Orthostatic Hypotension and Drugs: Drug-Induced Orthostatic Hypotension

6

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Abbreviations

ACE	Angiotensin Converting Enzyme
CCBs	Calcium Channel blockers
DOH	Drug-Induced Orthostatic Hypotension
L-DOPA	Levodopa
OH	Orthostatic Hypotension
PD	Parkinson's Disease
TCAs	Tricyclic Antidepressants

6.1 Introduction

Drug-Induced Orthostatic Hypotension (DOH) is an unnoticeable finding or symptom and one of secondary OHs in the elderly [1]. DOH or symptoms are associated with increased neurodegenerative changes or diseases leading to autonomic nervous system (ANS) malfunctioning. If DOH is not asymptomatic, DOH like OH is usually manifested by varying degrees of light-headedness on standing, a symptom tolerated by most individuals. In more progressive periods, it is inevitable that it leads to syncope, falls, injury, cerebrovascular accidents, and myocardial infarction as a result of reduced perfusion. Normally, decreased blood pressure is prevented by autonomy tone or reflex sympathetic system activation with an increase in heart rate, and constriction of peripheral veins and arteries, but not works sufficiently in patients with OH. Therefore, impairment or dysfunction of autonomic tone (or

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A. T. Isik, P. Soysal (eds.), *Orthostatic Hypotension in Older Adults*,
https://doi.org/10.1007/978-3-030-62493-4_6

reflexes) that regulate blood pressure may lead to OH. DOH is frequent due to drugs that may interfere with autonomic function (e.g., antihypertensive drugs, antidepressants, diuretics, and blocker drugs for the treatment of urinary retention), diseases which causes peripheral autonomic neuropathies such as diabetes, and less widely, primary degenerative disorders of the ANS [2]. As a result, orthostatic hypotension may be frequently triggered or developed easily by drugs in elderly and DOH occurs. The presence of DOH reflects a functional or structural sympathetic denervation or a deranged reflex readjustment of sympathetic outflow DOH frequently observed in elderly and patients with neurodegenerative diseases, diabetes, or hypertension.

In 1996, OH was described, as a drop in systolic blood pressure ≥20 mmHg or diastolic blood pressure ≥10 mmHg on postural challenge, with or without symptoms, after 3 min of standing or head-up tilt to at least 60° on a tilt table, by the American Academy of Neurology and the American Autonomic Society. In 2011, the definition was updated, as initial and delayed OH. A transient blood pressure decline (≥40 mmHg systolic blood pressure and/or ≥20 mmHg diastolic blood pressure) within 15 s of standing is defined as initial OH, whereas OH that occurs beyond 3 min of postural challenge, was defined as delayed OH [2]. Position change from supine to the upright is the significant parameter responsible for the degree of the decrease. Also, the occurrence of the symptoms of OH is due to the degree of decrease, rather than the low blood pressure value [3].

6.2 Epidemiology

OH is very common, affecting one in five community-dwelling older people, the prevalence ranges from 5% to 30%, increases with age and mostly seen in patients ≥65 years old [4–6]. Prevalence studies indicating that about 25% of type II diabetic patients, 30% of people aged ≥65 years, and 70% of Parkinson's disease patients are experiencing orthostatic hypotension [7]. Symptoms of patients suffering from OH are light-headedness, dizziness, nausea, weakness or blurred vision during in standing position. Due to the nonspecific symptoms of orthostatic hypotension like dizziness, fatigue, difficulties in concentration, and vision problems, it is estimated that it is a more common issue among geriatric population [8]. Risk factors are medications (particularly antihypertensive drugs), smoking, being on a bed rest for a long time and some comorbidities. Initial period of neurodegenerative diseases including Parkinson's disease and neuropathic diseases like Diabetes mellitus may provoke DOH, which is closely related to instability of autonomic nervous system, but it is also a frequent symptom among hypertensive patients [9] and frailty in elderly patients [10]. On the other hand, the underlying cause of the non-neurogenic OH may be hypovolemia, which can be caused by disorders such as chronic bleeding, diabetes insipidus, adrenal insufficiency, diarrhea or dehydration [3, 5, 11].

Increased diurnal BP variabilities and hypertension, which are both present in cases of primary and secondary OH, may provoke episodic attacks with increased afterload, leading to permanent organ damage, such as left ventricular hypertrophy

and reduced renal function, high risk of congestive heart failure, and also ischemia in myocardium. Moreover, altered autonomic tone in patients with hypertension [13] and sleep apnea [12]is known to be associated with the development of atrial fibrillation [14], which is itself accepted as a famous risk factor for heart failure [13, 14].

Disruption of blood pressure homeostasis is account for increasing the actions of neuroendocrine compensatory systems, also will possibly promote the occurrence of cardiovascular or cerebrovascular events. Supporting this theory, vascular endothelin system hyperactivation has been detected in patients with fall or syncope due to OH [15]. Therefore, endothelin 1 and vasopressin, which are considered as endogen vasoconstrictors and play a role to maintain adaptive mechanisms along orthostatic hypotensive stress, may cause atherothrombotic vascular events in predisposed individuals [16]. However, current literatures do not display us until now to reach any conclusion as to whether OH is a sign of mortality risk, an intermediate variable of the cardiovascular risk factors, a stage of disease severity, or a different causative mechanism.

