Fluoxetine vs. propranolol in the treatment of vasovagal syncope: a prospective, randomized, placebo-controlled study

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Aims To compare the therapeutic efficacy of placebo, propranolol, and fluoxetine in patients with vasovagal syncope (VVS).

Methods and results Ninety-six consecutive patients with VVS were randomized to treatment with placebo, propranolol, or fluoxetine and followed-up for 6 months. Before and during treatment, they reported their syncopal and presyncopal episodes and graded their well-being, expressed as the general evaluation of life, general activities, and everyday activities (each scaled from 1 = very good to 5 = very bad). Two patients refused follow-up. Among the remaining 94, no difference between groups was observed regarding the distribution of time of vasovagal events (syncopes or presyncopes) during follow-up (log-rank test). No difference was also observed when syncopes and presyncopes were assessed separately. Eighteen patients discontinued therapy. Among the remaining 76 ('on-treatment' analysis), the mean time to a vasovagal episode (syncope or presyncope) was significantly longer in the fluoxetine group when compared with the two other groups (log-rank test, \( P < 0.05 \)). A significant difference in favour of fluoxetine was also observed regarding presyncopes. The difference between groups regarding the syncope-free period was not significant. During therapy, patients’ well-being was improved (decreased) only in the fluoxetine group (13.4 ± 0.7 vs. 15.4 ± 0.9 before treatment, \( P < 0.01 \)).

Conclusion Fluoxetine seems to be equivalent to propranolol and placebo in the treatment of VVS. However, it improves patients’ well-being and might be more effective in reducing presyncopes and total vasovagal events in some patients with recurrent VVS.

KEYWORDS
Vasovagal syncope; Neurally mediated syncope; Drugs; Nervous system; Prevention

Introduction

The optimal medical therapy of patients with vasovagal syncope (VVS) is still controversial.\(^1\) A variety of drugs has been used, mainly aiming at the peripheral pathophysiological mechanisms of this syndrome.\(^2\) In order to inhibit the sympathetic stimulation that precedes the onset of the vasovagal reaction, beta-blockers have been proposed for the treatment of VVS.\(^3\)\(^-\)\(^5\) However, recent prospective, double-blind, randomized, placebo-controlled trials have given rather disappointing results.\(^6\)\(^,\)\(^7\) As we have recently shown, beta-blockers seem to be equally effective as placebo in treating patients with vasovagal syndrome.\(^8\)

The central serotonergic system seems to be involved in the pathogenesis of the vasovagal syndrome.\(^9\)\(^,\)\(^10\) Drugs acting upon the central nervous system by inhibiting the reuptake of serotonin in the synapse like fluoxetine, sertraline, and others have been used when other medical treatment has failed.\(^11\) In a recent placebo-controlled study, investigating the therapeutic efficacy of paroxetine in patients with VVS, it was reported that paroxetine hydrochloride is more effective than placebo.\(^12\) However, the abovementioned study included selected patients who had vasovagal episodes refractory to other medical interventions. For the time being, there is no prospective, randomized study comparing the therapeutic efficacy of fluoxetine with that of propranolol and placebo, in sequential patients with VVS.

Methods

Study population and initial evaluation

The study population consisted of patients with a history of VVS who were referred to the outpatient clinic of our hospital for further...
The diagnosis was based on the typical history and the exclusion of any other cause of syncope. Patients were eligible for the study if they had at least five syncopes in their lifetime, not less than two syncopal attacks during the last year, and their last syncopal episode had occurred at least 1 month before their initial evaluation. They were not under medical treatment and they had not been treated with drugs in the past. The study protocol was approved by the Ethics Committee of the hospital, and 96 of 101 eligible patients gave their informed consent and were initially included in the study. All patients underwent an initial head-up tilt test with clomipramine, before their inclusion in the study.13,14 A neurological, psychiatric, and cardiological evaluation ruled out any neurological, psychiatric, or structural heart disease. Patients with contraindications to the treatments (propranolol or fluoxetine) were excluded.

