes exist, classified as α1A, α1B, and α1D [32]. α1B-receptors are located in the vessels, and α1D receptors are located in the detrusor muscle, in the spinal cord, and in afferent nerves originating in the bladder [32]. Benefits on lower urinary tract symptoms derive from α1A- and α1D-receptor inhibition, due to

a relaxation of prostate and bladder smooth muscle and the blockade of spinal cord reflex originating from the bladder [32]. Conversely, hypotensive effects and orthostatic BP impairment mainly derive from α1B-receptor blockade. As a consequence, OH risk varies according to single molecules' affinity for α1B-receptors, with α1A selective molecules showing a lower risk of orthostatic BP impairment. Silodosin has the highest selectivity for urinary α-adrenergic receptors with an α1A:α1B affinity ratio of 162:1 (α1A affinity > α1D > α1B) [32, 33], thus showing a more favorable cardiovascular tolerability, although at the price of a higher risk of sexual dysfunction [34]. Indeed, an incidence of 0.2–1.4% is reported for silodosin-related OH, with no statistically significant differences versus placebo [35–37]. Tamsulosin also shows a high uroselectivity, with a 10-fold greater affinity for α1A- and α1D-receptors as compared with the α1B subtype [32]. Yet, a relevant incidence of OH has been reported (42.4 events/10000 person-years) [38]. OH risk is higher for alfuzosin, prazosin, terazosin, and doxazosin, which present the lowest uroselectivity. α-Blockers-related OH may be more pronounced in older patients, as a result of an age-related increase in vascular α1B receptors [32, 39]. Moreover, their hypotensive effect may be potentiated by the concomitant administration of phosphodiesterase type 5 inhibitors, which may be associated with α-blockers to enhance their efficacy on lower urinary tract symptoms [40, 41].

Given all of the above, α-blockers should be avoided as a treatment for high BP in older hypertensive subjects, as the European guidelines on hypertension recommend [42]. As concerns their use in prostatic hyperplasia, α-blockers should only be prescribed in the presence of bladder outflow obstruction and more selective molecules should be preferred, to minimize the risk of OH. The orthostatic BP fall may be more severe after the first dose (first-dose phenomenon), so that bed-time administration is advisable.

2.3 Nitrates

Nitrates have vasodilating effects deriving from nitric oxide release and vascular smooth muscle relaxation. Vasodilation predominantly involves the venous district, thus decreasing venous return and potentially impairing orthostatic BP. Therefore, nitrates are commonly listed among OH risk factors [12, 43, 44]. Additionally, nitrates are known to increase the risk of hypotensive syncope and falls in older patients, regardless of drug dosage [16, 45]. Conversely, their use as symptomatic treatment of chronic angina pectoris is widespread, while they can be safely discontinued in 90% of cases [27]. As an alternative, different anti-ischemic drugs with no or limited impact on orthostatic BP can be considered if indicated, such as calcium channel blockers, ivabradine, or ranolazine. Nevertheless, Kamaruzzaman et al. [15] identified a trend

towards a negative association between nitrates and OH in a community-based sample of women aged 60–80 years (adjusted RR 0.72, 95% CI 0.49–1.05), probably deriving from tolerance development during prolonged treatment. Additionally, absorption of transdermal nitrates may be reduced in older patients due to an age-related decrease in dermal vasculature, which may at least partly explain this result.

2.4 β-Blockers

Due to their negative inotropic and chronotropic effect, β-blockers may interfere with the compensatory responses to standing and predispose to an orthostatic BP fall. Additionally, the blockade of juxtaglomerular and presynaptic β1-adrenergic receptors reduces renin-angiotensin system activity and sympathetic outflow, respectively, thus counteracting vasoconstriction.