6.3 Drug-Induced Orthostatic Hypotension

Patients with DOH may show abnormal responses to a lot of pharmacological conditions or physiological changes, such as wide fluctuations in BP [17]. Medications and diseases conditions that may produce functional disruption of the autonomic nervous system cover treatment with antihypertensive drugs (vasodilators, α-adrenergic receptor antagonists, calcium channel blockers, diuretics, angiotensin converting enzyme inhibitors, diuretics, and β-adrenergic receptor blockers) antidepressants, antipsychotics and chemotherapeutic agents; relative decrease in circulating volume; peripheral venous pooling; and congestive heart failure [18]. List of drug groups causing OH are shown in Table 6.1.

Although, DOH is seen in patients who have progressive changes in cardiovascular physiology associated with normal aging, most patients do not experience OH unless they have concurrent diseases, or the patient is receiving drugs which are known to induce hypotension. There are increased number of unrecognized cases as majority of patients with OH are having few nonspecific findings and they are usually asymptomatic.

OH Patients may also suffer from wide BP swings and also recumbent hypertension, or they may have abnormal responses to some pharmacological or physiological difficulties [17, 19].

Immobilization, alcohol drinking, alcohol drinking, post-exercise, heat and fever are considered as predisposing conditions to dehydration and venous pooling, which may exacerbate the symptoms especially in the mornings after waking up. After consumption of large meals with carbohydrate-rich food, patients with autonomic dysfunction become more open to occurrence of postprandial hypotension, as a result of gastric distension, release of vasodilator endogen peptides and splanchnic blood pooling [20]. Nocturnal polyuria, resulting from the distribution of peripheral

Table 6.1 Main drug groups causing orthostatic hypotension

Calcium Channel blockers
Vasodilators (nitrates)
Angiotensin converting enzyme inhibitors
Diuretics
α-Adrenergic receptor antagonists
β-Adrenergic receptor blockers
Sympatholytics
Antipsychotics
Antianginals
Antiarrhythmics
Anti-parkinsonian drugs
Antidepressants
Monoamine oxidase inhibitors
Dopamine receptor agonists
Drugs for erectile dysfunction
Chemotherapeutic agents
Phenothiazines
Narcotics/tranquilizers/sedatives

Table 6.2 Predisposing factors affecting orthostatic hypotension by normal aging [28]

Predisposing factors		
Vascular	Cardiac	Renal
• Decreased baroreceptor activity • Decreased arterial compliance • Increased venous capacity • Decreased plasma volume • Low cerebral blood flow • Decrease in vasopressin response (via V_1 receptors)	• Reduced cardiac compliance • Reduced cardiac output	• Reduced renin/angiotensin activity • Decrease in vasopressin response (via V_2 receptors) • Reduced renal sodium conservation

blood to central regions in supine status, is a common complaint and also aggravated by natriuresis with accompanying supine hypertension. Thereby, tendency to morning hypotension may be enhanced in these patients and they may suffer from decreased intravascular volume overnight.

6.4 The Relationship of Orthostatic Hypotension with Age

Most patients with DOH are asymptomatic or have few nonspecific symptoms, so, it is very hard to predict the rate of unrecognized cases [21]. However, aging is the most important risk factor for DOH like OH [22, 23], also with some medications (nitrates, antihypertensive drugs, α-adrenergic blockers, antidepressants, polypharmacy) [24, 25] and other unspecific factors worsening OH (alcoholism, female sex, increased body temperature, insufficient body mass index, and smoking [26, 27]. Predisposing and protective factors affecting OH by normal aging are shown in Table 6.2 [28]. When the central arterial pressure and cerebral perfusion related

with cerebral tissue oxygenation declines critically during OH, patients may additionally report dizziness, blurred vision, fatigue, and, finally, suffer from loss of consciousness.

In the early periods of aging, low blood pressure or OH symptoms are not always observed with DOH, but may be triggered by medications. When there is an increase in neurodegenerative changes, OH symptoms including dizziness, light-headedness, and syncope, all related to insufficient blood flow to brain regions, and also fatigue, weakness, blurred vision, hearing impairments or cognitive slowing may be observed [21, 29]. As known, DOH is usually asymptomatic [21], but carries a risk for falls, syncope or cognitive dysfunction like OH [7]. If patients with DOH have symptoms at young and middle-ages, various neurodegenerative diseases are manifested by OH and it can be seen in early stages of the disease by some drugs. However, autonomic dysfunction is low to be drug-triggered or the level of disruption in the autonomic neuron is not enough [22].

6.5 Pathophysiology

Pathologically, OH are often classified as primary and secondary types [30] and clinically are subdivided into acute and chronic forms [17]. DOH, is considered as a secondary OH, it is triggered by medications and some chronic diseases such as diabetes mellitus and cardiovascular diseases. OH can be classified into pathophysiological categories as neurogenic (structural) and non-neurogenic (functional) causes of autonomic dysfunctions. Neurogenic OH is a critical manifestation of autonomic dysfunction related with primary chronic neurodegenerative disorders, such as multiple system atrophy, or Parkinson disease, however the diseases that cause neurological disorders such as diabetes, polypharmacy, or advanced renal failure can cause secondary type [30, 31].OH resulting from the autonomic dysfunctions originated to a primary neurodegenerative disease, is usually considered as neurogenic OH. Some systemic illnesses producing peripheral neuropathy can cause secondary autonomic dysfunction or failure. The etiology of secondary OH leading to autonomic dysfunctions is shown in Table 6.3.