During their initial evaluation, all patients completed a questionnaire assessing their well-being. The questionnaire consisted of three parameters: (i) the general evaluation of ‘well-being’ and quality-of-life; (ii) general activities; and (iii) everyday activities.8 General evaluation of the quality-of-life included general aspects and was graded from 1 to 5 (1 = very good, 2 = good, 3 = moderate, 4 = bad, and 5 = very bad). Evaluation of general activities included dyspnoea during exercise, dyspnoea at rest, chest discomfort, palpitations, and fatigue. Symptoms were characterized as ‘absent’, ‘mild’, ‘moderate’, and ‘severe’ and they were graded from 1 to 4, respectively. Everyday activities included bathing, walking, walking upstairs, carrying weights, and tolerance to exercise. Activities were characterized as ‘not limited’, ‘mildly limited’, and ‘severely limited’ and were graded from 1 to 3, respectively. Patients were asked to grade each of the three parameters and the sum of the three grades was the ‘well-being’ score; the lower the score, the higher the quality-of-life.

Treatment—follow-up—endpoints

Following their initial evaluation, patients were randomly treated with placebo, propranolol, or fluoxetine. The dose of propranolol ranged from 10 to 40 mg three times per day, according to the patients’ heart rate at rest and their tolerance of treatment. The dose of fluoxetine was 20 mg per day. A capsule containing lactose in powder form was administered once a day as a placebo treatment, so that patients in the placebo group were not aware of the fact that they were not administered an active drug. The placebo capsules were packed in our hospital and patients obtained them. Follow-up during treatment was performed every month and patients were asked about their compliance with treatment, the occurrence of syncope, presyncope, dizziness, or any other symptom. Presyncope was defined as the sensation of impending syncope and other symptoms (nausea, sweating, blurred vision), which were similar to the patient’s usual symptoms and accompanied by hypotension with or without bradycardia.15,16 Clinical examination and ECG recording were also performed. If necessary, extra visits were programmed in order to evaluate the patients’ clinical status. At the end of the 6-month period, patients were evaluated again and a second head-up tilt test was also performed. The physician who initially evaluated the patients was not aware of their randomization. Another doctor was responsible for the patients’ clinical follow-up and the dose adjustment, whereas a third evaluated their well-being score.

The exclusion criteria included: (i) patients’ refusal to continue the study; (ii) non-compliance with the study protocol or treatment; and (iii) drugs’ serious adverse effects. The primary endpoint of the study was the time to the first recurrence of syncope or presyncope. The secondary endpoints were: (i) the number of patients with recurrence of syncope during therapy; (ii) the number of patients with recurrence of presyncope during follow-up; (iii) the number of patients with any vasovagal event (syncope or presyncope) during therapy; (iv) the number of syncopal, presyncope, and total vasovagal episodes in the follow-up period; and (v) patients’ well-being during the therapy. The total vasovagal episodes were the sum of syncopal and presyncope attacks.

Statistical analysis

The t-test analysis was used to compare the baseline demographics and characteristics between patients randomized to treatment with placebo, propranolol, or fluoxetine. We performed survival analysis (log-rank test) in order to compare the time to the recurrence of syncope or presyncope between the three groups. Cox regression analysis was used to assess the hazard ratio between groups. Finally, analysis of variance (ANOVA) for repeated measures was used to compare: (i) the number of syncopal, presyncope, and total episodes; and (ii) the quality-of-life score, within the 6 months before and during treatment. A P-value <0.05 was considered as being statistically significant.

Results

Study population

A total of 96 patients was included in this study (49 men and 47 women), mean age 42 ± 15 years (minimum 15 and maximum 70 years). Of these, 32 patients were randomized to placebo (placebo-group), 32 to propranolol (propranolol-group), and 32 to fluoxetine (fluoxetine-group). Twenty-six patients in the fluoxetine-group (81%), 24 in the propranolol-group (75%), and 25 in the placebo-group (78%) had a positive response to tilt testing (P: NS between groups).

Of the 96 patients, 2 patients refused follow-up and were excluded from the study, which included one from the placebo-group and one from the propranolol-group. Another 18 more subjects [9 in the placebo-group (28%), 7 in the propranolol-group (22%), and 2 in the fluoxetine-group (6%)] interrupted medication after 1–4 months of therapy, mainly because of the significant decrease of their syncopal and presyncope episodes and secondarily because of the side effects of the drugs. The complaints reported were bradycardia, fatigue, drowsiness, and sleep disorders. The remaining 76 patients were under treatment for the entire follow-up period (Table 1). No difference was observed in demographics and clinical characteristics between the placebo-, propranolol-, and fluoxetine-group.

