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Medical Therapy and Physical Maneuvers in the Treatment of the Vasovagal Syncope and Orthostatic Hypotension

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Abstract

Patients with vasovagal syncope and neurogenic orthostatic hypotension can both present with pre-syncope and syncope resulting from systemic hypotension. While not directly responsible for increased mortality, both of these conditions can have a tremendous deleterious impact on the daily lives of patients. This negative impact can take the form of both physical symptoms and injury, but also a psychological impact from living in fear of the next syncopal episode. Despite these similarities, these are different disorders with fixed damage to the autonomic nerves in neurogenic orthostatic hypotension, as opposed to a transient reflex hypotension in “neurally mediated” vasovagal syncope.

The treatment approaches for both disorders are parallel. The first step is to educate the patient about the pathophysiology and prognosis of their disorder. Next, offending medications should be withdrawn when possible. Non-pharmacological therapies and maneuvers can be used, both in an effort to prevent the symptoms and to prevent syncope at the onset of presyncope. This is all that is required in many patients with vasovagal syncope. If needed, pharmacological options are also available for both vasovagal syncope and neurogenic orthostatic hypotension, many of which are focused on blood volume expansion, increasing cardiac venous return, or pressor agents to increase vascular tone. There is a paucity of high quality clinical trial data to support the use of these pharmacological agents. We aim to review the literature on these different therapy choices and to give recommendations on tailored approaches to the treatment of these conditions.

Keywords

syncope; vasovagal; orthostatic hypotension; treatment; medications; non-pharmacological; autonomic failure

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INTRODUCTION

The ability to maintain upright posture without syncope requires coordinated actions of an intact autonomic nervous system. Both exaggerated autonomic reflexes, as seen in vasovagal syncope (VVS), or autonomic nerve damage and hypofunction of the autonomic nervous system, as seen in neurogenic orthostatic hypotension (OH), can result in syncope.

While not life-threatening, VVS can be recurrent, causes significant injury in 5% of cases, and leads to impaired quality of life.^{1, 2} VVS occurs due to reflex bradycardia and hypotension that can occur in response to a wide variety of stimuli including prolonged sitting or standing (upright posture), cortical triggers such as pain or anxiety (e.g. with blood exposure), large muscle activation, and exercise.³ The proposed mechanism is a combination of increased cardiovagal tone with resultant bradycardia or asystole, and a reduction in peripheral sympathetic activity, which can lead to venodilation with resultant hypotension. The putative pathophysiology is discussed in more detail by van Dijk et al.⁴ in this issue. The treatment of VVS involves a layered approach with a combination of lifestyle changes, physical maneuvers, medications, and implantable devices.

Orthostatic Hypotension (OH) is another disorder that can also present with syncope. It is defined as a sustained reduction of systolic BP of ≥ 20 mmHg or diastolic BP of ≥ 10 mmHg within 3 minutes of standing or head-up tilt (≥ 60 degrees).⁵ OH is not acutely life-threatening, but can be associated with significant morbidity and leads to 80,000 adult hospitalizations per year in the United States.⁶ OH is also a risk factor for cardiovascular morbidity and all-cause mortality, likely due to disease associations.⁷ Common secondary causes include diseases that affect peripheral nerve function (e.g. diabetes mellitus). Neurodegenerative diseases can also be implicated. The symptoms that occur are likely due to cerebral hypoperfusion secondary to systemic hypotension. In an apparent paradox, about 50% of patients with severe orthostatic hypotension also have hypertension when supine (which can sometimes be very severe). This can make the management of the orthostatic hypotension even more challenging, since the 2 disorders (orthostatic hypotension and supine hypertension) can require opposing treatment strategies.

TREATMENT OF VASOVAGAL SYNCOPE

Non-Pharmacological Treatment of VVS

There are a variety of non-pharmacologic strategies in the treatment of VVS. One of the earliest priorities is to educate the patient about the benign nature of VVS.⁸ Episodes of VVS might lead to patients' first confronting their mortality. They might be concerned that they may be at increased risk of dying or suffering from a myocardial infarction related to these fainting spells. Educating and reassuring the patient is an important first step in treatment.⁹ Patients should be taught to maintain hydration, avoid hot conditions, and to pay attention to their early symptoms and prodromes, if present. If there are specific triggers (such as coughing or laughing), then efforts should target trigger avoidance. In the spirit of *primum non nocere* (first do no harm), potentially contributory medications such as diuretics, venodilators, and vasodilators should be removed, if possible.

The mainstay of therapy for VVS in Syncope Clinics is to increase the patient's intake of dietary salt and water. These common recommendations, along with the aforementioned teaching, are thought to result in a marked improvement in the vast majority of patients with VVS. Despite this clinical impression, there is a lack of strong evidence to support this strategy. Bellard et al. have shown that increased hydration alone does not improve orthostatic intolerance, though for short periods of time this strategy can be helpful.¹⁰ Patients do tend to have better orthostatic tolerance with high salt intake,¹¹ though this may

not be advisable in patients with renal failure, heart failure, or hypertension.³ Recurrent VVS can be associated with anxiety and a negative psychosocial impact. A higher level of psychosocial impairment predicts non-response to other treatments for VVS.¹² In these individuals, psychotherapeutic strategies may be a helpful component of treatment.