Dysautonomic manifestations related with neurodegenerative changes cause OH by the relation of different parts of the autonomous nervous system in elderly. For example, autonomic dysfunction of the cardiovascular system is connected to a loss or decrease of peripheral noradrenergic innervation. All of these dysautonomic symptoms are mainly associated to preganglionic autonomic neuron degeneration of the brainstem and spinal cord [32]. Although, there are many different symptom-specific scales that clinically being used, they are insufficient to identify OH symptoms according to degree of neuropathology or aging and to estimate OH prevalence [33].

Table 6.3 Etiology of autonomic dysfunction related with secondary orthostatic hypotension

Polypharmacy
Iatrogenic (drug-related)
Older age
Diabetes mellitus
Cerebrovascular disease
Cardiovascular diseases (essential hypertension, pulmonary hypertension, sick-sinus syndrome, AV-block, heart failure, aortic stenosis)
Renal failure
Volume reduction
Venous pooling
Polyneuropathy (alcohol and other)
Endocrine disorders (diabetes insipidus, adrenal insufficiency, thyroid diseases)
Amyloidosis
Autoimmune diseases
Multiple myeloma
Paraneoplastic syndromes
Multiple sclerosis
Spinal cord diseases

6.6 The Control Mechanisms in Maintaining Blood Pressure

Regulation mechanisms of BP are complicated physiological functions depending on continuous actions of the cardiovascular, endocrine renal and neurologic systems [31]. While central blood flow maintains as control of BP through the changes in vascular tonus and cardiac output, regional blood flow occurs through local mediators (eicosanoids, endothelin, nitric oxide, and tissue plasminogen activators). The maintenance of these physiological changes is provided by the intact autonomic nervous system consisting of the parasympathetic and sympathetic nervous systems. The sympathetic nervous system determines the size or magnitude of arterial BP and the distribution and regulation of cardiac output [32]. Therefore, adrenergic receptors will be discussed extensively in below. The parasympathetic contribution to the setting of vascular tone is less importance.

Baroreceptors and chemoreceptor feedback reflex mechanisms regulate the short-term reflex control of the sympathetic vasomotor activities. In cases of different external stimuli or stresses, central mechanisms will also produce sympathetic activities [33]. The long term control of cardiovascular homeostasis depends on various mechanisms, including renal changes in the control of extracellular volume, natriuresis, the levels of sympathetic vasomotor activity, and the renin-angiotensin-aldosterone systems [33–35].

DOH can be well accomplished by solving the likely causes and understanding the mechanisms related with the maintenance of blood pressure due to sudden position changes. Considering the effect of gravity, standing up causes the translocation of blood to lower parts of the body, decreased venous return and eventually reduced stroke volume and decreased cardiac output [5]. Compensating actions of the body

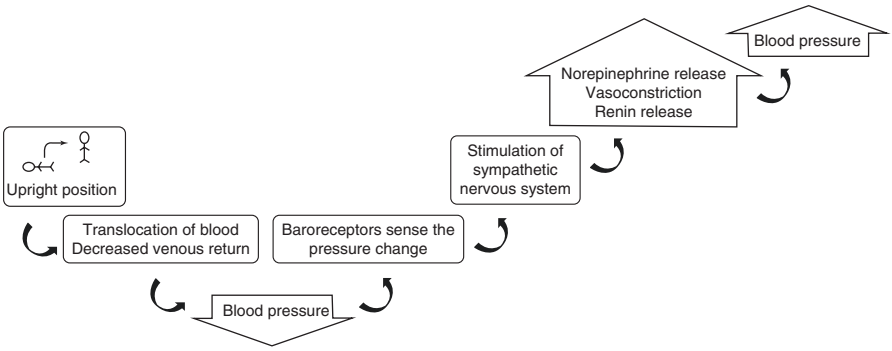

Fig. 6.1 Compensating actions to regulate blood pressure in response to standing

includes (1) muscle pump, (2) baroreflex mechanisms and (3) renin-angiotensin-aldosterone system (Fig. 6.1):

1. In the upright position, approximately 600 ml of blood are redistributed and pooled in lower extremities, venous return of the circulating blood to the heart is decreased. Muscle contractions compress capacitance vessels, increase venous return, and inhibit the excess pooling of the blood in lower parts of the body. Skeletal and gluteal muscles pump blood from the legs and force blood supply to the heart through the venous system. These muscle contractions are considered as the primary defense against decreased venous return [5, 36, 37].
2. The neurovascular adjustments start with a decrease in blood pressure and this decrease is detected immediately by the baroreceptors. These baroreceptors which are responsible from sensing the pressure changes, are located in the carotid sinus, intima of the aortic arch and also in the walls of the atrium and ventricles. When there is a sudden decrease in blood pressure, this information is noticed by baroreceptors, integrated in the medulla and the compensatory mechanisms are stimulated. This mechanism in the heart and vessels works within seconds via sympathetic nervous system. Increased norepinephrine release and α-adrenergic receptor stimulation lead to vasoconstriction and causes blood to move toward the upper parts of the body. Standing up causes a temporary drop in afferent arteriole perfusion pressure. Low or decrease in renal arterial pressure and sympathetic neural activity (through β-adrenergic receptors) stimulates release of renin by the juxtaglomerular apparatus and triggers the renin-angiotensin-aldosterone system [5, 36, 37].
3. Renin-angiotensin-aldosterone system is a longer-lasting control mechanism for the regulation of blood pressure. Angiotensinogen, which is produced in the liver, is converted to angiotensin I by an enzyme called renin. Renin production increases in case of reduction in sodium levels and in blood pressure, which is perceived by the kidneys. Decreased blood pressure can stimulate the sympa-

thetic activity, and also renin secretion is increased via β_1-adrenergic receptors. Angiotensin I, an important active precursor, is cleaved by the angiotensin converting enzyme to produce angiotensin II. Angiotensin II, a more active form leads to direct constriction of resistance vessels and stimulates the secretion of aldosterone from the adrenal glands. Aldosterone increases renal reabsorption of sodium and therefore leads to elevated blood sodium and increasing water retention and blood volume. These homeostatic actions of the renin–angiotensin aldosterone system occurs in minutes and hours, and responsible from the regulation of blood pressure [5, 36, 38].

