A 12-Week Double-Blind, Placebo-Controlled, Flexible-Dose Trial of Desvenlafaxine Extended-Release Tablets in Generalized Social Anxiety Disorder

Michael R. Liebowitz*, Ester Salmán, Ann Johnso and Rita Hanover

The Medical Research Network, LLC, New York

Abstract

Objective: The purpose of the study was to assess the efficacy of desvenlafaxine in patients with the generalized form of Social Anxiety Disorder (GSAD).

Methods: 63 patients with GSAD were randomized to desvenlafaxine or placebo in a 12 week double blind trial. Change from baseline to endpoint on the Liebowitz Social Anxiety Scale (LSAS) was the primary outcome measure. Secondary outcome measures included response, defined as much improved or very much improved on the Clinical Global Impression of Change (CGI-I) and remission rates (defined as the proportion of patients with an endpoint LSAS total score of 30 or less. Changes in depression and anxiety, measured by the Hamilton Depression (Ham-D 17) and Anxiety Scales (Ham-A), were also assessed. Outcome analyses were performed in the intent to treat (ITT) and completer samples.

Results: The mean baseline LSAS was 92.8 and mean Clinical Global Impression of Severity (CGI-S) was 5.4, indicating severe illness, with no baseline differences between treatment groups. At the end of treatment, in the ITT sample (N=58), the drug group had improved more than the placebo group by 9.7 points on the LSAS, a trend difference (p=0.085, 1 tailed). Cohen’s d was 0.36, indicative of a moderate effect size. There were also trend differences in response (69% versus 48.3%, p=0.09, 1 tailed) and remission rates (20.7% versus 3.4%, p=0.051, 2 tailed), and significant differences on the Hamilton Depression scale (2.5 versus 0.3, p=0.02, 1 tailed) in favor of desvenlafaxine. Findings in the completer sample were similar to those in the ITT sample.

Conclusions: These findings must be considered preliminary because the limited sample size reduced statistical power and renders interpretation of the findings less precise. Nevertheless these initial results suggest that desvenlafaxine has efficacy for social anxiety disorder similar to that seen with more extensively studied medications that have received FDA approval for this condition. Therefore, pending further study, desvenlafaxine may prove to be a useful treatment for Social Anxiety Disorder.

Keywords: Treatment; Anxiety; Phobia; Medication; Study; Social anxiety disorder; Desvenlafaxine

Introduction

Social Anxiety Disorder (SAD) is a prevalent, chronic and disabling condition [1]. DSM IV recognized two subtypes of SAD: the non-generalized form, which involved mostly public speaking or performance anxiety, and the generalized form, characterized by severe anxiety and avoidance in both interpersonal and performance situations. The age of onset of DSM IV Generalized Social Anxiety Disorder (GSAD) was early, and depression and alcohol abuse were common sequelae [2]. The subtyping of social anxiety disorder was changed in DSM 5, where patients who met DSM IV GSAD are now classified simply as having social anxiety disorder, and those whose fears are limited to performance situations are classified as having social anxiety disorder, performance only.

More therapeutic agents for Social Anxiety Disorder are needed. Paroxetine, sertraline, fluvoxamine controlled release, and venlafaxine extended release are approved in the United States for this indication but each helps only about 45-55% of any given sample [3-6]. Furthermore, the majority of those considered responders after an acute trial are still clinically symptomatic, as they are with the most effective form of psychosocial treatment for SAD, cognitive behavior therapy (CBT) [7], and other effective drug treatments such as phenelzine [8] and clonazepam [9]. Also, all of the drug treatments found effective to date have troubling adverse effects.

Desvenlafaxine (Pristiq)® is a recently approved antidepressant that is the desmethyl metabolite of venlafaxine. Desvenlafaxine was found effective for depression in the 50-100 mg per day dose range, and is easier to dose than venlafaxine or venlafaxine extended release, which generally require higher mg/day dosages and longer up-titration schedules [10]. Venlafaxine extended release, which is mechanistically similar to desvenlafaxine, was found effective for subjects with GSAD in five of five placebo-controlled trials [6,11-14]. Given this, and the greater ease of dosing with desvenlafaxine, it could become a suitable alternative therapy for Social Anxiety Disorder if found effective.

