Efficacy of pregabalin and venlafaxine-XR in generalized anxiety disorder: results of a double-blind, placebo-controlled 8-week trial

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The objective of this study was to evaluate the anxiolytic efficacy, and speed of onset of efficacy, of pregabalin (PGB) and venlafaxine-XR (VXR) in patients with generalized anxiety disorder (GAD). In this double-blind trial, outpatients, ages 18–65 years, who met Diagnostic and Statistical Manual of Mental Disorders, 4th edition, criteria for GAD were randomized to 8 weeks of flexible-dose treatment with PGB (300–600 mg/day), VXR (75–225 mg/day), or placebo (PBO). The intent-to-treat sample consisted of 121 patients on PGB (least square (LS) mean±SE baseline Hamilton Anxiety Rating Scale (HAM-A), 27.6±0.4), 125 patients on VXR (baseline HAM-A, 27.4±0.4), and 128 patients on PBO (baseline HAM-A, 26.8±0.4). Treatment with PGB was associated with a significantly greater LS mean change in the HAM-A compared with placebo in the treatment of GAD.


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Introduction

Generalized anxiety disorder (GAD) is a chronic illness with an estimated 1 year prevalence of approximately 3%, and a lifetime prevalence of approximately 6% (Kessler \textit{et al.}, 2005; Lieb \textit{et al.}, 2005). GAD (without depression comorbidity) is associated with significant impairment in quality of life (QoL) and functioning, which has been found to be comparable with major depressive disorder (MDD), and chronic medical illnesses such as diabetes and arthritis (Kessler \textit{et al.}, 1999; Wittchen, 2002).

At least half a dozen classes of drugs are available for the pharmacologic management of GAD (Bandelow \textit{et al.}, 2008), each acting through different mechanisms: benzodiazepines (diazepam, lorazepam, alprazolam etc), which augment inhibitory γ-amino butyric acid (GABA)-ergic activity; monoaminergic reuptake inhibitors, consisting of selective serotonin reuptake inhibitors drugs with serotonin selectivity (paroxetine, escitalopram, sertraline), serotonin-norepinephrine reuptake inhibitor drugs with dual serotonin/norepinephrine activity [venlafaxine-XR (VXR) duloxetine], as well as some first-generation tricyclics (imipramine); azapirones (buspironate), which modulate monoaminergic transmission; and pregabalin (PGB) that acts presynaptically to inhibit excitatory neurotransmission. Two other classes of medication (antihistamines such as hydroxyzine; antipsychotics such as quetiapine) have also shown efficacy in the treatment of GAD. Cross-study comparisons suggest that each class of drug has a different benefit-risk profile. Relatively few double-blind, placebo-controlled head-to-head trials, however, have been published, which provide direct comparisons of the efficacy and safety profiles of drugs in each class. The primary objective of this study was to evaluate the efficacy of PGB and VXR compared with placebo in the treatment of GAD.

The efficacy of VXR in GAD has been confirmed based on the results of eight large, placebo-controlled trials (Davidson \textit{et al.}, 1999; Gelenberg \textit{et al.}, 2000; Rickels \textit{et al.}, 2008).
2000; Allgulander et al., 2001; Hackett et al., 2003; Lenox-Smith et al., 2003; Hartford et al., 2007; Nicolini et al., 2008). Four of these trials were flexible-dose studies (Gelenberg et al., 2000; