



Vasovagal Syncope: A Review of Current and Emerging Therapies for a Common Cardiology Condition

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Abstract

Vasovagal syncope (VVS), characterized by transient loss of consciousness, is among the most prevalent reasons for emergency visits worldwide. Although benign in nature, VVS can be accompanied by traumatic injury, leading to morbidity and decreased quality of life, especially in those with VVS recurrence. The management includes non-pharmacologic and pharmacologic therapies (if resistant), patient education and reassurance, salt and fluid intake increase, and physical counter-pressure maneuvers. Among medications, midodrine has shown promising results in reducing VVS recurrence and positive head-up tilt tests. Fluoxetine and atomoxetine also might be suitable candidates for VVS therapy. Permanent pacemakers, such as closed-loop stimulation, are under research and can be effective in cases unresponsive to medical treatment. In summary, while data are scarce regarding the definite treatment of VVS, there is a need for further research with novel, easy-to-use and cost-effective therapeutic methods to enhance quality of life and prevent traumatic injury.

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Introduction

Vasovagal syncope (VVS), defined as transient loss of consciousness due to a global reduction in cerebral blood flow, is one of the most common reasons for hospital visits, with a lifetime prevalence of 40% and 1%–1.5% emergency department visits in the United States.¹ In typical presentations of VVS, the principal diagnosis pathway is based on clinical history and physical examinations, and

no other diagnostic test is routinely utilized.²⁻⁴ Although nonfatal in nature and predominantly not associated with any cardiovascular disease, VVS can affect the quality of life significantly.⁵ In a cohort of hospitalized patients with a history of VVS, one-third reported disruption in their daily activities, such as driving and working.⁶ The primary way it affects individuals is through traumatic injury and falls. This rate of traumatic syncope episodes is reported as high as 33.5% in patients with VVS (Figure

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1).⁷ A comprehensive study assessed the predictors and risk factors of injury in patients with VVS and identified several patients' characteristics, VVS presentations, and surrounding conditions as determinants of VVS-related injury.⁸ The medical costs of assessing patients presenting with VVS could also be very high, as mentioned in reports from the United States, the United Kingdom, and Austria.⁹⁻¹¹ Considering healthcare systems and patients, there is a need to focus on this disorder to discover improved preventive measures.

VVS Treatments

Several pharmacologic and non-pharmacologic approaches have been suggested for VVS management.² ³ First-line therapies are non-pharmacologic and include patient education and reassurance, salt and fluid intake increase, physical counter-pressure maneuvers, and counteracting techniques for VVS initiation.¹² Some of these recommendations, such as physical counter-pressure maneuvers and a rise in salt and fluid intake, are well-established suggestions for patients with recurrent VVS.^{2,12} Newer approaches such as tilt training and aerobic exercise along with yoga therapy have been recently investigated as well and shown promising results, which can be beneficial for addition to routine recommendations if confirmed in other studies.^{13,14}

Pharmacologic Treatments

Besides lifestyle changes advised to patients with VVS, pharmacologic interventions may be recommended.¹⁵ Several drugs have been suggested for use in VVS with conflicting results in trials. A recent systematic review and network meta-analysis study compared all possible medications trialed for VVS and found promising results for midodrine as an effective treatment for preventing VVS recurrence (Figure 1).¹⁶ The efficacy of midodrine in reducing VVS recurrence and positive head-up tilt tests (HUTTs) was also demonstrated in a meta-analysis study conducted for midodrine only.¹⁷ Based on a network meta-analysis, fluoxetine could also decrease VVS spells, especially in patients with concomitant anxiety. Knowing that patients with VVS suffer from anxiety and other psychological disorders more frequently than the general population,¹⁸ fluoxetine might be a suitable choice. Atomoxetine has shown significant results in diminishing positive HUTTs among patients with VVS.¹⁹ In a prior study, atomoxetine reduced the composite endpoint of presyncope and syncope; however, no significant difference concerning syncope was found.²⁰ Ongoing randomized, placebo-controlled trials, such as The Seventh Prevention of Syncope Trial (POST VII), will determine the clinical benefits of atomoxetine for preventing VVS recurrence.²¹ Regarding fludrocortisone

as another controversial treatment in VVS, the randomized controlled trial (POST II) failed to demonstrate efficacy with the initial dose, ultimately leading to a significant reduction in recurrent VVS.²² Nevertheless, the fact that many of these interventions could lead to higher blood pressure is a note of caution. For instance, the vasoactive nature of midodrine could lead to the relative contraindication of use in hypertensive patients and pregnant women with a higher risk of hypertension-related complications.^{17,23} Similar increased blood pressure has been demonstrated for atomoxetine.²⁴ Future head-to-head trials comparing suggested drugs for VVS are needed to confirm these findings.²⁵