Data from the Irish Longitudinal Study on Ageing (TILDA) demonstrate that monotherapy with β-blockers is associated with an increased risk of OH during all phases of standing (OR 2.05, 95% CI 1.31–3.21 for initial OH; OR 3.36, 95% CI 1.87–6.03 for sustained hypotension) [18]. Similarly, an association between β-blockers and OH has also been described in nursing home residents [46] and in patients with chronic kidney disease [47]. A higher incidence of OH has been reported for mixed α- and β-blockers (e.g., carvedilol), particularly after the first dose [48]. In view of the above described data, prescription of β-blockers should preferably be limited to patients with a specific indication (e.g., coronary artery disease, heart failure or atrial fibrillation), as the European guidelines on hypertension recommend [42]. Additionally, mixed α- and β-blockers should preferably be avoided in patients with OH.

2.5 Clonidine

Clonidine is an α-2 agonist stimulating the presynaptic receptors of the vasomotor center in the brain stem, which induces a decrease of sympathetic tone and norepinephrine plasma levels [49]. At present, the effects of clonidine on orthostatic BP have been poorly investigated [12]. As clonidine induces a reduction of sympathetic activity, it cannot be excluded that it may interfere with adrenergic compensatory responses to standing, thus favoring the development of OH. Additionally, clonidine is more frequently prescribed in patients with resistant hypertension and polypharmacy, which already carry increased risk of OH. Yet, according to some authors, clonidine only determines a baseline reduction in the sympathetic outflow, which does not interfere with compensatory

reflex responses to standing [49]. Finally, a single study describes a protective effect of centrally acting antihypertensive medications, which is currently unexplained [50]. Data on the α2 agonist methyl-dopa are scarce, but no increase in the risk of OH has been reported [51].

2.6 Calcium Channel Blockers

Data on calcium channel blockers as a risk factor for OH are conflicting. While an increased risk is reported in some studies [17, 30, 50], some others do not describe any association [43, 52, 53] or rather suggest a protective effect [54]. In a study by Gaxatte et al. [50], patients with OH more frequently received calcium antagonists (23% vs 16%, $p = 0.02$), which were significantly associated with an increased risk of impaired BP response to standing (OR 1.79, 95% CI 1.16–2.76). Similar results are reported by Press et al. [30] (OR 1.66, 95% CI 1.11–2.48). Conversely, calcium antagonists showed a protective effect against OH in older people from TILDA (OR 0.68, 95% CI 0.49–0.94, $p < 0.001$) [54]. The heterogeneity of this drug class may at least partly explain these inconsistent results. Indeed, dihydropyridine calcium channel blockers frequently induce a compensatory heart rate increase, which may counteract a BP fall after standing, thus suggesting a potential explanation for their neutral/protective effect. Conversely, non-dihydropyridine calcium channel blockers have negative chronotropic and inotropic effects, which probably interfere with compensatory cardiac responses to standing [55]. Additionally, the bioavailability of diltiazem and verapamil may be increased in older adults due to an age-related reduction of the first pass liver effect [12]. In contrast, amlodipine and lacidipine seem to have better tolerability, which is probably attributable to a slow binding to calcium channels and a slower onset of vasodilation [56]. A low risk of OH is also reported for isradipine [12].

2.7 ACE Inhibitors and Angiotensin II Receptor Blockers

The chronic use of ACE inhibitors (ACE-I) and angiotensin II receptor blockers does not seem to be associated with OH [18, 46, 47]. Conversely, a protective effect is reported by some studies [28, 46], which may be attributed to improved vascular compliance and increased baroreceptor sensitivity deriving from the inhibition of the renin-angiotensin system [57–59]. Yet, the 'first-dose' phenomenon has to be mentioned, which more likely occurs in patients with increased renin-angiotensin activity. A vasodilation in capacitance vessels or a transient baroreceptors down-regulation may give a rationale for this phenomenon [60]. As concerns single molecules, data specifically referring to valsartan [61] and

candesartan (OH incidence 0.2–0.8%) [62] do not report a clinically significant impact on orthostatic BP. Among ACE-I, OH risk seems to be higher for enalapril [63] and captopril, while it is lower for perindopril (incidence of hypotension 42% vs 15% for captopril and perindopril, respectively) [64].