6.7 Drug-Mediated Dysfunctions of Blood Pressure Maintenance in Older Age

The compensating actions of the body may become insufficient as a result of some age-related structural changes. Especially, evaluation of age-related pathological changes in the vessels should be the starting point of orthostatic hypotension. Advanced age may promote pathophysiological modifications that result in ineffective compensation to blood pressure changes. These modifications include thickening and dilation of large arteries, increased stiffness of barosensory vessel walls and decreased effectiveness of cardio-vagal autonomic control [39, 40]. Venous pooling and decreased venous return cause a reduced stroke volume due to the change of supine to standing position, and therefore decreases cardiac output. The natural response of the cardiovascular system will be increasing the heart rate and vasoconstriction in order to maintain blood supply to the cerebral tissues. In the elderly, blood vessels become inadequate to respond these blood pressure changes, and heart rate is more stable. These alterations of the autonomic nervous system have an important role in the development of age-dependent increase of the prevalence of OH [41]. On the other hand, the blood volume is reduced owing to the dehydration or reduced hematopoiesis in geriatric patients. These age-related changes that contribute to the occurrence of OH, are not temporary and will deteriorate consistently over time [42]. Risk of OH is increasing not only because of the pathophysiological changes but also some medical interventions, considering the fact that geriatric patients are under treatment with medications (prescription and non-prescription drugs) that may attenuate the normal physiologic response to standing. Also, regarding the increased prevalence of polypharmacy in elderly patients, DOH should become under review [19].

OH is a side effect of many common medications used by older persons including for α-adrenergic receptor antagonists, calcium channel blockers, diuretics, angiotensin converting enzyme inhibitors, antipsychotics, beta-adrenergic receptor blockers, anti-Parkinsonian drugs, antianginal, and antidepressant medications [24, 28]. All of the drugs that could potentially cause OH side effects are presented on Table 6.4 [43]. However, the drugs leading to potentially If OH occurrence is a side effects of drug, it need to evaluate again potential predisposing factors for definition of pathology. In some cases, it may be difficult and hazardous to stop the offending

Table 6.4 List of the drugs that lead to orthostatic hypotension and hypotension as side effect [43]

Drugs with orthostatic hypotension side effects				
Irinotecan	Labetalol	Pramipexole	Tamsulosin	
Drugs with hypotension side effects				
Acamprosate	Clonidine	Imipramine	Olanzapine	Silodosin
Acebutolol	Clozapine	Indapamide	Olmesartan	Sitagliptin
Alfuzosin	Codeine	Irbesartan	Olsalazine	Sitaxsentan
Amantadine	Conivaptan	Irinotecan	Oxcarbazepine	Sodium nitroprusside
Amiloride	Dacarbazine	Isocarboxazid	Oxprenolol	Sparfloxacin
Amisulpride	Dapagliflozin	Isosorbide	Oxycodone	Tacrolimus
Amitriptyline	Delavirdine	Itraconazole	Oxymorphone	Tadalafil
Amlodipine	Deprenyl	Ivermectin	Paclitaxel	Tamsulosin
Amphotericin B	Desmopressin	Ketoconazole	Paliperidone	Telmisartan
Anagrelide	Desvenlafaxine	Labetalol	Parecoxib	Terazosin
Apomorphine	Diazepam	Lamotrigine	Paroxetine	Tetrabenazine
Aripiprazole	Diltiazem	Lercanidipine	Pergolide	Thalidomide
Asenapine	Dipyridamole	Leuprorelin	Perindopril	Thiazide
Atenolol	Docetaxel	Levodopa	Perphenazine	Tiagabine
Atorvastatin	Dolasetron	Levomepromazine	Phenelzine	Tizanidine
Azilsartan	Donepezil	Linaclotide	Phenoxybenzamine	Tolvaptan
Baclofen	Dothiepin	Lisuride	Phentolamine	Topiramate
Benazepril	Doxazosin	Losartan	Phenylephrine	Tramadol
Bendrofluazide	Doxorubicin	Loxapine	Phenytoin	Trazodone
Betahistine	Duloxetine	Lurasidone	Pimozide	Trospium chloride
Bisoprolol	Empagliflozin	Maprotiline	Pindolol	Valproate
Bortezomib	Entacapone	Maraviroc	Polythiazide	Valsartan
Bosentan	Eplerenone	Mecamylamine	Posaconazole	Vardenafil
Bretylium	Eprosartan	Medroxyprogesterone	Pramipexole	Venlafaxine
Bromocriptine	Eslicarbazepine	Memantine	Prazosin	Verapamil
Bupivacaine	Ethionamide	Meperidine	Pregabalin	Vinflunine
Buprenorphine	Etoricoxib	Methadone	Propafenone	Voriconazole
Bupropion	Felodipine	Methysergide	Prostacyclin	Zaleplon
Cabazitaxel	Fenoldopam	Metolazone	Protriptyline	Ziconotide
Cabergoline	Fentanyl	Metoprolol	Quetiapine	Ziprasidone
Canagliflozin	Finasteride	Mirtazapine	Quinapril	Zolmitriptan
Candesartan	Flunitrazepam	Mitotane	Quinaprilat	Zolpidem
Capecitabine	Fluoxetine	Moexiprilat	Quinidine	
Captopril	Fluvoxamine	Morphine	Ramipril	
Carbamazepine	Fosinopril	Moxifloxacin	Ranolazine	
Carbidopa	Fosphenytoin	Moxonidine	Rapamycin	
Carisoprodol	Furosemide	Mycophenolate	Rasagiline	
Carvedilol	Gadobutrol	Mycophenolic acid	Reboxetine	
Cevimeline	Galantamine	Nabilone	Rifapentine	
Chlorpromazine	Granisetron	Nefazodone	Riluzole	
Chlorthalidone	Guanfacine	Niacin	Risperidone	
Cidofovir	Halofantrine	Nicardipine	Ritonavir	
Cilazapril	Haloperidol	Nicorandil	Rivastigmine	
Cilostazol	Hydrochlorothiazide	Nifedipine	Ropinirole	
Ciprofloxacin	Hydroflumethiazide	Nisoldipine	Ropivacaine	
Cisplatin	Hydromorphone	Nitroglycerin	Rotigotine	
Citalopram	Ibutilide	Norfloxacin	Sertraline	
Clomipramine	Icodextrin	Nortriptyline	Sibutramine	
Clonazepam	Iloperidone	Ofloxacin	Sildenafil	