There are a multitude of physical treatments and maneuvers that can be helpful in VVS. Exercise training was an early strategy in VVS management, although the evidence for its efficacy in preventing syncope is weak. Exercise training has been shown to increase blood volume and modulate baroreceptor function in VVS patients.^{3, 13}

In contrast, isometric muscle contractions have been shown to increase cardiac output and arterial blood pressure (BP) reproducibly in the literature.^{14–16} This can occur with either leg or arm contractions, but the more effective maneuver involves crossing ones' legs and clenching the buttocks, since these muscles are larger than the arm muscles. It is important that the patient not perform a coincident Valsalva maneuver (as this can accelerate syncope), so we often advise patients that they should be able to talk during these contractions. Of course, these maneuvers can only be effective at the time of presyncope if the patient has an adequate prodrome to allow for such a maneuver. The Physical Counterpressure Manoeuvres Trial was a randomized controlled trial that assessed adding physical maneuvers to conventional therapy in VVS patients. There was a 36% relative risk reduction for syncope, but 35% of VVS patients did not have a long enough prodrome to benefit.¹⁶ Notably, this relative risk reduction is among the largest seen in a randomized control trial of any VVS therapy. Despite these data, the maneuver that we recommend most commonly to our patients with VVS is to lie down at the onset of the prodrome. Although there is not trial data to support this recommendation, it is highly effective at preventing injury from syncope and may also prevent the syncopal spell altogether.

“Tilt Training” is another treatment option. This treatment was developed after the observation that there was a decrease in positivity of tilt tests with recurrent tilt testing. It was thought that there could be a training effect with enhanced peripheral sympathetic activity resulting from repeated testing. Ector et al. performed repeated daily tilt tests while patients were kept in the hospital until vasovagal responses improved and the patient tolerated the full duration of the test, which they found would happen after 3–8 sessions.¹⁷ Unfortunately, in most environments lengthy hospital stays for tilt training are not feasible. Many investigators therefore attempted outpatient orthostatic training (standing against a wall for 30 min, 1–2 times per day). The data for home training are mixed, with 1 Chinese trial suggesting a benefit¹⁸ while multiple studies reported negative findings.^{19–21} Home training is not costly and is relatively free of harm, but may suffer from limited compliance which might limit its efficacy.

Pharmacological Treatment of VVS

The vast majority of patients with VVS can be adequately controlled with non-pharmacological approaches and do not require pharmacological treatment. That is fortunate, as there are no pharmacological treatments for VVS that have been shown to be effective in large randomized controlled trials. There are, however, a minority of patients with refractory and recurrent VVS who can benefit from effective pharmacotherapy.

Several pharmacologic treatments for VVS have been studied. Beta-adrenergic blockers were once very commonly used to treat VVS. The historical rationale for considering beta-blockers included animal studies demonstrating beta-receptor involvement in ventricular baroreceptor reflexes, the ability of isoproterenol to trigger hypotension and bradycardia during tilt testing^{22, 23}, and the ability of beta-blockers to prevent the isoproterenol effect²⁴. There have been several small studies with different beta-blocking compounds (mainly

beta-1 selective blockers), with use of placebo control or not, and with different endpoints (tilt table test vs. clinical syncope), with the expected mixed results.^{25–30} Overall, they provided little convincing evidence for the effectiveness of beta-blockers in preventing vasovagal syncope. The Prevention of Syncope Trial (POST) was the pivotal randomized, placebo-controlled, double-blind trial, and assessed the effects of metoprolol in vasovagal syncope over a 1 year treatment period.³¹ A total of 208 patients were randomized to metoprolol or placebo. Metoprolol provided no benefit over placebo, with overlapping “freedom from syncope” curves for the 2 study arms. Of note, there was a significant interaction between age and the randomized treatment effect (interaction $p = 0.026$). The hazard ratio for metoprolol in older patients (≥ 42 years) who received metoprolol was 0.53 (95% confidence interval [95%CI] 0.25 to 1.10), but in younger patients (<42 years) the hazard ratio was 1.62 (95%CI 0.85 to 3.10). These data strongly suggest that metoprolol does not prevent VVS recurrence in younger patients with VVS³², but that it might be beneficial in older patients with VVS. From a practical viewpoint, beta-blockers are one of the few pharmacological treatments for VVS that do not increase BP, so beta-blockers might be a reasonable choice for older patients with co-morbid hypertension.

Serotonin is known to modulate central nervous system BP and heart rate. With this knowledge, investigators have attempted to use selective serotonin reuptake inhibitors (SSRIs) to raise serotonin levels in the nervous system. Di Girolamo et al. conducted a randomized, double-blind, placebo-controlled study of paroxetine 20mg daily (an SSRI) in patients with recurrent VVS.³³ Over a mean follow-up of 25 ± 8 months, they showed a reduction in syncope recurrence from 53% with placebo to 18% with paroxetine. Not all SSRI studies have been positive. Theodorakis et al. found that fluoxetine (SSRI), propranolol (beta-blocker), and placebo were all equally effective (or ineffective) in VVS treatment.²⁷ Overall, there is not convincing data for the efficacy of SSRIs in preventing VVS. While perhaps not effective for the prevention of fainting, SSRIs might be helpful in dealing with the psychosocial stress that can result from recurrent syncope.

Fludrocortisone is a fluorinated corticosteroid with primarily mineralocorticoid activity, with resultant sodium and water retention and potassium excretion. Fludrocortisone should not be viewed as an isolated therapy, but a next step after dietary salt and water expansion with the goal of increasing blood volume. Two open label uncontrolled studies reported that children had far less syncope and presyncope while taking fludrocortisone.³⁴ In contrast, the randomized, double-blinded, placebo controlled study by Salim et al. found more symptoms in children randomized to fludrocortisone.³⁵ The Second Prevention of Syncope Trial (POST II) assessed the effectiveness of fludrocortisone in adults.³⁶ POST II was a multinational, randomized, controlled clinical trial that randomized a total of 211 patients with recurrent VVS to receive either fludrocortisone or placebo for 1 year. The primary outcome of POST II was the proportion of patients with at least one syncope recurrence. The trial concluded in 2011 and showed only a trend toward benefit with a relative risk reduction of 26% ($P=0.066$) [personal communication RS Sheldon]. The average age of the subjects was 30 years and the oldest was 46 years, likely due to baseline hypertension in the older VVS patients. It is likely that POST II was a slightly underpowered study and that the fludrocortisone benefit was real, but smaller than had been anticipated. We still use fludrocortisone for younger patients with VVS.