3 Drugs Acting on Central Nervous System Predisposing to OH

3.1 Antidepressants

OH is the most common cardiovascular adverse effect of tricyclic antidepressants (TCA), occurring in 10–50% of treated patients [12, 30, 50, 65]. Indeed, pharmacodynamics of TCA also include a vasodilating effect deriving from α-adrenergic receptors blockade. Consistently, OH risk varies among single molecules according to their affinity for α-receptors, being higher for amitriptyline and clomipramine and lower for nortriptyline [12].

Serotonin-selective reuptake inhibitors (SSRI) are reported to cause OH less frequently than TCA [9, 12] and hypotension is included among uncommon ($\geq$ 1/1000 to < 1/100) or rare ($\geq$ 1/10000 to < 1/1000) adverse effects [66]. However, increasing evidence suggests that orthostatic BP may be impaired in patients on SSRI therapy, too [17, 30, 67], with a 2-fold increase in the risk of OH (OR 2.09, 95% CI 1.33–3.19 [30]; OR 2.11, 95% CI 1.25–3.57 [67]). The causal pathway is not definite, and the association observed between antidepressant treatment and OH in cross-sectional studies may be partially confounded, as OH has been associated with depression risk in longitudinal studies, independently of antidepressant treatment [68]. Yet, a vasodilating effect has been described for fluoxetine, sertraline, and citalopram, which is probably mediated by inhibition of calcium channels and calcium-elicited vasoconstriction [69, 70]. Additionally, a slight reduction in heart rate is reported for fluoxetine, citalopram, and paroxetine, which may contribute to OH [71]. A role of serotonin in central regulation of BP has also been hypothesized, as both serotonin and its precursor 5-hydroxytryptophan significantly lower BP in rats and the hypotensive effect is reduced by serotonin antagonists and enhanced by fluoxetine [72]. Finally, fluoxetine and paroxetine act as cytochrome CYP2D6 inhibitors, thus potentially reducing the metabolic rate of hypotensive drugs like nifedipine and β-blockers [73].

It is well known that serotonin-norepinephrine reuptake inhibitors (SNRI) may induce BP and heart rate increase. Nevertheless, a strong association between SNRI and OH has been described in a sample of older adults at high risk of falling (OR 5.37; CI 1.93–14.97) [50] and a mean decrease of standing BP values was observed after venlafaxine treatment in a small clinical study of older subjects, with OH developing in 29% of the sample [74]. Similarly, in a placebo-controlled trial, a small but significant drop of systolic BP was associated with duloxetine treatment, although no increase in incidence of OH was observed in the duloxetine group (OH incidence vs placebo 15.6% vs 20.5%) [75]. The hypotensive effects of SNRI may be explained by a dose-dependent overstimulation of presynaptic α2-adrenergic receptors, resulting in reduced noradrenaline outflow [76], although underlying mechanisms have been poorly investigated to date. Duloxetine is included among cytochrome CYP2D6 inhibitors [73] and may thus enhance the hypotensive effects of some medications.

Trazodone is a multifunctional drug that also determines inhibition of α-adrenergic receptors [77]. OH is reported in 1–7% of patients, thus representing the most common cardiovascular adverse effect [17, 78]. Trazodone-related hypotension more likely occurs in patients with advanced age or cardiac diseases. It is usually transient and related to plasma drug concentration, so that OH risk is expected to be lower when low doses or prolonged-release formulations are prescribed [79].