medications. In these cases, different treatment strategies including the use of salt tablets, elevation of the head of the bed, and fludrocortisone administration may be instituted prior to or while continuing the offending medication [44]. However, the main strategy in DOH is to change the treatment of the disease that causes drug use and then to confirm it.

6.8 α-Adrenergic Receptor Antagonists

Antihypertensive mechanism of action ofα-adrenergic receptor antagonists is the selective blockade of postsynaptic α_1 receptors located both in arterioles and venules. This blockade results a decrease in arterial blood pressure because of dilation in both resistance and capacitance vessels. Therefore, patients under therapy with α_1 receptor blockers are likely to have decreased blood pressure when changing from supine position to the upright position. Monitorization of the blood pressure should be maintained especially for elderly patients [28, 36, 45].α_2 receptor stimulation in the brain results in presynaptic inhibition or in a decrease in the release of norepinephrine from the vasomotor center centrally, increases the vagal tone and therefore reduces the blood pressure. The decrease in sympathetic tonus may result in decreased heart rate, cardiac output, peripheral resistance, level of plasma renin and activity of baroreceptor reflexes, therefore, may cause OH.

6.9 Diuretics

Diuretics are effective in lowering blood pressure by depleting the sodium stores in the great majority of patients and thereby causing volume depletion by increasing the volume of urine excreted. The decrease in plasma volume that results in response to an increased urine and Na excretion, lowers cardiac output and venous return. Most side effects of diuretics are, generally dose-dependent, including hyponatremia, hypovolemia, and hypotension. Diuretics can be used as monotherapy in patients with mild to moderate primary hypertension. In patients with severe hypertension, diuretics can be used in combination with sympatholytic and vasodilator drugs. Also, in the elderly, when considering the dehydration, weakness and volume depletion in these patients, the risk of OH due to the diuretic therapy will be increased [28, 36, 46, 47].

6.10 Angiotensin Converting Enzyme (ACE) Inhibitors

ACE Inhibitors inhibit competitively the activity of ACE (also termed kininase II) to prevent formation of angiotensin II (more active octapeptide) from angiotensin I (less active decapeptide). Its reduce total peripheral resistance and systolic and diastolic BP by decreasing vasoconstrictor effects of angiotensin II and sodium-retaining activities through aldosterone. ACE is also named as plasma kininase, which is responsible from the breakdown of a potent vasodilator bradykinin. Therefore, ACE inhibitors increase the actions of the kallikrein—kinin system, and the release of nitric oxide and prostacyclin will be increased. Patients with low cardiac output like in congestive heart failure and also patients with high plasma renin activity may experience excessive fall in blood pressure and are at risk of OH [28, 42, 47, 48].

6.11 Calcium Channel Blockers

Calcium channel blockers (CCBs) act on the L-type calcium channels found in the vascular smooth muscle and cardiac myocytes. Blockade of these channels inhibits the influx of calcium into muscle cells, thereby results in the inhibition of smooth muscle contraction and also cardiac muscle contraction [49].Dihydropyridine calcium channel blockers inhibit calcium influx into arterial smooth muscle cells and cause vasodilation more selectively, and their depressant effect on the heart is less than verapamil and diltiazem. Dihydropyridine calcium channel blockers require monitoring in elderly patients with hypertension, as they are potent vasodilators and overdose can lead to an excessive fall in blood pressure, also postural hypotension [3, 28, 36].

