Evidence-based treatment for vasovagal syncope

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Only a minority of patients with vasovagal syncope require treatment, and most can be managed conservatively. Patients should be encouraged to liberalize their fluid and salt intake, unless they have contraindications such as hypertension. All patients should be taught physical counterpressure maneuvers. Midodrine is the first-line therapy for patients having frequent presyncope or syncope or for those with brief or no prodromes. The routine use of beta-blockers, serotonin-specific reuptake inhibitors, fludrocortisone, and pacemakers is discouraged. Whether loop recorders can be used to target treatment is under investigation, as is fludrocortisone.

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Introduction

Vasovagal syncope frustrates patients and clinicians alike with its paucity of effective treatments. About 37% of people faint at least once in their lives.1,2 Usually beginning in adolescence or early adulthood, the predilection to fainting persists for decades.

Syncope is only one of several causes of transient loss of consciousness. A useful working definition is a transient, self-limited loss of consciousness that usually leads to falling, with a relatively rapid onset and a spontaneous, complete, and relatively rapid recovery. Vasovagal syncope is by far the most common cause of syncope in the community and the dominant cause in emergency wards.4 It is due to a variable combination of reflex bradycardia and hypotension, triggered by prolonged sitting or standing; exposure to pain, blood, or medical procedures; heavy exercise; or getting up and moving abruptly.5 Even in the same patient, the triggers and presentation vary from spell to spell. The hypotension may be due to a reduction in peripheral sympathetic neural outflow, leading to venous pooling and vasodepression. The central neurophysiology is unknown.

Syncope is usually recurrent. In the community, the median number of faints is about two, with a much higher symptom burden in the clinical population.1,3,4 Many patients injure themselves, and recurrent syncope is associated with significantly impaired quality of life.5 (Sheldon et al5 contains reports published before 2004, which therefore precede the articles covered in this review.) Given this reduced quality of life, effective therapies are necessary. The treatments considered to date range from dietary modification through physical training, physical maneuvers, medication, and even permanent pacemaker implantation. Surprisingly, there has not been a focused review of therapies with structured recommendations, although overviews of therapy have appeared in more general reviews. Here we review current treatments followed by a suggested management strategy. Each recommendation is presented with the treatment effect and level of evidence. Treatment effect is rated as probably helpful, debatable, or probably unhelpful. The evidence is summarized as good, moderate, or poor. The recommendations are summarized in Table 1. Important trials that appeared after 2003 are summarized in Table 2.

Education and lifestyle interventions

Salt and fluid

Many patients with syncope are encouraged to increase their salt and fluid intake, although the evidence that this treatment is effective is weak. Most patients with a positive tilt test convert to a negative response on a subsequent test after receiving an intravenous volume load, and plasma and blood volumes and orthostatic tolerance all improve with dietary salt supplementation.5 The usual reported dose of salt tablets is 6–9 g (100–150 mmol) per day. Salt supplementation should be avoided in patients with hypertension, renal disease, or cardiac dysfunction.

Recommendation: In the absence of contraindications, frequently symptomatic patients should liberalize their salt and fluid intake. Probably helpful, moderate evidence.

Exercise training

Although exercise acutely increases blood volume,5 there is limited evidence supporting the use of exercise training to prevent syncope. One study subjected 14 patients with syn-
cope to a regimen of 12 minutes of daily progressive exercise training. After this, their blood volume increased 3.9%, and orthostatic tolerance to lower body negative pressure increased by 5 minutes. A recent, very underpowered randomized study did not detect a reduction in the likelihood of syncope in exercised patients.

**Recommendation:** In the absence of contraindications, patients should follow relevant national guidelines regarding physical exercise. Debatable effect, weak evidence.

**Physical counterpressure maneuvers**

Considerable evidence supports the use of physical counterpressure pressure maneuvers (PCMs). During PCMs, the presyncopal patient does isometric contractions of either the legs (by leg crossing) or the arms and hands (by pulling apart gripped hands) or squats. These rely on a prodrome long enough to allow the technique to prevent the progression of presyncope to syncope and usually to prevent syncope during tilt tests.

PCM was initially thought to work by reversing the decline in total peripheral resistance that attends vasovagal response. However, Van Dijk et al. showed that leg crossing increased cardiac output 9% and arterial blood pressure 3% while reducing peripheral resistance. Adding leg tension further increased systolic blood pressure and cardiac output 10% and 8%, respectively, and peripheral resistance dropped even further. PCMs moved quickly into the clinical arena after two positive studies of PCMs during tilt testing and good outcomes in follow-up.