3.2 Benzodiazepines

Evidence on the hemodynamic effects of benzodiazepines (BDZs) is mainly limited to intensive care settings, referring to intravenous BDZ administration in the context of sedation or anesthesia [80–82]. However, in a recent study, BDZ users had lower systolic BP values than controls (149 vs 161 mmHg; p < 0.05) [83]. Additionally, BDZs were shown to significantly impact on the orthostatic BP response (Fig. 2), being independently associated with a greater BP drop at 10 seconds after standing [83]. Similarly, BDZs were found to induce orthostatic hypotension in deconditioned subjects [84], but the underlying mechanism is still debated. The presence of BDZ receptors has been demonstrated in the heart [85] and a negative inotropic effect has been described, both in animals [85] and humans [86, 87]. Moreover, previous data suggest that BDZs reduce the sympathetic tone [81] and the norepinephrine response to posture changes [88]. Finally, orthostatic BP impairment may develop as a consequence of BDZ-induced myorelaxation, which increases venous capacitance and lower-body venous pooling [83, 84]. The BDZ receptor agonist zolpidem does not exhibit myorelaxant effects and does not seem to be associated with OH [84].

3.3 Antipsychotics

OH develops in up to 40% of patients taking antipsychotics [89], with a higher incidence at advanced age. Once again, OH is mediated by inhibition of α1-adrenergic receptors

Fig. 2 Effects of benzodiazepines on orthostatic blood pressure. Reproduced with permission (Rivasi et al. 2019, [83], Copyright Elsevier). *BDZs* benzodiazepines
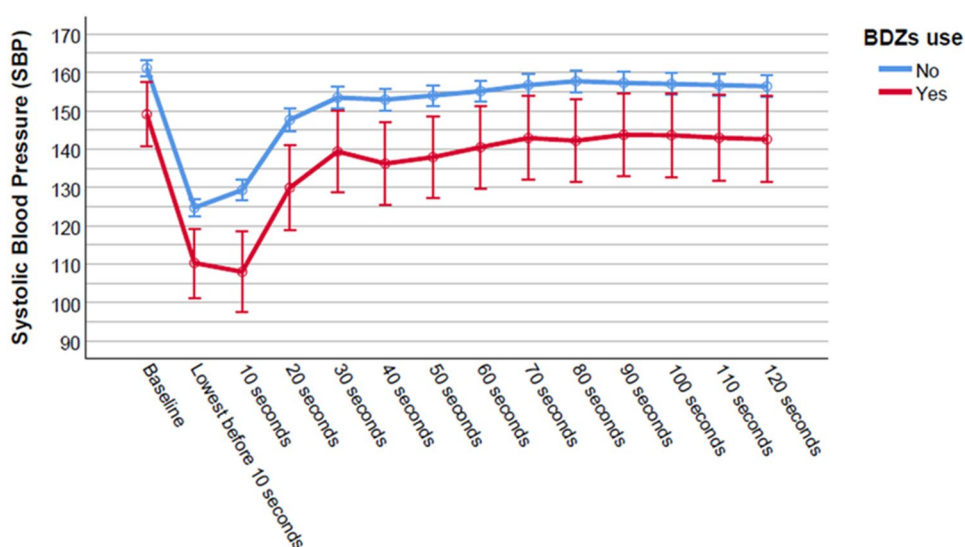
[77] and the risk profile of single molecules varies according to their binding affinity [90]. Clozapine and quetiapine show the highest risk, with an OH incidence of 24% and 27%, respectively [91]; a similar incidence is reported for chlorpromazine. Conversely, OH risk is lowest for haloperidol and olanzapine [12, 90]. Hypotensive effects are dose-related and the lowest effective dose should be prescribed, to minimize the risk of OH [91]. OH may be transient since tolerance usually develops within a few weeks [12]; however, an impairment of orthostatic BP response has been observed in chronic users as well [92].

3.4 Other Psychoactive Drugs

Dopaminergic drugs may cause OH through the activation of dopamine receptors, leading to cutaneous, mesenteric, and renal vasodilation [93]. Therefore, levodopa significantly contributes to OH associated with Parkinson disease, irrespective of the presence of autonomic dysfunction. Among antiparkinsonian drugs, the monoamine oxidase-B (MAO-B) inhibitor, selegiline, has also been reported to cause OH, even if the underlying mechanism is still unclear [94, 95]. Selegiline metabolites amphetamines and methamphetamines may be involved, causing a reduction in cardiac output and central norepinephrine levels [94]. Unlike selegiline, rasagiline, a second-generation MAO-B inhibitor, is less likely to cause hypotensive effects [96]. Conversely, treatment with entacapone, a catechol-*O*-methyltransferase (COMT) inhibitor, seems to have protective effects against OH, which are probably attributable to a reduced peripheral catabolism of catecholamines [97].