6.12 Beta-Adrenergic Receptor Antagonists

β-Adrenergic receptors have three subtypes: β_1, β_2, and β_3. Beta-1 receptors are predominantly found in two locations: the heart and the kidneys. Norepinephrine binds to the beta-1 and beta-2 receptors and activation of these receptors results in positive inotropic, dromotropic, and chronotropic effects on the heart. Activation of beta-1 receptors increases renin release from the juxtaglomerular apparatus of the kidney [47]. β-adrenergic receptor antagonists decrease blood pressure by blocking β_1 adrenergic receptors, decreasing cardiac output and inhibiting the stimulation of renin production. The cardiac-selectivity, partial agonist activity, and associated vasodilating properties of β-adrenergic receptor antagonist drugs, originated from the receptor selectivity and emphasize their pharmacodynamics properties. Some β-blockers having partial agonistic activity or intrinsic sympathomimetic activity, also having inhibitor activity both on α and β adrenergic receptors, may reduce blood pressure with a low incidence of side effects. If there isn't a problem with the electrical conduction system of the heart and cardiac functions are not impaired, β-blockers considered as safe and effective for hypertension and the incidence of OH is low [3, 28, 36, 50].

6.13 Antipsychotic Drugs

Desired pharmacological activity of antipsychotic drugs is through the blockade of dopaminergic (D_2) receptors in the central nervous system. The excess dopaminergic activity in the limbic system plays a critical role in the development of psychosis and the most of antipsychotic drugs block postsynaptic D_2 receptors especially in the mesolimbic and striatal-frontal pathways [36].Although the most of effective antipsychotic drugs block D_2 receptors, the levels of this blockade varies considerably among drugs and blockade of α adrenergic, muscarinic, H_1 histaminic, and serotonin receptors is responsible from their possible adverse reactions. Decreased baroreceptor reflex during orthostatic stress, and also decreased venous return and

cardiac output may contribute to orthostatic hypotension, which is one of the clinical side effects of antipsychotic drugs [51–53]. These effects are originated from the presence of autonomic actions of these agents; manifestations of the muscarinic cholinergic receptor blockade are dry mouth, difficulty urinating and constipation, while α adrenergic receptor blockade are orthostatic hypotension.

6.14 Tricyclic Antidepressant Drugs

Antidepressants mostly focus on the monoamine hypothesis of depression suggesting that depression is related to decreased levels of serotonin, norepinephrine and dopamine as neurotransmitter in the central nervous system. Antidepressant activity of the tricyclic antidepressants (TCAs) is through the inhibition of serotonin and norepinephrine reuptake. Although the TCAs were the most important class of antidepressant agents, the use of TCAs is reserved for the patients who are unresponsive to selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors, due to their poorer tolerability. TCAs may cause dry mouth and constipation and these adverse effects are originated to the potent anti-muscarinic actions of these drugs. However, these drugs can also act as potent antagonists of the histamine (especially H_1) receptor, causing weight gain and sedation. In addition to these, OH due to the α_1 adrenergic receptor blocker properties, is a significant adverse effect of TCAs particularly seen in older patients [28, 36, 54].

6.15 Anti-parkinsonian Drugs

Decreased dopaminergic activity in the central nervous system is the major concern for Parkinson's disease (PD) and considered as the major cause of the motor symptoms. Patients with Parkinson's disease, when compared with age-matched people in general population, generally have lower blood pressure levels. This posture related drop in blood pressure is frequently seen in PD patients, but it is generally asymptomatic [55]. Drugs used for the treatment of Parkinson's disease mainly focus on dopaminergic activity and may cause OH by interfering the autonomic or cardiovascular compensation mechanisms. OH has commonly seen and more often become symptomatic with levodopa (L-DOPA) treatment. L-DOPA is converted to dopamine and may act as a false transmitter. Also, dopamine receptor agonists may cause arterial and venous dilation by inhibiting the sympathetic activity and may aggravate OH [56–58].

6.16 Conclusion

The management of DOH is critical in elderly, concerning the higher risk of falls and its results that may adversely affect quality of life of the patients. Interdisciplinary and professional teamwork with a geriatric specialist, cardiologist and clinical

pharmacologist or pharmacist should take part for the diagnosis and treatment. DOH is a frequent issue in geriatric patients and removal of the triggering factors should be the first action. Medications can be revised, decreased, changed, or stopped completely. The initial steps in the treatment of DOH are to (a) control or check the patient's inappropriate medications, (b) evaluate the patient's fluid, salt, and nutritional intake, and (c) provide patient education to prevent further problems such as falling and dizziness. Optimization of the patient's drug regime will help to ameliorate the symptoms and avoid related morbidity. Patients with diabetes mellitus, hypertension, PD, and dehydrated patients are more likely to develop OH, therefore should be closely monitored. Decent documentation of medical history is required to determine and overcome drug-induced problems. In particular, it is necessary to be very careful in treatment to prevent the development of geriatric syndromes in the elderly. If DOH attacks cannot be avoided despite discontinuation, switch or changing of the potential drugs for OH, DOH should be evaluated and treated as a primary OH.