Midodrine is a pro-drug whose active metabolite is a peripheral alpha-1 adrenergic receptor agonist. The efficacy of midodrine in VVS has not been clearly established. It is known to cause venoconstriction and arteriolar constriction, thereby increasing cardiac output and increasing peripheral resistance. Four clinical studies reported promising but inconclusive evidence for the efficacy or effectiveness of midodrine in preventing vasovagal syncope,^{37–40} and one reported negative results.⁴¹ To resolve whether or not midodrine

prevents VVS, the Prevention of Syncope Trial 4 (POST4) will randomize frequent fainters to midodrine vs. placebo, with results expected in 2017.⁴² Midodrine 2.5–10 mg Q4H x 3/ day is fairly well-tolerated, and is a reasonable option in patients without significant hypertension. The challenges with midodrine include compliance (with frequent dosing), eccentric dosing to avoid bedtime administration, and side effects that include hypertension and urinary retention that might limit its utility in older patients.

Pacemakers for VVS

There have been multiple studies of permanent pacemakers for VVS, with wildly varying results. Sud et al. conducted a meta-analysis that showed non-significant reduction in symptoms when including all studies, but an 84% reduction in symptoms in open-label studies where the control group did not receive a pacemaker.⁴³ More recently, the ISSUE 3 study reported that there was a statistically significant reduction in syncope recurrence among patients randomized to having their pacemaker programmed to a pacing mode instead of a sense-only mode⁴⁴. Unique to this study, patients with syncope underwent implantation with a loop recorder and awaited a future syncopal spell. If they had asystole with a further episode of clinical syncope, then they were eligible for randomization. The issues surrounding pacing for VVS are discussed in more detail by Parry et al.⁴⁵ in another article in this issue.

Treatment of VVS - Summary

First line therapy should revolve around patient education about VVS physiology and prognosis. Patients should be encouraged to increase water and dietary salt intake on a daily basis. Patients with a clear symptomatic prodrome (the majority of patients) should be encouraged to lie down or to sit down on the ground in a squatting position upon feeling prodromal symptoms. They can also be taught other physical counterpressure maneuvers, but patients may still faint. If pharmacological therapy is needed, age and co-morbid conditions should guide the approach. If a patient is older (>40 years) or has hypertension, then we suggest using metoprolol. In a younger patient who is otherwise healthy, we recommend starting with fludrocortisone 0.1–0.2 mg daily. In patients with very frequent syncope, psychosocial factors that might be compromising therapeutic response should be addressed. An implantable loop recorder should also be considered to look for asystole during a faint, which may be amenable to treatment with a permanent pacemaker. There are ongoing randomized treatment trials for recurrent VVS, and eligible patients should ideally be randomized into these trials when this is feasible.

TREATMENT OF ORTHOSTATIC HYPOTENSION

Non-Pharmacological Treatment of OH

Similar to the approach to VVS, the guiding principle in the management of OH is *primum non nocere*. In many cases, OH can be made worse (or converted from asymptomatic to symptomatic) by medications prescribed by physicians. Patients with OH are very dependent on cardiac preload for their blood pressure. Likely due to this reason, patients with OH are exquisitely sensitive to diuretics and venodilators such as nitrates. These medications should be withdrawn first whenever possible. The next agents that should be withdrawn are direct vasodilators. Many patients with OH have concomitant bladder dysfunction due to autonomic nervous system failure. If patients are male, it is common for the bladder dysfunction to be attributed to benign prostatic hypertrophy and the patients are often treated with alpha-adrenergic antagonists (e.g. tamsulosin or doxazosin). These agents can have the “off-target” effect of inducing syncope in susceptible individuals. Among anti-hypertensive agents, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are well tolerated in these patients.

Patients are routinely advised to hydrate aggressively. Due to the aforementioned preload dependence in patients with OH, these patients do not tolerate even mild volume depletion well. Renal perfusion pressure is often highest at night due to the higher supine blood pressures that these patients experience compared to seated or standing blood pressures during the day. This can lead to more nocturnal urine production and subsequently a nocturnal reduction in blood volume, resulting in worsened OH upon awaking in the mornings. This problem can be blunted by elevating the head of the bed (effectively tilting the patient) at night, similar to the strategy used in patients with gastroesophageal reflux disease. Patients should be encouraged to use physical countermeasures such as standing up slowly and contracting the calf muscles while standing to encourage venous return from the legs. These easy changes can be effective maneuvers when OH is not overly severe.

In response to rising to upright posture, there is a significant downward shift of fluid from the thorax. It is because of a concern for “blood pooling” in the legs that patients will sometimes wear compression stockings up to the knees or thighs. This is often ineffective, as most of the pooled blood resides in the abdomen rather than the legs.⁴⁶ Studies have shown a benefit to compression of either the abdomen only (abdominal binder) or both the abdomen and the legs (panty hose style compression garments).^{47–49} Both of these approaches have practical challenges. In our experience, it can be difficult to tighten the abdominal binder enough to generate a significant amount of abdominal pressure. The compression garments are rated at different degrees of tightness, and we usually recommend starting with 30–40 mmHg of compression. This is tight enough that it can be difficult for an older patient with OH to put on the garments without the assistance of another person.