Patients with syncopal and presyncope episodes during follow-up

Among the 94 patients who were followed-up, 12 in the fluoxetine-group (37%), 10 in the propranolol-group (32%), and 12 in the placebo-group (38%) had a positive response to the head-up tilt test, after 6 months of therapy (P: NS between groups).

Of the 94 patients, 36 (38%) experienced a syncopal or presyncope episode: 7 of 32 patients in the fluoxetine-group (22%); 13 of 31 in the placebo-group (41%); and 16 of 31 in the propranolol-group (51%). As regards the syncopal episodes, they occurred in 13 of the 94 patients (14%): 5 of them were treated with placebo (16%); 5 with propranolol (16%); and 3 with fluoxetine (9%). Finally, 23 of the 94 patients had presyncope episodes during the 6 months of treatment (24%): 8 of them were treated with placebo (25%), 11 with propranolol (35%) and 4 with fluoxetine (12%).
Table 1  Patient demographics and characteristics

<table>
<thead>
<tr>
<th>Patients</th>
<th>Treatment</th>
<th>Total</th>
<th>Placebo</th>
<th>Propranolol</th>
<th>Fluoxetine</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 76)</td>
<td>(n = 22)</td>
<td>(n = 24)</td>
<td>(n = 30)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>40.1 ± 2.0</td>
<td>41.8 ± 3.6</td>
<td>39.66 ± 3.5</td>
<td>39.3 ± 2.7</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>36</td>
<td>8</td>
<td>11</td>
<td>17</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>40</td>
<td>14</td>
<td>13</td>
<td>13</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Total number of syncopes</td>
<td>5.9 ± 0.8</td>
<td>5.6 ± 0.8</td>
<td>6.0 ± 1.0</td>
<td>5.8 ± 0.9</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5.0</td>
<td>5.0</td>
<td>5.0</td>
<td>5.0</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.0</td>
<td>1.25</td>
<td>1.75</td>
<td>1.0</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>(5.0–11.0)</td>
<td>(5.0–10.0)</td>
<td>(5.0–11.0)</td>
<td>(5.0–11.0)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Total number of presyncopes</td>
<td>6.5 ± 0.8</td>
<td>8.6 ± 1.8</td>
<td>5.9 ± 1.5</td>
<td>5.7 ± 1.1</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3.5</td>
<td>6.5</td>
<td>3.0</td>
<td>4.0</td>
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</tr>
<tr>
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<td>9.0</td>
<td>18.0</td>
<td>7.5</td>
<td>7.5</td>
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<tr>
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<td>(0.0–30.0)</td>
<td>(0.0–25.0)</td>
<td>(0.0–30.0)</td>
<td>(0.0–25.0)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Number of syncopes in the last year</td>
<td>3.3 ± 0.2</td>
<td>3.3 ± 0.4</td>
<td>3.6 ± 0.4</td>
<td>3.1 ± 0.2</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3.0</td>
<td>2.5</td>
<td>3.0</td>
<td>3.0</td>
<td>NS</td>
<td></td>
</tr>
<tr>
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<td>2.0</td>
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<td>3.0</td>
<td>2.0</td>
<td>NS</td>
<td></td>
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<tr>
<td></td>
<td>(2.0–10.0)</td>
<td>(2.0–10.0)</td>
<td>(2.0–10.0)</td>
<td>(2.0–10.0)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Number of presyncopes in the last year</td>
<td>2.9 ± 0.3</td>
<td>3.7 ± 0.6</td>
<td>2.4 ± 0.4</td>
<td>2.6 ± 0.4</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>3.0</td>
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<td>2.0</td>
<td>2.0</td>
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<td></td>
</tr>
<tr>
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<td>3.0</td>
<td>5.25</td>
<td>2.0</td>
<td>3.25</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(0.0–11.0)</td>
<td>(0.0–11.0)</td>
<td>(0.0–10.0)</td>
<td>(0.0–10.0)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Number of syncopes in the last 6 months</td>
<td>2.3 ± 0.2</td>
<td>2.2 ± 0.2</td>
<td>2.6 ± 0.4</td>
<td>2.1 ± 0.2</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.0</td>
<td>2.0</td>
<td>2.0</td>
<td>2.0</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.0</td>
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<td>2.0</td>
<td>1.25</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(1.0–8.0)</td>
<td>(1.0–6.0)</td>
<td>(1.0–8.0)</td>
<td>(1.0–5.0)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Number of presyncopes in the last 6 months</td>
<td>2.1 ± 0.2</td>
<td>2.0 ± 0.4</td>
<td>2.0 ± 0.3</td>
<td>2.2 ± 0.4</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.0</td>
<td>2.0</td>
<td>2.0</td>
<td>2.0</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.0</td>
<td>1.25</td>
<td>2.0</td>
<td>3.25</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(0.0–10.0)</td>
<td>(0.0–8.0)</td>
<td>(0.0–6.0)</td>
<td>(0.0–10.0)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Quality-of-life score before therapy</td>
<td>14.9 ± 0.5</td>
<td>14.6 ± 0.7</td>
<td>14.6 ± 0.6</td>
<td>15.4 ± 0.9</td>
<td>NS</td>
<td></td>
</tr>
</tbody>
</table>