The Physical Counterpressure Manoeuvres Trial (PC Trial) was a randomized controlled trial comparing conventional therapy (fluid and salt intake, counselling, avoidance) against conventional therapy augmented by one of three maneuvers in 208 patients with vasovagal syncope. After 18 months of follow-up, both groups experienced a similar number of presyncopal episodes, yet PCMs provided a significant relative risk reduction of 36% of patients who

### Table 1: Suggested levels of recommendations with their treatment effect and level of evidence

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Treatment effect</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lifestyle changes:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increase salt and fluid</td>
<td>Probably helpful</td>
<td>Moderate</td>
</tr>
<tr>
<td>Physical exercise</td>
<td>Debatable effect</td>
<td>Weak</td>
</tr>
<tr>
<td>Physical counterpressure</td>
<td>Probably helpful</td>
<td>Good</td>
</tr>
<tr>
<td>Orthostatic training:</td>
<td>Debatable effect</td>
<td>Moderate</td>
</tr>
<tr>
<td>Tilt training</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Home orthostatic training</td>
<td>Possibly helpful</td>
<td>Good</td>
</tr>
<tr>
<td>Pharmacologic therapy:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>Probably helpful</td>
<td>Good</td>
</tr>
<tr>
<td>SSRI antidepressants</td>
<td>Debatable effect</td>
<td>Moderate</td>
</tr>
<tr>
<td>Midodrine</td>
<td>Probably helpful</td>
<td>Good</td>
</tr>
<tr>
<td>Fludrocortisone</td>
<td>Debatable effect</td>
<td>Weak</td>
</tr>
<tr>
<td>Cardiac pacemakers:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac pacemakers: routine</td>
<td>Possibly helpful</td>
<td>Good</td>
</tr>
<tr>
<td>Cardiac pacemakers: selected</td>
<td>Debatable effect</td>
<td>Weak</td>
</tr>
<tr>
<td>use in refractory cases with</td>
<td></td>
<td></td>
</tr>
<tr>
<td>asystole</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table 2: Summary results of major randomized clinical trials of treatment for vasovagal syncope

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Senior author</th>
<th>Sites, n</th>
<th>Subjects, n</th>
<th>Mean age</th>
<th>Clinical outcome</th>
<th>Effect</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical counterpressure</td>
<td>Van Dijk</td>
<td>15</td>
<td>223</td>
<td>39</td>
<td>Syncope recurrence</td>
<td>51% control, 32% PCM</td>
<td>.005</td>
</tr>
<tr>
<td>Home orthostatic</td>
<td>Foglia-Manzillo</td>
<td>8</td>
<td>68</td>
<td>40</td>
<td>Positive tilt test</td>
<td>60% controls vs. 59% training</td>
<td>NS</td>
</tr>
<tr>
<td>Home orthostatic</td>
<td>Duygu</td>
<td>1</td>
<td>82</td>
<td>41</td>
<td>Syncope recurrence</td>
<td>56% control, 37% training</td>
<td>.1</td>
</tr>
<tr>
<td>Home orthostatic</td>
<td>On</td>
<td>1</td>
<td>42</td>
<td>39</td>
<td>Syncope or presyncope recurrence</td>
<td>47% control, 42% training</td>
<td>.82</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>Sheldon</td>
<td>14</td>
<td>208</td>
<td>42</td>
<td>Syncope recurrence</td>
<td>36% controls, 36% metoprolol</td>
<td>.99</td>
</tr>
<tr>
<td>Fluoxetine, propranolol</td>
<td>Theodorakis</td>
<td>1</td>
<td>96</td>
<td>42</td>
<td>Syncope or presyncope recurrence</td>
<td>41% controls, 51% propranolol</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Midodrine</td>
<td>Qingyou</td>
<td>1</td>
<td>26</td>
<td>12</td>
<td>Syncope recurrence</td>
<td>22% fluoxetine, 80% controls, 22% midodrine</td>
<td>.023</td>
</tr>
<tr>
<td>Fludrocortisone</td>
<td>Salim</td>
<td>1</td>
<td>33</td>
<td>14</td>
<td>Syncope or presyncope recurrence</td>
<td>36% controls, 55% fludrocortisone</td>
<td>&lt;.04</td>
</tr>
<tr>
<td>Pacemakers</td>
<td>Connolly</td>
<td>15</td>
<td>100</td>
<td>49</td>
<td>Syncope recurrence</td>
<td>40% controls, 31% pacing</td>
<td>.14</td>
</tr>
<tr>
<td>Pacemakers</td>
<td>Raviele</td>
<td>7</td>
<td>29</td>
<td>53</td>
<td>Syncope recurrence</td>
<td>38% controls, 50% pacemakers</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Only publications after 2003 are cited. NS = not stated.*
follow-up, provided that they continued training at home. In contrast, Foglia-Manzillo et al\textsuperscript{13} randomized 68 patients with syncope and two positive tilt tests to a daily 30-minute self-training regimen. After 3 weeks, 60% of patients in both groups had positive tilt tests. These patients were then encouraged to continue with self-training over the subsequent year, but of the 62, only five actually did so, with 28% having recurrent syncope. Two recent randomized open-label studies by Dugyu et al\textsuperscript{14} and On et al\textsuperscript{15} also failed to detect a benefit from orthostatic self-training at home.