Methods

Subjects

The study was a 12-week, placebo-controlled, flexible-dose trial.

Received May 13, 2015; Accepted June 17, 2015; Published June 20, 2015

Copyright: © 2015 Liebowitz MR, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.
Enrollment was planned for 60 subjects (30 per arm). Subjects included males and females, ages 18-75, who met DSM-IV-TR criteria for GSAD and had a minimum total Liebowitz Social Anxiety Scale (LSAS) [15] score at screening and baseline of 60, as well as a minimum Clinical Global Impression of Severity (CGI-S) [16] score of 4 (Moderately Ill). Sexually active heterosexual subjects also had to agree to practice effective contraception methods. Both English and monolingual Spanish-speaking subjects were enrolled.

Exclusion criteria included lifetime bipolar disorder, schizophrenia, or body dysmorphic disorder, as well as other axis I disorders such as PTSD, OCD, panic disorder, or substance dependence within the past 24 weeks. Subjects with certain co-morbid disorders, including Major Depression, Dysthymia, Generalized Anxiety Disorder and Specific Phobias, were allowed if GSAD was the primary disorder in terms of clinical severity. However, subjects with a Hamilton Depression 17-item (HAM-D) [17] score greater than 15 were excluded, as were subjects at risk for suicide, having any current unstable or clinically significant medical condition, or any history of cancer. Subjects with treatment refractory GSAD (failure to respond to adequate trials of two effective agents) or in active CBT were also excluded, as were women who were currently pregnant or lactating. Zolpidem PRN was allowed for insomnia if not taken more than three times per week.

4.2 This clinical trial was conducted in compliance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) and the standards established by Asentral IRB and Pfizer, Inc. Subjects were recruited via IRB-approved advertising and from the site's database for this single-site study. They were screened by an in-person psychiatric interview with the investigator. Subjects deemed appropriate and interested in the study signed the IRB-approved informed consent after full explanation of study procedures and having all questions asked and answered. Subjects were specifically informed that desvenlafaxine was approved by the U.S. FDA only for the treatment of major depressive disorder [18], and use of it for the treatment of SAD was "off label" and considered experimental. They were then further evaluated by administration of the LSAS, HAM-D 17, Hamilton Anxiety scale (HAM-A) [19], CGI-S, and Mini-International Neuropsychiatric Interview (MINI) [20]. Samples were obtained for routine blood and urine tests, and screened for drugs of abuse and pregnancy; a physical exam and ECG were also done. If present, psychotropic medications were tapered.

Subjects returned for the baseline visit 1-2 weeks after screening, and the LSAS, CGI-S, and HAM-D were administered again. Those eligible were randomized to Pristiq® 50 mg per day (taken in the morning) or matching placebo, on a double-blind basis. Subjects were randomized to drug or placebo in cohorts of 6.

Subjects were seen weekly for the first 6 weeks of study treatment and then biweekly during weeks 7-12. Desvenlafaxine or placebo was dose at 50 mg per day for weeks 1-6, and then 100 mg per day for weeks 6-12, unless adverse events necessitated continuation or reduction back to 50 mg per day. At week 12 or early termination, subjects on 100 mg per day or the placebo equivalent were lowered to 50 mg per day for one week, and then no medication for one week before their final safety visit, while those on 50 mg per day or the placebo equivalent were taken off medication for 2 weeks before their final safety visit. Subjects who could not tolerate desvenlafaxine 50 mg per day or the placebo equivalent were removed from the trial. Compliance with study drug was calculated at each visit by pill counts and subject interviews. Subjects found to be at <80% or >120% compliance at ≥2 subsequent visits were early terminated. All subjects participating in the trial were offered open clinical care after their study termination.