No difference was observed in demographics, clinical characteristics, and quality-of-life score between patients treated with placebo, propranolol, or fluoxetine. Values are expressed as mean ± 1 SE. The median values are shown under the mean values. The interquartile ranges are shown under the mean values (bold italics). The minimum and maximum values of each parameter are shown in the parenthesis. NS, not statistically significant.

No significant difference between groups was observed in the distribution of event-free time during follow-up, regarding the total events (syncopes and presyncopes), the syncopal episodes, and the presyncopal spells (log-rank test, P > 0.05). Furthermore, no difference was observed in the proportion of symptomatic patients during follow-up between the three groups (P > 0.05).

On-treatment analysis

In the ‘on-treatment’ analysis, only the 76 patients who continued therapy for the entire 6-month follow-up period were included. A significant difference was observed between the fluoxetine-group and the two other groups in the distribution of the total event-free time (regarding both syncopes and presyncopes) during the follow-up period: 5.4 ± 0.3 in the fluoxetine-group vs. 4.2 ± 0.5 in the placebo-group (P = 0.05) and 4.1 ± 0.4 in the propranolol-group (P = 0.046), as shown in Figure 1A (log-rank test).

Regarding the distribution of syncope-free time during follow-up, the mean time was longer in the fluoxetine-group when compared with that in the placebo-group and the propranolol-group (5.9 ± 0.1 vs. 5.1 ± 0.4 and 5.1 ± 0.4, respectively). However, this difference was not statistically significant (Figure 1B, log-rank = 2.02, d.f. = 2, P = 0.364). The hazard ratio was 0.39 for the fluoxetine-group (CI: 0.94–1.64, P = 0.20) and 0.91 for the propranolol-group (CI: 0.26–3.16, P = 0.88) when compared with the placebo-group.

Finally, significant difference was observed between the fluoxetine-group and the two other groups regarding the distribution of presyncope-free time during the follow-up period: 5.5 ± 0.2 in the fluoxetine-group vs. 4.6 ± 0.4 in the placebo-group (P = 0.048) and 4.5 ± 0.4 in the propranolol-group (P = 0.008), as shown in Figure 1C (log-rank test). The hazard ratio was 0.31 for the fluoxetine-group (CI: 0.95–1.05, P = 0.05) and 1.27 for the propranolol-group (CI: 0.51–3.15, P = 0.6) when compared with the placebo-group.

A significant difference was also observed between the fluoxetine-group and the two other groups regarding the total number of patients who experienced vasovagal events (syncopes or presyncopes) during the follow-up period: 7 among the 30 patients (23%) in the fluoxetine-group vs. 13 among 24 patients (59%) in the placebo-group (P < 0.05) and 16 among 24 patients (66%) in the propranolol-group (P < 0.05).

Regarding patients with syncopes, the proportion during follow-up was lower in the fluoxetine-group when compared with that in the placebo-group and the propranolol-group [3/30 (10%) vs. 5/22 (23%) and 5/24 (21%), respectively].
However, this difference was not statistically significant ($P > 0.05$).

Finally, the recurrence of presyncopal attacks in the fluoxetine-group was significantly less than in the two other groups [4/30 (13%) vs. 8/22 (36%) in the placebo-group, $P < 0.05$ and 11/24 (46%) in the propranolol-group, $P < 0.01$, respectively].

The number of vasovagal episodes during therapy

When the mean number of the total vasovagal events (syncope and presyncope) was assessed (Table 2), a significant decrease was observed in the fluoxetine-group (ANOVA for repeated measures, $P < 0.01$). In the propranolol-group and the placebo-group, the total episodes were also significantly decreased ($P < 0.01$ for each group).

Regarding the mean number of the syncopal episodes, a significant decrease was observed in all three groups during the follow-up period compared with the last 6 months before therapy, as shown in Table 2. No significant difference was observed between the three groups (ANOVA for repeated measures).

Finally, when we assessed the mean number of presyncopepal episodes, a significant decrease was observed in the fluoxetine group ($P < 0.01$, ANOVA for repeated measures). Similarly, the mean number of presyncopepal in the propranolol- and the placebo-group ($P < 0.01$ for each group). The decrease in presyncopepal during therapy was significantly larger in the fluoxetine-group than that in the placebo-group (ANOVA, post hoc analysis, $P < 0.05$).

Well-being questionnaire

Before treatment, no significant difference in 'well-being' score was observed between the three groups (placebo-, propranolol-, and fluoxetine-group), as shown in Table 1. Following 6 months of treatment, the 'well-being' score was significantly decreased (indicating an improvement) in the fluoxetine-group (Table 3), whereas no significant decrease in 'well-being' score was observed in the two other groups.

Discussion

This is the first, to our knowledge, prospective placebo-controlled study that randomly compares a beta-blocker (propranolol) with a serotonin reuptake inhibitor (fluoxetine) and placebo regarding their therapeutic effect in patients with vasovagal syndrome. The advantage of our study is that it prospectively included sequential, non-selected vasovagal patients, referred to our outpatient clinic. Our study population was not limited to patients with long-standing history of VVS refractory to any other medication, but included patients who had not previously been under medical treatment.

Main findings of the study

According to our observations, all medications, including placebo, were almost equally effective in reducing vasovagal episodes during the follow-up period. The survival analysis did not document any superiority of fluoxetine over placebo and propranolol regarding the distribution of the episode-free time during follow-up. Furthermore, no superiority was observed regarding the number of patients who had syncopal episodes, those with presyncopepal, and the total number of patients with any vasovagal event (syncope or presyncope) during therapy. No difference was also observed regarding the decrease in the mean number of syncopal or presyncopepal episodes, and the number of the total vasovagal events.

The equal effectiveness of placebo, propranolol, and fluoxetine could be attributed to the fact that the drug administration (regardless of which drug was administered), the reassurance about the benign prognosis of the
syndrome, or even a tilt-test may have a therapeutic effect on patients with VVS.17 Another possible reason for the similar response to the three different therapies may be the relatively short period of follow-up, during which a small number of patients experienced recurrence of syncope.

Secondary findings
Among patients who did not interrupt treatment (‘on-treatment’ analysis), fluoxetine seems to be more effective than the other two drugs regarding: (i) the time to the first vasovagal episode; (ii) the total number of patients who experienced at least one vasovagal episode (syncopal or presyncope); (iii) the number of patients with recurrence of presyncope; and (iv) the mean number of presyncopal episodes during follow-up. In these patients, the fluoxetine treatment seems to be associated with a significant improvement in quality-of-life, which is not observed in placebo- or propranolol-treated subjects.

General aspects
The central serotonergic activity may play a crucial role in VVS.18,19 Fluoxetine increases serotonin in the pre- or post-synaptic space.20,21 The elevated concentrations of serotonin cause the down-regulation of serotonin receptors by activating the potential discharge and feedback-inhibitory loops. These observations have raised the hypothesis that fluoxetine might have a long-term therapeutic effect in some patients with vasovagal syndrome.22,23 However, in the present study, fluoxetine was equally effective as propranolol and placebo in the intention to treat analysis. This observation points to the fact that it is still unclear which of vasovagal patients will benefit from fluoxetine.

In the ‘on-treatment’ analysis, the number of patients with presyncope during follow-up was less in the fluoxetine-group than in the placebo- and propranolol-groups. The evaluation of presyncope during a follow-up study remains a field of controversy. Presyncopal episodes may indicate syncopal attacks that are aborted, probably because the patient recognizes the onset of syncopal symptoms and learns how to avoid loss of consciousness.17,24,25 However, other investigators are of the opinion that presyncope may represent a non-specific symptom that may be because of many different mechanisms.24–26 Regardless of how one interprets presyncopal episodes, fluoxetine may have a positive psychological impact on patients with VVS, who often suffer a severe psychological burden.27,28 The therapeutic efficacy of fluoxetine may be attributed, at least partially, to the improvement of the psychological profile of patients with VVS.