There is no high-level evidence of the effectiveness of orthostatic training, no obvious physiologic rationale, and three small negative randomized controlled trials. Whether these results are due to poor compliance or inefficacious therapy is unclear. Due to these factors, orthostatic training cannot be recommended yet for routine use.

**Recommendation:** Frequently symptomatic patients with a positive tilt test might undergo tilt table training. Debatable effect, moderate evidence. Self-administered orthostatic training with prolonged standing without tilt training should not be used. Probably unhelpful, good evidence.

**Pharmacological therapy**

**Beta-adrenoceptor blockers**

Beta-blockers were used for a variety of reasons and underwent at least 19 controlled trials of their effect on tilt test outcome. A large majority of patients on beta-blockers have negative tilt tests, particularly if the tilt tests include an isoproterenol infusion. Early nonrandomized studies provided conflicting information about whether beta-blockade prevents syncope, with some reporting marked reductions in syncope in groups that received beta-blockers and others reporting no benefit at all.

There have been five randomized clinical trials of the efficacy or effectiveness of \(\beta\)-adrenergic blockers for the prevention of syncope.\textsuperscript{5} On the whole, they were negative. One small, early study of atenolol was positive, and one did report a remarkable 80%–90% reduction in all measures of presyncope and syncope in all three treatment arms (placebo, propranolol, and nadolol), with no significant difference among the three arms.

We reported the results of the first Prevention of Syncope Trial in 2006.\textsuperscript{16} It was a randomized, placebo-controlled, double-blind trial that assessed the effects of metoprolol in vasovagal syncope over a 1-year treatment period. A total of 208 patients were randomized to metoprolol or placebo. Metoprolol provided no benefit, with nearly identical outcome rates in both study arms (Figure 1).

**Recommendation:** Unselected, frequently symptomatic patients should not receive beta-adrenoceptor blockers as first-line therapy. Probably unhelpful, good evidence.

**Selective serotonin reuptake inhibitors (SSRIs)**

Serotonin plays important roles in the regulation of heart rate and blood pressure. This has led to speculation that fluctuation in central serotonin levels may contribute to vasovagal syncope. Indeed, a randomized, double blind,
placebo-controlled study5 of 68 consecutive patients who had not responded to other treatments was reported to be positive in 1999. Disappointingly, a recent second randomized, placebo-controlled study of 96 patients found fluoxetine, propranolol, and placebo to have equal effects, although a post hoc on-treatment analysis found an improved quality of life and decreased syncope and presyncope with fluoxetine.17 Therefore, the evidence for the use of SSRIs with vasovagal syncope is mixed at best. The SSRI drugs should not be used early in the treatment of vasovagal syncope.

Recommendation: Frequently symptomatic patients might be prescribed serotonin-specific reuptake inhibitors. Debatable effect, moderate evidence.

Midodrine

This drug is a peripherally active alpha-agonist, as is its metabolite. It is used is to ameliorate the reduction in peripheral sympathetic neural outflow that is responsible for venous pooling and vasodepression that are central to vasovagal syncope. Its inability to cross the blood-brain barrier and lack of gastrointestinal side effects are useful features. An early randomized crossover placebo-controlled study of a small number of highly symptomatic patients reported a marked reduction in symptoms, and also in the likelihood of a positive tilt test.5 Kaufmann et al5 confirmed these results when they reported that midodrine obviated the postural hypotension induced by head-up tilt in patients with vasovagal syncope.5 An early, randomized, controlled, open-label trial of midodrine, in which the investigators titrated midodrine from 5 to 15 mg three times a day over 3 weeks in an effort to render tilt tests negative, was also positive.5

Finally, Qingyou et al18 studied 26 children in a randomized, open-label trial. The children had experienced at least three vasovagal episodes per year. Midodrine was titrated from 1.25 to 2.5 mg twice a day commensurate with tilt test results in comparison with conservative diet and posture training. Clinical recurrence rates over 10 months were 20% and 80% in the midodrine and control groups, respectively.