The Osmopressor Response and OH

In 1999, Jordan et al. first reported that the rapid ingestion of water 16 fl oz (~500 ml) by patients with autonomic failure and orthostatic hypotension resulted in a short term increase in systolic BP by an average of >40 mmHg.⁵⁰ This pressor response takes 5–10 min to initiate, peaks between 20–40 min, and wanes by 60 min. There seems to be a dose response, with smaller pressor responses to smaller amounts of water ingestion.⁵¹ When 500 ml of D5W was intravenously infused in the same patients, the BP increase was only 25% as large, suggesting that this response was not primarily due to blood volume expansion. Interestingly, when OH patients drank salt water compared with plain water, the pressor response was only half as strong.⁵² These data suggest that the hypoosmolality of the water may be the key to triggering this Osmopressor Response.

Significant increases in blood pressure in response to water ingestion are seen in patients with autonomic failure, but not in young healthy subjects⁵¹. This is likely because there is efferent baroreflex failure in patients with autonomic failure, whereas baroreflex function is robust in young healthy individuals. This has been elegantly demonstrated McHugh et al, who reproduced the Osmopressor Response with intragastric or intraduodenal water infusion in mice with surgical afferent baroreflex failure, but found no pressor response in mice with intact baroreceptors.⁵³

Using the same surgical model on the background of different genetic mice, McHugh et al. were able to show that TRPV4^{-/-}, but not TRPV1^{-/-} mice had a severely blunted Osmopressor Response. These data suggest that TRPV4 plays a role in the sensing or signally of this response.⁵³ The Osmopressor response is of comparable magnitudes whether the water is infused into the stomach or directly into the duodenum, suggesting that the signaling occurs distal to the pylorus. Significant acute alterations to portal vein osmolality in response to water ingestion suggest that this might be a location for the osmosensing. Afferent hepatic sensory neurons have been identified in dorsal root ganglia that innervate

hepatic blood vessels.⁵⁴ These neurons no longer exhibit osmosensitive currents in mice lacking TRPV4.

The effector limb of the Osmopressor Response is likely mediated by the sympathetic nervous system. In the mouse model, the pressor response can be eliminated almost completely with alpha-1 adrenoreceptor blockade.⁵³ In healthy young volunteers, systemic vascular resistance increases in response to acute bolus water ingestion.⁵⁵ There is a simultaneous decrease in cardiac output, which maintains a normal blood pressure. Plasma norepinephrine levels, the primary vascular sympathoneural neurotransmitter, increases with water ingestion.⁵² Taken together, these data suggest that the Osmopressor Response utilizes the residual sympathetic tone in patients with autonomic failure. Further details about the Osmopressor Response are separately published.⁵⁶

Using this knowledge, we usually advise our patients to keep a pitcher of water at the bedside, and to drink 500 ml rapidly (over 2 min) in the morning about 10 min before getting out of bed. The water can be ingested with other medications, though the osmopressor response can have a significant synergistic effect with some sympathomimetic medications.⁵⁷

Pharmacological Treatment of OH

The pharmacological therapy of OH involves one of 2 main strategies. The first approach is to attempt to increase the blood volume. As can be seen in Fig 1a, blood volume expansion is akin to “raising the level of the ocean” compared to baseline conditions. This strategy is long-acting and will usually increase the BP during both the day (when it may be clinically helpful) and at night (when it is not likely to be helpful, and may be deleterious). The other main strategy is to use short acting pressor agents to increase the BP for several hours per dose. These pressor agents don’t raise the level of the ocean (to continue the water analogy), but they increase the size of the waves (Fig 1b) with peaks (hopefully when upright and clinically useful) and valleys (hopefully at night when a higher BP is not needed).

Volume Expansion—Fludrocortisone is a mineralocorticoid hormone that can be used to increase renal sodium reabsorption, increase total body water, and ideally increase intravascular volume. The effect on plasma volume may be transient, but there can be an added long-term potentiation on norepinephrine with a resultant lasting pressor effect.^{58, 59} Since fludrocortisone increases both daytime and nighttime BP, it can exacerbate supine hypertension. Therefore, fludrocortisone is not an optimal first line agent for patients with supine hypertension. In one series of elderly patients with OH, fludrocortisone use was limited due to significant side-effects including hypertension, heart failure, and severe edema.⁶⁰

Recombinant erythropoietin (EPO) is another agent used to increase intravascular volume. Many patients with severe autonomic failure have concomitant anemia, and EPO in these patients could help with both volume repletion and correction of symptomatic anemia. In addition to blood volume expansion, the extra red blood cells and hemoglobin might act as a nitric oxide scavenger, which would result in more peripheral vasoconstriction.⁶¹ Biaggioni et al. showed that EPO use in OH patients improved standing BP and symptoms, but also noted that use was limited by exaggerated supine hypertension in some patients.⁶² Other barriers to the use of EPO include the need for injections (as opposed to tablets), the very high cost of EPO, and reports of increased cardiovascular events with EPO in some populations.⁶³

Short Acting Pressor Agents—Midodrine is currently the only US Food & Drug Administration approved medication for the treatment of orthostatic hypotension. Each dose

starts working within 20–30 minutes and lasts for about 4 hours. Midodrine raises blood pressure while the patient is supine, seated, or standing. It is important that the patient be instructed not to lie down within 4 hours of a dose, and the drug is not to be taken within 4–5 hours of bedtime. Multiple studies have shown that midodrine increases BP in OH patients,^{64–66} but symptomatic improvement has not been shown to the satisfaction of the FDA.⁶⁷ The starting dose in OH patients is 2.5mg PO Q4H x3/day as some patients can be very sensitive to alpha-1 agonists, but this can be increased up to 10mg/dose quite safely. Another commonly available alpha-1 agonist is pseudoephedrine 30–60 mg PO TID. Common side effects include piloerection, goose bumps, and an odd tingling scalp sensation due to scalp piloerection.