Measures

The MINI was used at screening for diagnostic assessment. The CGI-S, CGI-I (16), and LSAS were administered at each study visit to assess SAD severity and change. The LSAS is a 24-item instrument with established reliability and validity that assesses anxiety and avoidance in a variety of commonly encountered performance and social situations [15,21]. The HAM-D 17 and the HAM-A were used to quantify depressive and anxiety symptoms, and were administered at screening, week 4, week 8, and week 12 or Early Termination. A subject-rated Patient Global Impression of Change (PGIC) form for global improvement was also done biweekly, starting at week 2. Safety measures included routine laboratory tests, ECGs, and physical exams. Subjects were asked about adverse events and concomitant medications at each study visit.

To enhance the precision, validity, and reliability of assessments in this protocol, an electronic data capture system developed by ChiMatrix™ was utilized; this system has been used in several Social Anxiety Disorder trials [22]. It is a Palm OS-based system that captures all the rating scale data in real-time, and serves as the eCRF for the trial. Rating scale conventions and cross-scale checks are built in to enhance reliability and validity. Drop-down menus and checks across visits also enhance the acquisition of data. Data were transmitted daily to a secure central server, and were viewed and checked for accuracy and completeness by site staff; data was managed by ChiMatrix” and site staff had no access to the study data.

Data analyses

Data analyses include intent-to-treat (ITT) and completer samples. Pre- and post-treatment comparisons on dimensional ratings were done using the last observation carried forward (LOCF). In addition, subjects rated as 1 (Very Much Improved) or 2 (Much Improved) on the CGI-I were considered categorical treatment responders. Subjects whose endpoint total LSAS score was 30 or less were considered treatment remitters.

The primary outcome measure was change in total LSAS score from baseline to endpoint in the ITT sample (all subjects with at least one post randomization efficacy rating). Secondary outcome measures included CGI dimensional and categorical ratings, and HAM-D, HAM-A, and PGIC in the ITT sample, and similar comparisons in the completer sample. Outcomes at visits before week 12 were also examined on an exploratory basis. Subjects who rated themselves as 1 (Very Much Improved) or 2 (Much Improved) on the PGIC were considered self-rated responders.

With the planned enrollment of 30 subjects per treatment arm, the sample size was considered sufficient to calculate reliable drug versus placebo differences, and to make comparisons to other effect sizes found with established treatments. The hypothesized effect size for this study was 0.65, and the power was 0.8 for a one-tailed test (drug superior to placebo) with an alpha level of 0.05.

Group differences in treatment outcome were evaluated using a one-tail t-test for independent samples, while baseline comparisons utilized 2-tail tests. For the bivariate responder analyses (CGI-Improvement, PGIC, and LSAS remitters), a test of two binary proportions based on Fisher's exact test and hypothesized difference of 0 between the active and placebo groups was conducted. Effect sizes were estimated using Cohen's d (the difference between group means divided by pooled standard deviation). Relative benefit was calculated by dividing the response rate of drug by the response rate of placebo. Odds ratios were...
calculated by dividing the ratio of responders to nonresponders in the active group by the ratio of responders to nonresponders in the placebo group.

**Results**

**Baseline**

Seventy-three subjects were accepted for the trial and signed informed consent (Figure 1). Ten subjects subsequently screen failed, while 63 were randomized to study drug. Of these 63, 42 (67%) completed the trial, and 16 others provided sufficient data to be included in the efficacy analyses, providing an ITT sample of 58 (29 drug and 29 placebo). Five other randomized subjects (1 on drug, 4 on placebo) were excluded from the ITT sample because of insufficient data (n=4) or poor compliance (n=1). The completer sample was 42 (20 desvenlafaxine and 22 placebo).

Drug and placebo groups in the ITT sample did not differ on age, sex or ethnicity (Table 1). Most subjects reported an onset of illness in their grade school years, or at least being shy and uncomfortable with peers at that age. The groups did not differ with regard to average age of onset or number of years with SAD. The mean baseline total LSAS score was 92.7 for the whole sample, and the mean CGI-Severity score was 5.4, indicating a markedly ill group; there were no differences between treatment arms (Table 1). HAM-D and HAM-A scores were low for both treatment groups (Table 1). For the subset of completers for each group, there were no significant baseline differences, although there was a trend (p=0.052, two tailed) for the placebo group to have an older age of onset of SAD.