Opioids can decrease cardiac output when administered with BDZs or as part of anesthesia. Additionally, acute administration of opioids can lead to vasodilation and decreased sympathetic outflow. Moreover, the chronic use of opioids, including morphine, hydrocodone, hydromorphone, and meperidine can also induce histamine release, resulting in a significant decrease of vascular resistance and BP [13, 77]. Opioid treatment may thus favor OH, particularly in patients with reduced cardiac function or taking hypotensive medications [13].

The *N*-methyl-D-aspartate (NMDA) antagonist, memantine, was found to be significantly associated with OH in geriatric ward patients [31]. Additionally, a 2-fold increased risk of reflex syncope has been reported (RR 2.11) [98]. As memantine is typically prescribed to patients with moderate-to-severe dementia, a condition typically associated with OH, and the cited studies did not adjust for cognitive impairment severity, it is likely that a great extent of confounding is presented in the cited associations. Yet, a sympatholytic action of memantine may be involved, since NMDA receptors are also located in the cardiovascular system and mediate an increase in adrenergic activity [99]. French pharmacovigilance data are consistent with this hypothesis, reporting bradycardia as the most common cardiovascular adverse effect of memantine [100]. Similarly, a non-competitive NMDA receptor antagonist was found to induce bradycardia in pigs [101].

4 Drug Treatment of OH

In addition to a review of medical therapy, the first-line strategy for the management of OH is represented by non-pharmacological interventions including hydration, avoidance of precipitating factors for low BP, application of compression stockings or abdominal binders, and physical conditioning [2]. Pharmacological treatment options are limited, but can be considered in patients with more severe forms of OH if symptoms persist in spite of non-pharmacological strategies, provided that drug treatment is added to, rather than

replacing lifestyle measures [102–104]. Evidence supporting the efficacy of drug treatment for OH is scarce and mainly refers to patients with primary forms of autonomic failure, who actually represent a minority of OH subjects in routine clinical practice [102]. Among the available drug therapies, only droxidopa and midodrine have shown positive results in randomized controlled clinical trials and they represent the sole Food and Drug Administration-approved molecules for OH treatment [102].

It is important to consider that pharmacological strategies should not aim to achieve pre-defined BP values, but should rather target the improvement of patients' symptoms and quality of life [102]. Consequently, drug treatment of OH should be managed on an individual basis and progressively titrated to reach to lowest effective dose. In patients with symptoms refractory to treatment, combination therapy can be considered [104, 105].

4.1 Midodrine

Midodrine is an α1-agonist that acts through an increase in peripheral vascular resistance and the reduction of venous pooling in the splanchnic and leg vessels [106]. The use of midodrine in patients with neurogenic OH is supported by high quality of evidence [102]. Three randomized, double-blind trials have demonstrated that midodrine (2.5–30 mg/day) has a greater pressor effect than placebo in patients with autonomic failure [107–109], while Fouad-Tarazi et al. [110] have showed that midodrine significantly improves standing BP and orthostatic tolerance in these patients.

Midodrine is characterized by a short half-life, which requires frequent dosing and may limit long-term compliance [107]. Yet, this allows for its use in patients with supine hypertension (i.e., systolic BP values ≥ 140 mmHg and/or diastolic BP values ≥ 90 mmHg in the supine position [111]), as daytime administration does not significantly increase the risk of high nocturnal BP. Midodrine is usually administered at an initial dose of 2.5–5 mg twice to three times a day and then titrated, as tolerated, up to a maximum dose of 30 mg/day [112]. The most common adverse effects are pilomotor reactions, chills, and urinary retention, which requires special caution in older males [108, 109]. Dosing should not be administered within 4 hours of bedtime to avoid supine hypertension.