An alternative pressor option is yohimbine, which is an alpha-2 antagonist. Alpha-2 receptors work centrally and in the peripheral sympathetic nervous system to decrease sympathetic nervous outflow (this is how clonidine works in hypertension). By blocking the “brake” on sympathetic outflow, yohimbine allows for an increase in sympathetic nervous system activity and unrestrained norepinephrine release from sympathetic neurons. Yohimbine has been shown to have a similar pressor response to midodrine in patients with OH.⁶⁸ Yohimbine was originally on the market for erectile dysfunction. Given the competition in that market, it is no longer manufactured, although it is still available through compounding pharmacies. The typical dose range is 5.4–10.8 mg PO TID.

Pyridostigmine is a peripheral acetylcholinesterase inhibitor (on the market for myasthenia gravis) that acts to increase synaptic acetylcholine concentrations in the autonomic ganglia. Since it does not directly activate a receptor but rather increases the neurotransmitter concentration with nervous system activation, pyridostigmine should have more pressor action when a patient is upright than while supine. Singer et al. have shown that pyridostigmine did significantly reduce the fall in standing diastolic BP, but did not make a significant difference in supine BP. This findings was seen both with pyridostigmine alone and with concurrent midodrine,⁶⁹ although the magnitude of the effect is more modest than with yohimbine.⁷⁰ The target dose is pyridostigmine 60 mg PO TID. An additional salutary effect of pyridostigmine is increased bowel motility in autonomic failure patients who are often chronically constipated.

Norepinephrine transporter inhibitors work by increasing the concentration of synaptic norepinephrine (primary neurotransmitter in the vascular sympathetic nervous system), which leads to increased peripheral activation of sympathetic neurons and increased BP. A proof of concept study showed that atomoxetine (a drug marketed for attention deficit hyperactivity disorder) significantly increased blood pressure in patients with central autonomic failure and OH.⁷¹

Other options for refractory patients include Cafergot, octreotide, or droxidopa. Cafergot is a combination tablet with caffeine 100 mg and ergotamine 1 mg that was originally marketed for migraine headaches. Cafergot can be used in conjunction with midodrine in refractory cases since it causes vasoconstriction through a non-sympathomimetic mechanism. Octreotide is a peptide that requires subcutaneous injection. While its exact mechanism of action is poorly understood, it likely works through splanchnic vasoconstriction and shunting of blood into the central circulation. Even patients refractory to several other agents will often respond to octreotide 12.5–50 mcg SQ BID. Droxidopa is a false precursor of norepinephrine that is taken up by sympathetic neurons and converted to norepinephrine by native enzymes, effectively increasing endogenous norepinephrine. Droxidopa is approved for use in Japan, but is still in development in the USA.

SUMMARY

In both VVS and OH, the initial phase of treatment involves patient education about the nature and prognosis of their disorder. Patients should be trained to recognize their presyncopal prodrome and to take corrective measures to avoid frank syncope and injury. After that, treatment involves a tailored approach starting with non-pharmacological approaches and adding in medications as needed.

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Abbreviations

BID	take medication twice per day
BP	Blood Pressure
EPO	Erythropoietin
OH	Orthostatic Hypotension
PO	per os (by mouth)
POST II	Second Prevention of Syncope Trial **
Q4h	every 4 hours
SQ	subcutaneous
SSRI	Selective Serotonin Reuptake Inhibitor
TID	take medication three times per day
VVS	Vasovagal Syncope

Reference List

1. Bartoletti A, Fabiani P, Bagnoli L, et al. Physical injuries caused by a transient loss of consciousness: main clinical characteristics of patients and diagnostic contribution of carotid sinus massage. *Eur Heart J*. 2008; 29:618–624. [PubMed: 18086659]
2. van Dijk N, Sprangers MA, Boer KR, Colman N, Wieling W, Linzer M. Quality of life within one year following presentation after transient loss of consciousness. *Am J Cardiol*. 2007; 100:672–676. [PubMed: 17697827]
3. Sheldon R, Morillo C, Krahn A. Management of vasovagal syncope: 2004. *Expert Rev Cardiovasc Ther*. 2004; 2:915–923. [PubMed: 15500436]
4. van Dijk JG. Pathophysiologic basis of syncope and neurological conditions that mimic syncope. *Prog Cardiovasc Dis*. 2012:55.
5. Freeman R, Wieling W, Axelrod FB, et al. Consensus statement on the definition of orthostatic hypotension, neurally mediated syncope and the postural tachycardia syndrome. *Clin Auton Res*. 2011; 21:69–72. [PubMed: 21431947]
6. Shibao C, Grijalva CG, Raj SR, Biaggioni I, Griffin MR. Orthostatic hypotension-related hospitalizations in the United States. *Am J Med*. 2007; 120:975–980. [PubMed: 17976425]
7. Shibao C, Biaggioni I. Orthostatic hypotension and cardiovascular risk. *Hypertension*. 2010; 56:1042–1044. [PubMed: 21059992]
8. Soteriades ES, Evans JC, Larson MG, et al. Incidence and prognosis of syncope. *N Engl J Med*. 2002; 347:878–885. [PubMed: 12239256]