**Effects of treatment**

At the end of the treatment phase, 17 of the 29 subjects receiving the active drug had been increased to the higher dose of 100 mg per day compared to 23 of the 29 subjects receiving placebo. The mean endpoint desvenlafaxine dose was 79 mg per day and the mean placebo dose was the equivalent of 90 mg per day.

**Primary Outcome:** In the ITT sample (n=58), the mean reduction in total LSAS from baseline to endpoint was showed a trend toward being greater on drug than placebo (t(56)=1.39, p=0.085, one tail), with
toward significance (z=1.74, p (Fisher’s exact)=0.09, one tail). The CI [0.815, 6.96].

Response to desvenlafaxine versus placebo on the CGI-I were 2.38 (95% CI [0.912, 2.24]). Odds ratios for (z=1.64, p (Fisher’s exact)=0.09, one tail). The relative benefit of and 48.3% in the placebo group, which also trended toward significance (z=1.64, p (Fisher’s exact)=0.09, one tail). The relative benefit of drug versus placebo was 1.43 (95% CI [0.912, 2.24]). Odds ratios for response to desvenlafaxine versus placebo on the CGI-I were 2.38 (95% CI [0.815, 6.96]).

Among the completers, 75% of the desvenlafaxine group were CGI-I responders compared to 50% of the placebo group, also trending toward significance (z=1.74, p (Fisher’s exact)=0.09, one tail). The relative benefit of drug versus placebo among completers was 1.5 (95% CI [0.920, 2.45]). Odds ratios for response to desvenlafaxine versus placebo on the CGI-I were 3.0 (95% CI [0.807, 11.147]).

Looking at remission rates, in the ITT sample, six subjects randomized to desvenlafaxine (20.7%) and one randomized to placebo (3.4%) had endpoint LSAS scores below 30, which trended toward a difference between groups (z=2.09, p (Fisher’s exact)=0.051, one-tail). Among the completers, 25% of the desvenlafaxine group and 45.5% of the placebo group were LSAS remitters (z=1.92. p (Fisher’s exact)=0.072, one-tail), a trend difference.

On the subject-rated global outcome scale (the PGIC), in the ITT sample, 44.8% of subjects randomized to desvenlafaxine and 40.7% randomized to placebo rated themselves as responders at the study endpoint, a non-significant difference. Among the completers, 60% of the desvenlafaxine and 45.5% of the placebo subjects rated themselves as responders, also not a significant difference.

In the ITT sample, the mean reduction on the HAM-D 17 from screening to endpoint was greater for drug than placebo (t (52)=2.11, p=0.02, one tail) (Table 2). Cohen’s d was 0.57 (95% CI [0.03, 1.12]), indicating a moderate effect size.

Among the completer sample, the mean reduction (sd) on the HAM-D 17 from screening to endpoint was 3.2 (3.0) for the desvenlafaxine group and 0.59 (4.3) for the placebo group, a significant difference (t (40)=2.26, p=0.015, one tail) (Table 2). Cohen’s d was 0.70 (95% CI [0.07, 1.32]), a moderate effect size.

In the ITT sample the mean reduction (sd) in HAM-A between screening and endpoint did not differ between groups (t (52)=1.15, p=0.127, one tail) (Table 2). The effect size was moderate, with Cohen’s d=0.31 (95% CI [-0.22, 0.85]).

Among the completers, the mean reduction (sd) in HAM-A between screening and endpoint was 3.35 (3.3) for the desvenlafaxine group and 1.64 (5.3) for the placebo group (Table 2). The difference was not significant (t (40)=1.24, p=0.110, one tail). The effect size was moderate, with Cohen’s d=0.31 (95% CI [-0.22, 0.85]).