References

1. Ricci F, De Caterina R, Fedorowski A. Orthostatic hypotension: epidemiology, prognosis, and treatment. J Am Coll Cardiol. 2015;66:848–60.
2. Mills PB, Fung CK, Travlos A, Krassioukov A. Nonpharmacologic management of orthostatic hypotension: a systematic review. Arch Phys Med Rehabil. 2015;96(2):366–75.
3. Mets TF. Drug-induced orthostatic hypotension in older patients. Drugs Aging. 1995;6(3):219–28.
4. Saedon NI, Pin Tan M, Frith J. The prevalence of orthostatic hypotension: a systematic review and meta-analysis. J Gerontol A Biol Sci Med Sci. 2020;75(1):117–22.
5. Joseph A, Wanono R, Flamant M, Vidal-Petiot E. Orthostatic hypotension: a review. Nephrol Ther. 2017;13:S55–67.
6. Méndez AS, Melgarejo JD, Mena LJ, Chávez CA, González AC, Boggia J, Terwilliger JD, Lee JH, Maestre GE. Risk factors for orthostatic hypotension: differences between elderly men and women. Am J Hypertens. 2018;31(7):797–803.
7. Low PA. Prevalence of orthostatic hypotension. Clin Auton Res. 2008;18(1):8–13.
8. Frith J, Parry SW. New horizons in orthostatic hypotension. Age Ageing. 2017;46(2):168–74.
9. Gangavati A, Hajjar I, Quach L, et al. Hypertension, orthostatic hypotension, and the risk of falls in a community-dwelling elderly population: the maintenance of balance, independent living, intellect, and zest in the elderly of Boston study. J Am Geriatr Soc. 2011;59:383–9.
10. Gupta V, Lipsitz LA. Orthostatic hypotension in the elderly: diagnosis and treatment. Am J Med. 2007;120:841–7.
11. Metzler M, Duerr S, Granata R, Krismer F, Robertson D, Wenning GK. Neurogenic orthostatic hypotension: pathophysiology, evaluation, and management. J Neurol. 2013;260(9):2212–9.
12. Gami AS, Hodge DO, Herges RM, et al. Obstructive sleep apnea, obesity, and the risk of incident atrial fibrillation. J Am Coll Cardiol. 2007;49:565–71.
13. Okin PM, Wachtell K, Kjeldsen SE, et al. Incidence of atrial fibrillation in relation to changing heart rate over time in hypertensive patients: the LIFE study. Circ Arrhythm Electrophysiol. 2008;1:337–43.
14. Nakagawa H, Scherlag BJ, Patterson E, et al. Pathophysiologic basis of autonomic ganglionated plexus ablation in patients with atrial fibrillation. Heart Rhythm. 2009;6:S26–34.
15. Fedorowski A, Burri P, Struck J, et al. Novel cardiovascular biomarkers in unexplained syncopal attacks: the SYSTEMA cohort. J Intern Med. 2013;273:359–67.

16. Berger R, Pacher R. The role of the endothelin system in myocardial infarction—new therapeutic targets? Eur Heart J. 2003;24:294–6.
17. Kanjwal K, George A, Figueredo VM, et al. Orthostatic hypotension: definition, diagnosis and management. J Cardiovasc Med (Hagerstown). 2015;16:75–81.
18. Goldstein DS, Sharabi Y. Neurogenic orthostatic hypotension: a pathophysiological approach. Circulation. 2009;119:139–46.
19. Grubb BP, Karas B. Clinical disorders of the autonomic nervous system associated with orthostatic intolerance: an overview of classification, clinical evaluation, and management. Pacing Clin Electrophysiol. 1999;22:798–810.
20. Trahair LG, Horowitz M, Jones KL. Postprandial hypotension: a systematic review. J Am Med Dir Assoc. 2014;15:394–409.
21. Moya A, Sutton R, Ammirati F, et al. Guidelines for the diagnosis and management of syncope (version 2009). Eur Heart J. 2009;30:2631–71.
22. Poon IO, Braun U. High prevalence of orthostatic hypotension and its correlation with potentially causative medications among elderly veterans. J Clin Pharm Ther. 2005;30:173–8.
23. Rutan GH, Hermanson B, Bild DE, et al. Orthostatic hypotension in older adults. The cardiovascular health study. CHS collaborative research group. Hypertension. 1992;19:508–19.
24. Bradley JG, Davis KA. Orthostatic hypotension. Am Fam Physician. 2003;68:2393–8.
25. Perez-Lloret S, Rey MV, Fabre N, et al. Factors related to orthostatic hypotension in Parkinson's disease. Parkinsonism Relat Disord. 2012;18:501–5.
26. Pathak A, Lapeyre-Mestre M, Montastruc JL, et al. Heat-related morbidity in patients with orthostatic hypotension and primary autonomic failure. Mov Disord. 2005;20:1213–9.
27. Narkiewicz K, Cooley RL, Somers VK. Alcohol potentiates orthostatic hypotension: implications for alcohol-related syncope. Circulation. 2000;101:398–402.
28. Schoenberger JA. Drug-induced orthostatic hypotension. Drug Saf. 1991;6(6):402–7.
29. Freeman R, Wieling W, Axelrod FB, et al. Consensus statement on the definition of orthostatic hypotension, neurally mediated syncope and the postural tachycardia syndrome. Auton Neurosci. 2011;161:46–8.
30. Goldstein DS, Robertson D, Esler M, et al. Dysautonomias: clinical disorders of the autonomic nervous system. Ann Intern Med. 2002;137:753–63.
31. Chopra S, Baby C, Jacob JJ. Neuro-endocrine regulation of blood pressure. Indian J Endocrinol Metab. 2011;15(Suppl 4):S281–8.
32. Dampney RA, Coleman MJ, Fontes MA, et al. Central mechanisms underlying short- and long-term regulation of the cardiovascular system. Clin Exp Pharmacol Physiol. 2002;29:261–8.
33. Douglas E. Rollins, Donald K. Blumenthal. Workbook and casebook for Goodman and Gilman's the pharmacological basis of therapeutics, chapter 15: drug therapy of hypertension, edema, and disorders of sodium and water balance, © 2016, by the McGraw-Hill Companies, Inc., Printed in the United States of America.
34. Wadei HM, Textor SC. The role of the kidney in regulating arterial blood pressure. Nat Rev Nephrol. 2012;8:602–9.
35. Rhaleb NE, Yang XP, Carretero OA. The kallikrein-kinin system as a regulator of cardiovascular and renal function. Compr Physiol. 2011;1:971–93.
36. Katzung BG, Trevor AJ, editors. Basic & clinical pharmacology. New York: McGraw-hill Education; 2017.
37. Perlmuter LC, Sarda G, Casavant V, Mosnaim AD. A review of the etiology, asssociated comorbidities, and treatment of orthostatic hypotension. Am J Ther. 2013;20(3):279–91.
38. Rüster C, Wolf G. Renin-angiotensin-aldosterone system and progression of renal disease. J Am Soc Nephrol. 2006;17(11):2985–91.
39. Goswami N, Blaber AP, Hinghofer-Szalkay H, Montani JP. Orthostatic intolerance in older persons: etiology and countermeasures. Front Physiol. 2017;8:803.
40. Monahan KD, Dinenno FA, Seals DR, Clevenger CM, Desouza CA, Tanaka H. Age-associated changes in cardiovagal baroreflex sensitivity are related to central arterial compliance. Am J Phys Heart Circ Phys. 2001;281(1):H284–9.