9. White WD, Sheldon RS, Ritchie DA. Learning needs of patients with vasovagal syncope. *Can J Cardiovasc Nurs.* 2003; 13:26–30. [PubMed: 12703103]
10. Bellard E, Fortrat JO, Custaud MA, Victor J, Greenleaf J, Leftheriotis G. Increased hydration alone does not improve orthostatic tolerance in patients with neurocardiogenic syncope. *Clin Auton Res.* 2007; 17:99–105. [PubMed: 17464552]
11. El-Sayed H, Hainsworth R. Salt supplement increases plasma volume and orthostatic tolerance in patients with unexplained syncope. *Heart.* 1996; 75:134–140. [PubMed: 8673750]
12. Flint B, Baker C, Freeston M, Newton JL. Level of psychosocial impairment predicts early response to treatment in vasovagal syncope. *Europace.* 2009; 11:231–236. [PubMed: 19059994]
13. Gardenghi G, Rondon MU, Braga AM, et al. The effects of exercise training on arterial baroreflex sensitivity in neurally mediated syncope patients. *Eur Heart J.* 2007; 28:2749–2755. [PubMed: 17561494]
14. Krediet CT, de Bruin IG, Ganzeboom KS, Linzer M, van Lieshout JJ, Wieling W. Leg crossing, muscle tensing, squatting, and the crash position are effective against vasovagal reactions solely through increases in cardiac output. *J Appl Physiol.* 2005; 99:1697–1703. [PubMed: 16227457]
15. van Dijk N, de Bruin IG, Gisolf J, et al. Hemodynamic effects of leg crossing and skeletal muscle tensing during free standing in patients with vasovagal syncope. *J Appl Physiol.* 2005; 98:584–590. [PubMed: 15475601]
16. van Dijk N, Quartieri F, Blanc JJ, et al. Effectiveness of physical counterpressure maneuvers in preventing vasovagal syncope: the Physical Counterpressure Manoeuvres Trial (PC-Trial). *J Am Coll Cardiol.* 2006; 48:1652–1657. [PubMed: 17045903]
17. Ector H, Willems R, Heidbuchel H, Reybrouck T. Repeated tilt testing in patients with tilt-positive neurally mediated syncope. *Europace.* 2005; 7:628–633. [PubMed: 16216768]
18. Zeng H, Ge K, Zhang W, Wang G, Guo L. The effect of orthostatic training in the prevention of vasovagal syncope and its influencing factors. *Int Heart J.* 2008; 49:707–712. [PubMed: 19075486]
19. Foglia-Manzillo G, Giada F, Gaggioli G, et al. Efficacy of tilt training in the treatment of neurally mediated syncope. A randomized study. *Europace.* 2004; 6:199–204. [PubMed: 15121070]
20. On YK, Park J, Huh J, Kim JS. Is home orthostatic self-training effective in preventing neurally mediated syncope? *Pacing Clin Electrophysiol.* 2007; 30:638–643. [PubMed: 17461874]
21. Tan MP, Newton JL, Chadwick TJ, Gray JC, Nath S, Parry SW. Home orthostatic training in vasovagal syncope modifies autonomic tone: results of a randomized, placebo-controlled pilot study. *Europace.* 2010; 12:240–246. [PubMed: 19919966]
22. Sheldon R, Killam S. Methodology of isoproterenol-tilt table testing in patients with syncope. *J Am Coll Cardiol.* 1992; 19:773–779. [PubMed: 1545073]
23. Waxman MB, Yao L, Cameron DA, Wald RW, Roseman J. Isoproterenol induction of vasodepressor-type reaction in vasodepressor-prone persons. *Am J Cardiol.* 1989; 63:58–65. [PubMed: 2909160]
24. Sra JS, Murthy VS, Jazayeri MR, et al. Use of intravenous esmolol to predict efficacy of oral beta-adrenergic blocker therapy in patients with neurocardiogenic syncope. *J Am Coll Cardiol.* 1992; 19:402–408. [PubMed: 1346266]
25. Mahanonda N, Bhuripanyo K, Kangkagate C, et al. Randomized double-blind, placebo-controlled trial of oral atenolol in patients with unexplained syncope and positive upright tilt table test results. *Am Heart J.* 1995; 130:1250–1253. [PubMed: 7484777]
26. Flevari P, Livanis EG, Theodorakis GN, Zarvalis E, Mesiskli T, Kremastinos DT. Vasovagal syncope: a prospective, randomized, crossover evaluation of the effect of propranolol, nadolol and placebo on syncope recurrence and patients' well-being. *J Am Coll Cardiol.* 2002; 40:499–504. [PubMed: 12142117]
27. Theodorakis GN, Leftheriotis D, Livanis EG, et al. Fluoxetine vs. propranolol in the treatment of vasovagal syncope: a prospective, randomized, placebo-controlled study. *Europace.* 2006; 8:193–198. [PubMed: 16627439]
28. Cohen MB, Snow JS, Grasso V, et al. Efficacy of pindolol for treatment of vasovagal syncope. *Am Heart J.* 1995; 130:786–790. [PubMed: 7572587]

29. Iskos D, Dutton J, Scheinman MM, Lurie KG. Usefulness of pindolol in neurocardiogenic syncope. *Am J Cardiol.* 1998; 82:1121–4. A9. [PubMed: 9817494]
30. Nair N, Padder FA, Kutalek SP, Kantharia BK. Usefulness of pindolol for treatment of neurocardiogenic syncope. *Am J Cardiol.* 2004; 94:1189–1191. [PubMed: 15518620]
31. Sheldon R, Connolly S, Rose S, et al. Prevention of Syncope Trial (POST): a randomized, placebo-controlled study of metoprolol in the prevention of vasovagal syncope. *Circulation.* 2006; 113:1164–1170. [PubMed: 16505178]
32. The European Society of Cardiology Guidelines for the diagnosis and management of syncope reviewed by Angel Moya, MD FESC Chair of the Guideline Taskforce with J Taylor, MPhil. *Eur Heart J.* 2009; 30:2539–2540. [PubMed: 19880943]
33. Di Girolamo E, Di IC, Sabatini P, Leonzio L, Barbone C, Barsotti A. Effects of paroxetine hydrochloride, a selective serotonin reuptake inhibitor, on refractory vasovagal syncope: a randomized, double-blind, placebo-controlled study. *J Am Coll Cardiol.* 1999; 33:1227–1230. [PubMed: 10193720]
34. Scott WA, Pongiglione G, Bromberg BI, et al. Randomized comparison of atenolol and fludrocortisone acetate in the treatment of pediatric neurally mediated syncope. *Am J Cardiol.* 1995; 76:400–402. [PubMed: 7639169]
35. Salim MA, Di Sessa TG. Effectiveness of fludrocortisone and salt in preventing syncope recurrence in children: a double-blind, placebo-controlled, randomized trial. *J Am Coll Cardiol.* 2005; 45:484–488. [PubMed: 15708690]
36. Raj SR, Rose S, Ritchie D, Sheldon RS. The Second Prevention of Syncope Trial (POST II)--a randomized clinical trial of fludrocortisone for the prevention of neurally mediated syncope: rationale and study design. *Am Heart J.* 2006; 151:1186–1187. [PubMed: 16781217]
37. Perez-Lugones A, Schweikert R, Pavia S, et al. Usefulness of midodrine in patients with severely symptomatic neurocardiogenic syncope: a randomized control study. *J Cardiovasc Electrophysiol.* 2001; 12:935–938. [PubMed: 11513446]
38. Ward CR, Gray JC, Gilroy JJ, Kenny RA. Midodrine: a role in the management of neurocardiogenic syncope. *Heart.* 1998; 79:45–49. [PubMed: 9505918]
39. Kaufmann H, Saadia D, Voustianiouk A. Midodrine in neurally mediated syncope: a double-blind, randomized, crossover study. *Ann Neurol.* 2002; 52:342–345. [PubMed: 12205647]
40. Qingyou Z, Junbao D, Chaoshu T. The efficacy of midodrine hydrochloride in the treatment of children with vasovagal syncope. *J Pediatr.* 2006; 149:777–780. [PubMed: 17137891]
41. Romme JJ, van DN, Go-Schon IK, Reitsma JB, Wieling W. Effectiveness of midodrine treatment in patients with recurrent vasovagal syncope not responding to non-pharmacological treatment (STAND-trial). *Europace.* 2011; 13:1639–1647. [PubMed: 21752826]
42. Raj SR, Faris PD, McRae M, Sheldon RS. Rationale for the prevention of syncope trial IV: assessment of midodrine. *Clin Auton Res.* 2012
43. Sud S, Massel D, Klein GJ, et al. The expectation effect and cardiac pacing for refractory vasovagal syncope. *Am J Med.* 2007; 120:54–62. [PubMed: 17208080]
44. Brignole M, Menozzi C, Moya A, et al. Pacemaker therapy in patients with neurally mediated syncope and documented asystole: Third International Study on Syncope of Uncertain Etiology (ISSUE-3): a randomized trial. *Circulation.* 2012; 125:2566–2571. [PubMed: 22565936]
45. Parry SW. Update on the role of pacemaker therapy in vasovagal syncope and carotid sinus syndrome. *Prog Cardiovasc Dis.* 2012:55.
46. Diedrich A, Biaggioni I. Segmental orthostatic fluid shifts. *Clin Auton Res.* 2004; 14:146–147. [PubMed: 15241642]
47. Denq JC, Opfer-Gehrking TL, Giuliani M, Felten J, Convertino VA, Low PA. Efficacy of compression of different capacitance beds in the amelioration of orthostatic hypotension. *Clin Auton Res.* 1997; 7:321–326. [PubMed: 9430805]
48. Podoleanu C, Maggi R, Brignole M, et al. Lower limb and abdominal compression bandages prevent progressive orthostatic hypotension in elderly persons: a randomized single-blind controlled study. *J Am Coll Cardiol.* 2006; 48:1425–1432. [PubMed: 17010806]