In accordance with the abovementioned effects, in the ‘on-treatment’ analysis, fluoxetine was associated with a significant improvement in the quality-of-life score, which was not observed in the propranolol- and the placebo-groups. This finding is of great importance, as it is known that VVS affects patients’ quality-of-life.29-30 Following treatment, the proportion of patients with a positive tilt test was considerably decreased in all three groups. Although tilt testing is not considered as a reliable method to assess the therapeutic efficacy of treatment in VVS, our observations are in accordance with the reported improvement in patients’ symptoms and ‘well-being’.

Study limitations
Our patients have been followed-up for 6 months. Taking the clinical course of vasovagal syndrome under consideration, this is not a long period. In addition, this is a single centre study and the sample size of the study is small, as a consequence of the relatively strict inclusion criteria. However, the aim of our study was to investigate patients with recurrent VVS and also recent episodes, in order to make the effect of the treatment as clear as possible.

A significant rate of discontinuation of therapy has been observed in all three groups. However, this high rate of dropout mainly reflects the improvement in symptoms and may be an important observation regarding the clinical course of vasovagal syndrome and ‘well-being’ status from the patient’s point of view.

A significant decrease in syncopal and presyncopal episodes has been observed in all three groups during

Table 2 The syncopal, presyncopal, and total vasovagal episodes during the last 6 months before treatment and during follow-up

<table>
<thead>
<tr>
<th>Groups</th>
<th>Last 6 months</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Synapses</td>
<td>Presynapses</td>
</tr>
<tr>
<td>Placebo</td>
<td>2.2 ± 0.2</td>
<td>2.0 ± 0.4</td>
</tr>
<tr>
<td>Propranolol</td>
<td>2.6 ± 0.4</td>
<td>2.0 ± 0.3</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>2.1 ± 0.2</td>
<td>2.2 ± 0.4</td>
</tr>
</tbody>
</table>

No significant difference has been observed between the placebo-, the propranolol-, and the fluoxetine-groups regarding their therapeutic efficacy. Values are expressed as mean ± 1 SE.

Table 3 Well-being score in patients treated with (i) placebo, (ii) propranolol, and (iii) fluoxetine

<table>
<thead>
<tr>
<th>Patients</th>
<th>Well-being score</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
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<td>Following treatment</td>
</tr>
<tr>
<td>Placebo-group</td>
<td>14.6 ± 0.7</td>
<td>13.5 ± 0.7</td>
</tr>
<tr>
<td>Propranolol-group</td>
<td>14.6 ± 0.6</td>
<td>14.1 ± 0.9</td>
</tr>
<tr>
<td>Fluoxetine-group</td>
<td>15.4 ± 0.9</td>
<td>13.4 ± 0.7</td>
</tr>
</tbody>
</table>

A significant improvement in patients’ well-being was observed only in fluoxetine-treated patients (decrease in ‘well-being’ score). Values are expressed as mean ± 1 SE.
follow-up and this might weaken the impact of the comparisons regarding the therapeutic efficacy of the three medications. However, it is an observation that had to be reported.

Fluoxetine is an effective anti-depressant agent and one could argue that it may improve patients’ symptoms through its antidepressant action. We think, however, that this limitation has been diminished by the psychiatric examination and the exclusion of patients with a depressive substrate.

Although fluoxetine might be more effective in reducing presyncopal attacks in the analysis on treatment, this might not be strong evidence of superiority, as presyncope is a less profound expression of the vasovagal syndrome and thus not always remembered. We faced this possibility by re-evaluating the clinical status of our patients with frequent appointments (every month).

The placebo capsule was different from that containing fluoxetine and the tablet of propranolol, and this may lead to a bias in the assessment of the results. For this reason, the physician who evaluated the number of vasovagal episodes and patient’s well-being was not aware of their medication.

Conclusion

Fluoxetine seems to be equivalent to propranolol and placebo in the treatment of VVS. There are indications suggesting that fluoxetine might be more effective in some patients refractory to other vasovagal syndrome treatment and that it might have a greater impact on their quality-of-life. However, the question ‘which treatment for which patient’ still remains unanswered and further studies are necessary to investigate which patient will benefit from drug therapy.

References