Pacemaker Therapy

Permanent pacemaker therapy is sometimes indicated in patients unresponsive to standard therapy.²⁶ Nevertheless, its use in preventing VVS has not been fully understood due to the vasodepressor component of VVS. Early trials of pacing showed a decrease in syncope recurrences in HUTT-positive patients with VVS,^{27,28} but these were open-label unblinded trials. Later trials in the 2000s demonstrated no significant benefits of pacing for patients with VVS.²⁹ ³⁰ Recently, 2 double-blinded randomized controlled trials (RCTs) have investigated dual-chamber pacing with a closed-loop stimulation (DDD-CLS) algorithm in recurrent VVS patients with positive HUTTs and asystole as inclusion criteria.^{31,32} DDD-CLS pacing decreased the risk of VVS recurrence by 89% relative risk reduction in the SPAIN (Closed-Loop Stimulation for Neuromediated Syncope) trial.³¹ Moreover, the Benefit of Dual-Chamber Pacing with Closed-Loop Stimulation in Tilt-Induced Cardioinhibitory Reflex Syncope (BIOSync CLS) study, a double-blinded RCT, showed that patients with recurrent VVS, positive HUTTs, and asystolic pauses ≥ 3 seconds randomized to DDD-CLS had a significant decrease in VVS recurrence compared with inactive pacing.³² In summary, permanent pacing might be a viable solution for older patients with more than 2 VVS spells in a year and positive HUTTs (cardioinhibitory response). Still, further studies are needed to enlighten the characteristics of patients for which pacing might be beneficial.

Future Directions

Some patients may have comorbidities limiting the available intervention for VVS, hence the need for inexpensive and easy-to-use interventions not affecting the comorbidities. A recently suggested intervention is elastic compression stockings (ECSs). ECSs have been investigated in other populations and for conditions.³³ They can benefit patients with VVS by increasing venous blood return and reducing venous pooling.³⁴ Moreover, ECS efficacy has been demonstrated among patients with orthostatic

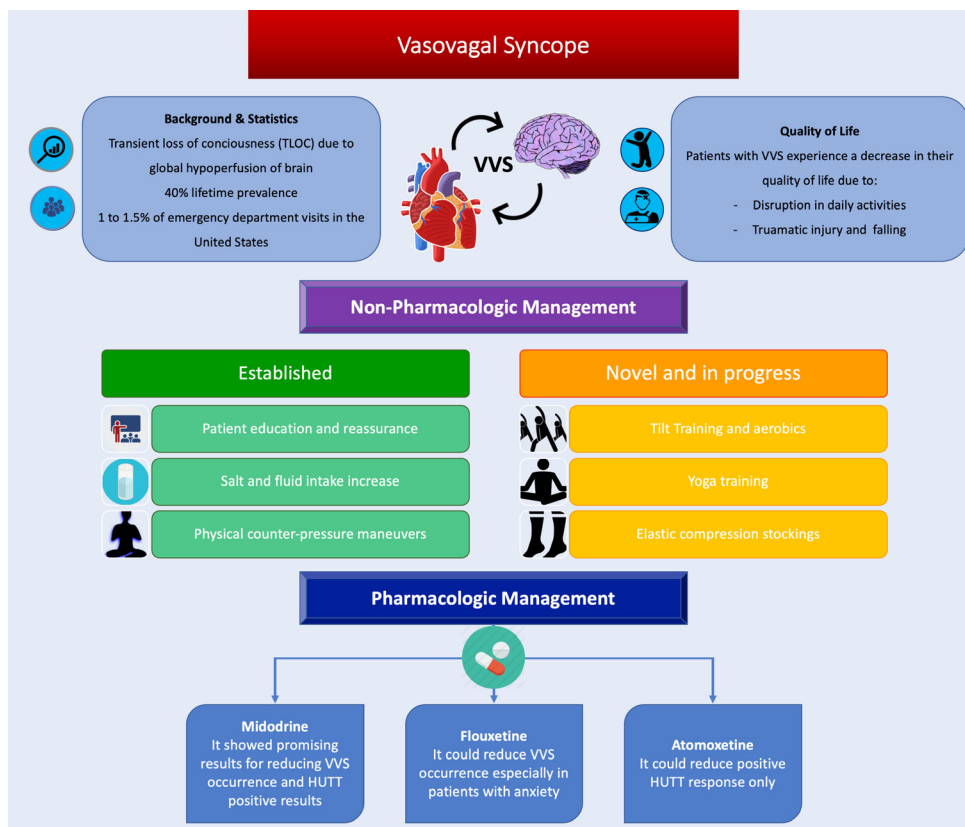


Figure 1. The image presents a summary of vasovagal syncope management and novel therapeutic approaches.

hypotension.^{33,35} Among the mentioned VVS medications, midodrine, a vasopressor, alleviates VVS symptoms by raising blood pressure. Similarly, using fludrocortisone as a synthetic corticosteroid could lead to higher blood pressure since it causes sodium retention. Consequently, close monitoring of blood pressure levels seems necessary when administering these agents, which is even of higher significance in VVS patients who also have hypertension. Management in these conditions could become a challenge for clinicians, and the lack of data on addressing the issue of hypertension in patients with VVS strongly suggests the need for more exploration and investigation of mechanical treatments, such as compression stockings. Ongoing trials such as COMFORTS-II (COMpression stockings FOR Treating vasovagal Syncope) can be decisive.³⁶ Cardioneuroablation (CNA) is another promising treatment for refractory VVS. In a meta-analysis of 14 studies using CNA in patients with VVS, Vandenberg et al³⁷ found a high freedom rate (91.9%) from syncope. Given the inadequacy of available treatments for VVS, these novel therapeutic strategies have high value.

Conclusion

Considering all treatment methods mentioned, there is no definite treatment for VVS prevention, and there is a need

for further research. Specialized syncope units constitute one of the principal ways of evaluating patients with VVS and finding novel strategies aiming at reducing spells in patients with VVS.^{38, 39}

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