Figures 2 show the mean total LSAS scores and effect sizes for group differences at each visit for the ITT sample and completer subset. Interestingly, both samples show numerically larger effect sizes at weeks 6 and 8 of treatment as compared to the 12 week study endpoint, seemingly due to continued improvement in the placebo group after week 8.

Attrition
Sixteen subjects (9 desvenlafaxine, 7 placebo) were early terminators: six (4 desvenlafaxine, 2 placebo) due to withdrawal of consent, five (3 desvenlafaxine, 2 placebo) being lost to follow-up, two (1 desvenlafaxine, 1 placebo) due to having difficulty adhering to required protocol visits, two (both placebo) due to adverse events (insomnia in one subject and swelling of the throat, mental confusion, and headache in the other), and one (desvenlafaxine) due to a protocol violation involving a prohibited medication.

Adverse Events
There were no Serious Adverse Events (SAEs) in the trial. Table 3 lists the Adverse Events (AEs) that occurred in more than two desvenlafaxine or more than two placebo subjects. The most common were dizziness, nausea, drowsiness and decreased appetite, as noted in prior studies of desvenlafaxine [10]. All AEs were assessed as mild or moderate in severity. There were no clinically significant abnormalities found on routine laboratory tests, ECGs or physical exams over the course of the study. There were no differences between groups in

<table>
<thead>
<tr>
<th>Age in years (standard deviation)</th>
<th>Active drug (n=29)</th>
<th>Placebo (n=29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asian</td>
<td>3 (10.3%)</td>
<td>2 (6.9%)</td>
</tr>
<tr>
<td>Black</td>
<td>3 (10.3%)</td>
<td>9 (31.0%)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>9 (31.0%)</td>
<td>6 (20.7%)</td>
</tr>
<tr>
<td>White</td>
<td>10 (34.5%)</td>
<td>10 (34.5%)</td>
</tr>
<tr>
<td>Other</td>
<td>4 (13.8%)</td>
<td>2 (6.9%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sex</th>
<th>Male (n=30)</th>
<th>Female (n=28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>14 (48.3%)</td>
<td>16 (55.2%)</td>
</tr>
<tr>
<td>Female</td>
<td>15 (51.7%)</td>
<td>13 (44.8%)</td>
</tr>
</tbody>
</table>

| Average age of SAD onset (standard deviation) | 10.2 (7.1) | 13.8 (12.7) |

| Average number of years with SAD (standard deviation) | 29.7 (17.4) | 28.1 (16.9) |

| Mean baseline LSAS total (standard deviation) | 93.4 (17.1) | 92.1 (16.8) |

| Mean baseline CGI-Severity (standard deviation) | 5.4 (0.7) | 5.3 (0.7) |

| Mean HAM-D 17 total at Visit 1 (standard deviation) | 6.7 (2.8) | 5.9 (2.5) |

| Mean HAM-A total at Visit 1 (standard deviation) | 8.6 (2.7) | 9.1 (3.5) |

| Endpoint LSAS total (standard deviation) | 55.0 (27.4) | 63.4 (22.4) |

| Mean LSAS change from baseline (standard deviation) | 38.4 (28.8) | 28.7 (24.2) |

| HAM-D 17 total at week 12/Early Termination (standard deviation) | 4.0 (2.7) | 5.5 (4.4) |

| HAMD 17 change from baseline (standard deviation) | 2.5 (3.1) | 0.3 (4.5) |

| HAM-A total at week 12/Early Termination (standard deviation) | 5.5 (3.5) | 7.3 (4.4) |

| HAM-A change from baseline (standard deviation) | 3.0 (3.2) | 1.7 (4.8) |

Table 1: Baseline summary.

Table 2: Endpoint data for the ITT population.
Table 3: Common adverse events.

<table>
<thead>
<tr>
<th></th>
<th>Active drug (n=29)</th>
<th>Placebo (n=29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dizziness/</td>
<td>11</td>
<td>4</td>
</tr>
<tr>
<td>lightheadedness/</td>
<td></td>
<td></td>
</tr>
<tr>
<td>feeling faint</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea/queasiness*</td>
<td>11</td>
<td>3</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Insomnia</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Headache</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Fatigue</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Indigestion</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Fluffy symptoms</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Soft stools/diarrhea</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>

Note: *A significantly greater number of subjects receiving the active drug reported nausea or queasiness (p=0.03). Other AEs did not differ between groups (p's>0.05).