Midodrine has demonstrated short- and medium-term therapeutic success while being well tolerated in both adult and pediatric populations. The drug is reasonably well tolerated, with side effects including supine hypertension, nausea, scalp paresthesias, piloerection, and rash. These are dose-related and easily reversible. It should not be used in patients with hypertension or heart failure. It also requires careful attention to both dosing and interdose intervals and is usually best managed in specialty clinics. More robust trial designs with greater patient numbers are required to improve the strength of evidence behind its recommendation.

Recommendation: In the absence of contraindications, frequently symptomatic patients should be prescribed midodrine. Probably helpful, good evidence.

Fludrocortisone

Fludrocortisone is a corticosteroid with mainly mineralocorticoid activity resulting in sodium and water retention and potassium excretion, which would increase blood volume. The use of fludrocortisone in vasovagal syncope has been assessed in pediatric studies. Two open-label uncontrolled studies reported that children had far less syncope and presyncope while taking fludrocortisone.5 In contrast, the randomized, double-blinded, placebo-controlled study by Salim and Di Sessa19 found more symptoms in the fludrocortisone group than in children treated with placebo. There have been no controlled studies of fludrocortisone in adults with vasovagal syncope, and the utility of fludrocortisone in the prevention of syncope remains unclear.

To assess its effectiveness, we are conducting the second Prevention of Syncope Trial (POST II), a multinational, randomized, controlled clinical trial.20 Patients with recurrent vasovagal syncope are receiving either fludrocortisone or placebo for 1 year; the primary outcome is the proportion of patients with at least one syncope recurrence. Enrollment is underway in both North and South America, and the trial should conclude in 2010.

Recommendation: In the absence of contraindications, frequently symptomatic patients might be prescribed fludrocortisone. Debatable effect, weak evidence.
One unresolved question is whether the subset of patients with vasovagal syncope who have astyolic pauses during syncpe might benefit from pacing. The second International Study on Syncpe of Uncertain Etiology (ISSUE 2) used implantable loop recorders (ILRs) to test whether therapy targeted to the findings of the recorders could prevent syncpe. ISSUE 2 implanted ILRs in 417 patients with recurrent syncpe and followed them until their first syncpe or for a maximum of 2 years. Further treatment was assigned based on the electrocardiogram findings during the episode. This resulted in 57 patients receiving a pacemaker for asystole. The patients who received pacing had a 1-year recurrence rate of 10%, compared with 41% in the 50 patients who did not receive a specific treatment and a 90% relative risk reduction for syncope. Although highly impressive, the results were very similar to those of the three earlier unblinded, studies in which patients either received a pacemaker or did not. This did not resolve the question of the efficacy of targeted therapy, and there is considerable debate about how to interpret the results. Accordingly, the investigators are now conducting ISSUE 3, a multicenter, placebo-controlled, prospective, double-blind, randomized study of 710 patients. This study will implant ILRs in patients with frequently recurrent, suspected vasovagal syncpe. Patients with asystolic pauses will have a pacemaker implanted with double-blinded randomization to active pacing or sensing only, that is, with a VPS 2 design. This study is underway.

**Recommendation:** Pacemakers should not be used routinely to treat vasovagal syncpe. Probably unhelpful, good evidence. Drug-resistant, highly symptomatic patients with documented asystole during syncpe might be prescribed dual-chamber pacing with rate-drop sensing. Debatable effect, weak evidence.

**The treatment cascade**

All patients should be encouraged to liberalize their fluid and salt intake, unless they have contraindications such as hypertension. Helpful goals include about 2 extra teaspoons of salt per day and oral fluids such that their urine is very pale. All patients with prodromal symptoms should be taught secondary prevention maneuvers such as leg crossing, isometric exercise, and squatting. For many patients, particularly those with infrequent symptoms, these will suffice. However, for patients having troublesome presyncope or syncpe occurring daily to weekly or for those with brief or no prodromes it is worth trying midodrine, starting at 5 mg 3 times daily during waking hours. The first dose should be taken when the patient wakes up, with subsequent doses 4 hours apart. Usually the dose level and interval will require modification. With current knowledge, the routine use of beta-blockers, serotonin-specific reuptake inhibitors, fludrocortisone, and pacemakers is discouraged. Whether loop recorders can be used to target treatment is a matter of investigation.

Two further points. Given the widespread interest in useful treatments for vasovagal syncope, and progress both within the review period and before it, we suggest that a formal consensus document in the risk stratification and treatment of vasovagal syncope is overdue. Finally, only randomized trials will provide evidence of effective treatments, and a consensus commitment to conducting these difficult studies is necessary.

**References**