4.2 Droxidopa

Droxidopa is a synthetic norepinephrine prodrug that is converted into norepinephrine by aromatic L-amino acid (DOPA) decarboxylase in both central nervous system and peripheral tissues, thus promoting vasoconstriction [102]. The efficacy of droxidopa in neurogenic OH has been investigated in five randomized placebo-controlled trials. Most of

these showed beneficial effects on supine and standing BP and orthostatic tolerance [113–116], while two studies failed to demonstrate a significant improvement in patients' symptoms [117, 118]. Several additional small-sized studies and case reports further support the use of droxidopa in neurogenic OH [119–122], and a review by Keating confirms that droxidopa is associated with an improvement in orthostatic tolerance, a reduction in symptom impact on daily activities and an increase in standing systolic BP of approximately 10 mmHg [123]. However, the long-term efficacy of droxidopa remains to be confirmed and quality of evidence is considered to be moderate [102, 123].

Droxidopa is usually administered at an initial dose of 100 mg three times per day and is then titrated until symptom reduction occurs to a maximum dose of 600 mg three times per day [112]. Droxidopa has a favorable safety profile, showing an incidence of adverse events comparable to placebo and a relatively low reported incidence of adverse events related to supine hypertension [102]. However, it is not recommended to be taken within 3–5 h of bedtime to reduce the risk of high nocturnal BP. Other typical adverse effects include headache, dizziness, and nausea, which are often dose dependent [112]. Droxidopa may exacerbate symptoms in patients with heart failure, arrhythmias, and ischemic heart disease. Caution is also recommended in patients receiving other medications increasing norepinephrine levels (e.g., α1-agonists and α2-agonists) [124].

4.3 Fludrocortisone

Fludrocortisone is a synthetic mineralocorticoid, which expands intravascular volume by increasing renal water and sodium reabsorption [102]. Increase in plasma volume is usually transient, due to a mineralocorticoid escape [125]. The long-term effects of fludrocortisone are mainly attributed to an increase in vascular resistance, which is supposed to derive from enhanced sensitivity of α-adrenoreceptors and potentiation of the pressor effect of norepinephrine and angiotensin II [105, 124].

Fludrocortisone is commonly prescribed in patients with neurogenic OH, as it has been shown to improve standing and supine BP in small-sized, open-label studies involving patients with diabetes and Parkinson disease [126–130]. Yet, evidence supporting the use of fludrocortisone for OH therapy is considered to be weak [102].

Fludrocortisone is usually administered at the initial dose of 0.1–0.2 mg/day and then gradually increased up to 0.3–0.4 mg/day [112]. Common side effects include hypokalemia, supine hypertension, volume overload, and headaches. Given the risk of fluid overload, heart failure and renal impairment are relative contraindications to the use of fludrocortisone [112].

△ Adis

4.4 Pyridostigmine

Pyridostigmine is a cholinesterase inhibitor that prevents the metabolism of acetylcholine, thus potentiating cholinergic neurotransmission in sympathetic ganglia [102]. Consequently, pyridostigmine leads to an increase in BP that is especially to be expected when sympathetic tone is increased (i.e., on standing), while it has limited effects on supine BP. For the same reason, it is likely more useful in less severe patients with residual sympathetic function [131–133].

Evidence supporting the use of pyridostigmine is weak [102] and side effects associated with cholinergic stimulation may occur, such as abdominal cramps, diarrhea, sialorrhea, excessive sweating, urinary incontinence, and increased bronchial secretions/bronchospasm [102, 124]. However, some of these may be beneficial in patients with neurogenic OH and autonomic failure presenting with constipation and anhidrosis. Pyridostigmine should be used with caution in patients with bradycardia, glaucoma, renal impairment, or respiratory diseases, such as asthma or chronic obstructive pulmonary disease [124]. Typical dosing is 30–60 mg once to three times per day [112].