41. Juraschek SP, Daya N, Appel LJ, Miller ER, Windham BG, Pompeii L, Griswold ME, Kucharska-Newton A, Selvin E. Orthostatic hypotension in middle-age and risk of falls. Am J Hypertens. 2017;30(2):188–95.
42. Liguori I, Russo G, Coscia V, Aran L, Bulli G, Curcio F, Della-Morte D, Gargiulo G, Testa G, Cacciatore F, Bonaduce D. Orthostatic hypotension in the elderly: a marker of clinical frailty? J Am Med Dir Assoc. 2018;19(9):779–85.
43. The list of drugs with orthastatic hypotension and hypotension drug. Web application; SIDER 4.1:Side Effect Resource; 2020, January 9. http://sideeffects.embl.de/se/C0020649/
44. Finucane C, O'Connell MD, Donoghue O, et al. I mpaired orthostatic blood pressure recovery is associated with unexplained and injurious falls. J Am Geriatr Soc. 2017;65:474–82.
45. Bylund DB (2009) Norepinephrine: Adrenergic Receptors. 1231–1236.
46. Testa G, Ceccofiglio A, Mussi C, Bellelli G, Nicosia F, Bo M, Riccio D, Curcio F, Martone AM, Noro G, Landi F. Hypotensive drugs and syncope due to orthostatic hypotension in older adults with dementia (syncope and dementia study). J Am Geriatr Soc. 2018;66(8):1532–7.
47. Laurent S. Antihypertensive drugs. Pharmacol Res. 2017;124:116–25.
48. Davidson E, Fuchs J, Rotenberg Z, Weinberger I, Agmon J. Drug-related syncope. Clin Cardiol. 1989;12(10):577–80.
49. Elliott WJ, Ram CV. Calcium channel blockers. J Clin Hypertens (Greenwich). 2011;13(9):687–9.
50. Frishman WH. Beta-adrenergic receptor blockers. Adverse effects and drug interactions. Hypertension. 1988;11(3):21–9.
51. White WB. Hypotension with postural syncope secondary to the combination of chlorpromazine and captopril. Arch Intern Med. 1986;146(9):1833–4.
52. Takata Y, Kurihara J, Suzuki S, Okubo Y, Kato H. A rabbit model for evaluation of chlorpromazine-induced orthostatic Shypotension. Biol Pharm Bull. 1999;22(5):457–62.
53. Nourian Z, Mow T, Muftic D, Burek S, Pedersen ML, Matz J, Mulvany MJ. Orthostatic hypotensive effect of antipsychotic drugs in Wistar rats by in vivo and in vitro studies of α 1-adrenoceptor function. Psychopharmacology. 2008;199(1):15.
54. Briggs R, Carey D, McNicholas T, Claffey P, Nolan H, Kennelly SP, Kenny RA. The association between antidepressant use and orthostatic hypotension in older people: a matched cohort study. J Am Soc Hypertens. 2018;12(8):597–604.
55. Mcdowell FH, Lee JE. Levodopa, Parkinson's disease, and hypotension. Ann Intern Med. 1970;72(5):751–2.
56. Kujawa K, Leurgans S, Raman R, Blasucci L, Goetz CG. Acute orthostatic hypotension when starting dopamine agonists in Parkinson's disease. Arch Neurol. 2000;57(10):1461–3.
57. Mehagnoul-Schipper DJ, Boerman RH, Hoefnagels WH, Jansen RW. Effect of levodopa on orthostatic and postprandial hypotension in elderly parkinsonian patients. J Gerontol Ser A Biol Med Sci. 2001;56(12):M749–55.
58. Piha SJ, Rinne JO, Rinne UK, Seppänen A. Autonomic dysfunction in recent onset and advanced Parkinson's disease. Clin Neurol Neurosurg. 1988;90(3):221–6.