49. Smit AA, Wieling W, Fujimura J, et al. Use of lower abdominal compression to combat orthostatic hypotension in patients with autonomic dysfunction. *Clin Auton Res*. 2004; 14:167–175. [PubMed: 15241645]
50. Jordan J, Shannon JR, Grogan E, Biaggioni I, Robertson D. A potent pressor response elicited by drinking water. *Lancet*. 1999; 353:723. [PubMed: 10073520]
51. Jordan J, Shannon JR, Black BK, et al. The pressor response to water drinking in humans: a sympathetic reflex? *Circulation*. 2000; 101:504–509. [PubMed: 10662747]
52. Raj SR, Biaggioni I, Black BK, et al. Sodium paradoxically reduces the gastropressor response in patients with orthostatic hypotension. *Hypertension*. 2006; 48:329–334. [PubMed: 16785332]
53. McHugh J, Keller NR, Appalsamy M, et al. Portal osmopressor mechanism linked to transient receptor potential vanilloid 4 and blood pressure control. *Hypertension*. 2010; 55:1438–1443. [PubMed: 20385965]
54. Lechner SG, Markworth S, Poole K, et al. The molecular and cellular identity of peripheral osmoreceptors. *Neuron*. 2011; 69:332–344. [PubMed: 21262470]
55. Lu CC, Diedrich A, Tung CS, et al. Water ingestion as prophylaxis against syncope. *Circulation*. 2003; 108:2660–2665. [PubMed: 14623807]
56. May M, Jordan J. The osmopressor response to water drinking. *Am J Physiol Regul Integr Comp Physiol*. 2011; 300:R40–R46. [PubMed: 21048076]
57. Jordan J, Shannon JR, Diedrich A, Black B, Robertson D, Biaggioni I. Water potentiates the pressor effect of ephedra alkaloids. *Circulation*. 2004; 109:1823–1825. [PubMed: 15066944]
58. Hickler RB, Thompson GR, FOX LM, Hamlin JT III. Successful treatment of orthostatic hypotension with 9-alpha-fluorohydrocortisone. *N Engl J Med*. 1959; 261:788–791. [PubMed: 14401690]
59. van Lieshout JJ, ten Harkel AD, Wieling W. Fludrocortisone and sleeping in the head-up position limit the postural decrease in cardiac output in autonomic failure. *Clin Auton Res*. 2000; 10:35–42. [PubMed: 10750642]
60. Hussain RM, McIntosh SJ, Lawson J, Kenny RA. Fludrocortisone in the treatment of hypotensive disorders in the elderly. *Heart*. 1996; 76:507–509. [PubMed: 9014799]
61. Rao SV, Stamler JS. Erythropoietin, anemia, and orthostatic hypotension: the evidence mounts. *Clin Auton Res*. 2002; 12:141–143. [PubMed: 12269543]
62. Biaggioni I, Robertson D, Krantz S, Jones M, Haile V. The anemia of primary autonomic failure and its reversal with recombinant erythropoietin. *Ann Intern Med*. 1994; 121:181–186. [PubMed: 8017744]
63. Singh AK, Szczech L, Tang KL, et al. Correction of anemia with epoetin alfa in chronic kidney disease. *N Engl J Med*. 2006; 355:2085–2098. [PubMed: 17108343]
64. Kaufmann H, Brannan T, Krakoff L, Yahr MD, Mandeli J. Treatment of orthostatic hypotension due to autonomic failure with a peripheral alpha-adrenergic agonist (midodrine). *Neurology*. 1988; 38:951–956. [PubMed: 2452997]
65. Low PA, Gilden JL, Freeman R, Sheng KN, McElligott MA. Efficacy of midodrine vs placebo in neurogenic orthostatic hypotension. A randomized, double-blind multicenter study. Midodrine Study Group. *JAMA*. 1997; 277:1046–1051. [PubMed: 9091692]
66. Wright RA, Kaufmann HC, Perera R, et al. A double-blind, dose-response study of midodrine in neurogenic orthostatic hypotension. *Neurology*. 1998; 51:120–124. [PubMed: 9674789]
67. Dhruva SS, Redberg RF. Accelerated approval and possible withdrawal of midodrine. *JAMA*. 2010; 304:2172–2173. [PubMed: 21081731]
68. Jordan J, Shannon JR, Biaggioni I, Norman R, Black BK, Robertson D. Contrasting actions of pressor agents in severe autonomic failure. *Am J Med*. 1998; 105:116–124. [PubMed: 9727818]
69. Singer W, Sandroni P, Opfer-Gehrking TL, et al. Pyridostigmine treatment trial in neurogenic orthostatic hypotension. *Arch Neurol*. 2006; 63:513–518. [PubMed: 16476804]
70. Shibao C, Okamoto LE, Gamboa A, et al. Comparative efficacy of yohimbine against pyridostigmine for the treatment of orthostatic hypotension in autonomic failure. *Hypertension*. 2010; 56:847–851. [PubMed: 20837887]

71. Shibao C, Raj SR, Gamboa A, et al. Norepinephrine transporter blockade with atomoxetine induces hypertension in patients with impaired autonomic function. *Hypertension*. 2007; 50:47–53. [PubMed: 17515448]

Figure 1.

Blood volume expansion is akin to “raising the level of the ocean [or blood pressure]” (Fig 1a) compared to baseline conditions. This strategy will usually increase the BP all the time – both day and night. An alternative strategy is to use short acting pressor agents, which will increase the size of the waves [or blood pressure] (Fig 1b), with peaks in BP (hopefully when patient is upright) and valleys (hopefully at night when patient will be lying down).

TABLE 1**Treatment of Vasovagal Syncope****Non-pharmacologic Interventions**

Avoid exacerbating situations (hot weather, volume depletion)

Increase sodium and water intake in an effort to increase blood volume

Discontinue potentially offending medications

Diuretics

Venodilators

Isometric muscle contractions / Physical countermeasures with presyncope

Get down (supine) at onset of prodromal symptoms

Outpatient "tilt training"

Pharmacologic Interventions

Fludrocortisone PO 0.1–0.2 mg qdaily (especially in young patients)

Midodrine PO 2.5–10 mg Q4H x 3/day (avoid within 4–5h of bedtime)

Metoprolol PO 25 mg BID (would use in the elderly or hypertensive patient)

SSRI (would only use if psychosocial issues are present)

Other Interventions

Implantable Loop Recorder to document asystole with clinical syncope

Consider Permanent Pacemaker if asystole is present during syncopal episodes

TABLE 2**Treatment of Neurogenic Orthostatic Hypotension****Non-pharmacologic interventions**

Discontinue potentially contributory medications

- Alpha-antagonists (including drugs for benign prostatic hypertrophy)
- Diuretics
- Venodilators

Avoid suddenly standing up

Avoid standing motionless

Leg crossing or calf clenching when standing

Increase fluid and salt intake

Use waist-high stocking compression devices or abdominal binders

Elevate head of bed 6–9 inches

Pharmacologic interventions

Increase plasma volume (PRN or daily)

- Fludrocortisone PO 0.1–0.2 mg qdaily
- Erythropoietin SQ 25–50 units/kg body weight if Hgb less than 12 g/dL

Pressor Agents (PRN, planned situational use, or regular daily dosing [listed])

- Midodrine PO 2.5–10 mg q4H x 3/day
- Yohimbine PO 5.4–10.8 mg TID
- Pyridostigmine PO 60 mg TID
- Pseudoephedrine PO 30 mg TID
- Atomoxetine PO 18 mg BID

Other Pressor Agents

- Ergotamine/cafeine PO 1mg/100mg BID
- Octreotide SQ 12.5µg–50µg BID