4.5 Emerging Treatment Options

4.5.1 Octreotide

Octreotide is a somatostatin analog that reduces the release of gastrointestinal vasodilatory peptides and the subsequent postprandial splanchnic hyperemia, thus counteracting venous pooling in the splanchnic district [124]. Alam et al. analyzed the effects octreotide on 24-hour ambulatory BP in 18 subjects with primary autonomic failure and reported an increase in systolic and diastolic BP (+ 5 and + 2 mmHg, respectively) and a reduction in postural and post-prandial hypotension and related symptoms. Additionally, a decrease in nocturnal BP was observed [134]. However, quality of evidence showing the efficacy of octreotide is considered to be low [102]. Octreotide is administered through subcutaneous injections at a dose of 12.5–25 µg [124]. The development of gallstones or biliary sludging, abdominal pain and nausea, dysglycemia, and hypothyroidism may occur as adverse effects. For this reason, octreotide is not recommended in patients with diabetes mellitus, especially in case of concomitant gastroparesis [124].

4.5.2 Atomoxetine

Pharmacologic inhibition of the norepinephrine transporter with atomoxetine was found to improve orthostatic tolerance in patients with autonomic failure, thus representing a promising treatment option [135]. Yet, the potential use of atomoxetine is limited by low quality of evidence and safety concerns [102]. Attention should be given to potential adverse effects including depression, aggressive behavior, priapism, and urination retention. Additionally, hepatotoxicity can occur, thus making liver function monitoring advisable and dose adjustment necessary in patients with hepatic impairment [124]. Finally, death, stroke, and myocardial infarction have been described in patients with severe structural cardiac diseases or heart rate abnormalities receiving atomoxetine [124].

4.5.3 Desmopressin

The vasopressin analog desmopressin acts as a volume expander, increasing water reabsorption. Desmopressin has been shown to reduce nocturnal polyuria and the related morning fall in orthostatic BP in patients with autonomic failure [135]. However, its efficacy remains uncertain [102]. Additionally, careful treatment monitoring is required to avoid water overload and hyponatremia, which seem to be less likely with low-dose intranasal formulations [135].

4.5.4 Erythropoietin

As anemia predisposes to an impairment of the BP response to standing, recombinant erythropoietin may play a role in the pharmacological approach to OH [102]. Data from a small sample of patients with neurogenic OH indicate that erythropoietin may increase orthostatic systolic and diastolic BP and improve orthostatic symptoms, with no relevant changes in supine BP [136]. Erythropoietin-mediated BP increase is likely related to multiple mechanisms involving an increase in red-cell volume, nitric oxide resistance, and endothelin-1 production [136, 137]. However, its use is limited by the risk of cardiovascular events and mortality [137].

5 Conclusion

Medical therapy is one of the most common causes of OH. Medications at highest risk of OH include cardiovascular drugs (e.g., diuretics, nitrates, β- and α-receptor blockers), and non-cardiovascular drugs (e.g., antidepressants, antipsychotics, trazodone, and BDZs). Table 1 provides a risk stratification for commonly used medications. There is virtually no head-to-head comparisons of different drug classes and the available literature referring to drug-related OH mainly includes small studies with a cross-sectional design, with most providing conflicting results. Therefore, the risk stratification provided in Table 1 may be questionable, somewhat arbitrary, and not supported by strong evidence but mostly by clinical experience and available scientific data. Nevertheless, since our paper aims to be a

Table 1 Cardiovascular (a) and psychoactive drugs (b) predisposing to drug-related orthostatic hypotension: overview of hypotensive mechanisms, risk profiles and therapy optimization strategies