Nausea or queasiness (p=0.03). Other AEs did not differ between groups (p's>0.05).

Discussion and Conclusions

In this trial involving markedly ill GSAD subjects, desvenlafaxine reduced total LSAS scores by 9.7 points over that in the placebo group, with an effect size of 0.36; desvenlafaxine also had a CGI-I response rate of 69% versus 48.3% for placebo, a relative benefit of 1.43. Desvenlafaxine demonstrated a remission rate of 20.7% versus 3.4% for placebo, and a significantly greater effect on reducing HAM-D scores. While the comparisons on mean LSAS reduction and CGI response and remission rates showed only trend significance, this is most likely due to the small sample size. With a planned sample size of 30 subjects per treatment arm, the study was powered at 0.80 assuming an effect size of 0.65 with a one tailed test (drug would be superior to placebo), and was lacking in power with the actual smaller effect sizes observed in this sample.

In trying to gauge the efficacy of desvenlafaxine in GSAD it is useful to compare the current findings to those of previous trials with medications that have received FDA approval for this condition. As demonstrated below, the current study's findings for desvenlafaxine appear to fall within the range of outcomes reported for fluvoxamine, sertraline, venlafaxine and paroxetine in GSAD.

In a 2008 meta-analysis of prior drug trials in GSAD, Hanson et al. [23] calculated relative benefits of drug versus placebo, derived from responder rates on the CGI-I and differences in reduction on the LSAS. In the current trial, in terms of CGI responder rates, desvenlafaxine had a relative benefit over placebo of 1.43 (95% CI [0.92, 2.24]). According to Hanson et al., the pooled relative benefit for fluvoxamine was 1.49 (95% CI [0.94, 2.36]), for venlafaxine 1.68 (95% CI [1.27, 1.93]), for sertraline 1.78 (95% CI [1.45, 2.16]), and for paroxetine 1.85 (95% CI [1.49, 2.29]). In the current trial’s ITT sample, desvenlafaxine exceeded placebo in change on Ham D, baseline Ham D scores were relatively low, and we do not feel that improvement in depression accounted for benefits seen in social anxiety.

While further study is indicated, data from this initial trial suggest that desvenlafaxine may be a viable alternative for patients with GSAD with efficacy comparable to that seen for sertraline, fluvoxamine, and venlafaxine ER. Moreover, the mean reduction in total LSAS scores seen with desvenlafaxine was clinically meaningful. Subjects treated with desvenlafaxine had a baseline mean LSAS score of 93.5, which is in the severe range, usually indicative of great impairment in social or work function or both. Their endpoint mean LSAS score was 55, indicating some social and performance anxiety symptoms without impairment in functioning, and below the minimum required for entry into this study. Thus if the present findings are confirmed by subsequent research, desvenlafaxine could prove a useful addition to the therapeutic armamentarium for GSAD.

Acknowledgements

This study was supported by an investigator initiated grant from Pfizer, the manufacturer of desvenlafaxine.

The authors would also like to acknowledge the contributions of Sub Investigator Dr. Kyra Blatt, Rita Lemming, and Nicole Flowers.

ClinicalTrials.gov identifier: NCT01316302

Conflicts of Interest Disclosure

This study was supported by an investigator initiated grant from Pfizer, the manufacturer of desvenlafaxine. Dr. Liebowitz is the copyright holder of the Liebowitz Social Anxiety Scale. Ms. Salmán is the CEO of ChiMatrix LLC, with which Dr. Liebowitz was formerly affiliated. Dr. Liebowitz is the Managing Director of the Medical Research Network LLC, where Ms. Hanover is employed and where Ms. Salmán was formerly employed. Dr. Hanover performed data analyses and was paid from research funds as an independent contractor.

References