Drug class	Main mechanism responsible for drug-related OH	Risk profile	Practical advice for drug review in patients with OH
A. Cardiovascular drugs			
α-Blockers	Reduced vascular resistance [29–31]	+++	Avoid as a treatment for hypertension in older patients [32, 39, 42] Prefer uroselective molecules (e.g., silodosin) in patients with bladder outflow obstruction [35–37] Preferably administer at bedtime
Nitrates	Vasodilation	+++	Prescribe the lowest effective dose for symptom (angina) control and attempt discontinuation if patient is asymptomatic [27]
Diuretics	Volume depletion	++	Prescribe the lowest effective dose and consider withdrawal if fluid overload is absent and OH is clinically significant [27] Avoid loop diuretics (e.g., furosemide) as a treatment for hypertension if high risk of volume depletion is present, unless specifically required (e.g., renal dysfunction) [26]
β-Blockers	Interference with compensatory reflex responses to standing (e.g., sympathetic-mediated vasoconstriction, increased heart rate response and inotropism) [77]	++	Consider withdrawal in presence of OH, unless specifically indicated (e.g., heart failure) [42] Preferably avoid mixed α- and β-blockers (e.g., carvedilol) in patients with OH [48]
Calcium channel blockers	Reduced heart rate response and inotropism (non-dihydropyridines), vasodilation [77]	++	Prefer dihydropyridine calcium antagonist (e.g., amlodipine or lacidipine), unless a negative chronotropic effect is required [56]
Clonidine	Reduced sympathetic tone [49]	+	OH risk debated [12, 49, 50], preferably use as a second-line antihypertensive therapy
ACE-inhibitors, Angiotensin II receptor blockers	Low risk, possible protective effect [18, 28, 46, 47]	+	Preferably use as a first line antihypertensive therapy First-dose phenomenon to be considered [60–64]
B. Psychoactive drugs			
Levodopa	Vasodilation [93]	+++	Prescribe the lowest effective dose
Antipsychotics	Reduced vascular resistance [77]	+++	Start with a low dose Prescribe at the lowest effective dose Highest risk for clozapine, quetiapine, and chlorpromazine [91]
Tricyclic antidepressants	Reduced vascular resistance [12]	++	Prefer SSRI or SNRI antidepressants (e.g., sertraline, paroxetine, citalopram, venlafaxine) [12]
Benzodiazepines	Unclear (myorelaxation, reduced sympathetic tone) [83–87]	++	Avoid in older people [83] Prescribe the lowest effective dose
Trazodone	Reduced vascular resistance [77]	++	Start with a low dose [79] Prefer prolonged-release formulations or fractioned doses [69, 70, 72]
Opioids	Reduced vascular resistance [13, 77]	++	Prescribe the lowest effective dose Caution in patients with cardiac dysfunction and/or hypotensive drugs [13]
SSRI, SNRI	Unclear (inhibition of calcium channels, central serotonin agonism, overstimulation of presynaptic α2-adrenergic receptors) [73, 77]	+	OH possible but less common than with tricyclic antidepressants [9, 12, 66]
Memantine	Unclear [98–101]	+	OH risk potentially related to both therapy and dementia [98–100]

+++, Highest risk of drug-related OH; ++, intermediate risk of drug-related OH; +, lowest risk of drug-related OH

OH orthostatic hypotension, *SNRI* serotonin-norepinephrine reuptake inhibitors, *SSRI* serotonin-selective reuptake inhibitors

practical tool for therapy optimization in patients with OH, this risk stratification may be useful to increase awareness on potential causative drugs and to identify priorities in the context of medication review. Withdrawal or reduction of potentially causative medications may reduce drug-related OH and represents a first-line treatment strategy in patients with orthostatic BP impairment.

Specific drug treatment for OH may be considered if symptoms persist despite non-pharmacological measures. Health care professionals should thus be educated to optimize medical therapy in subjects with OH, in the context of a comprehensive assessment of clinical status and preferences of individual patients.

Declarations

Conflicts of interest/competing interests Giulia Rivasi, Martina Rafanelli, Enrico Mossello, Michele Brignole, and Andrea Ungar declare that they have no potential conflicts of interest that might be relevant to the contents of this manuscript.

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Consent to participate Not applicable.

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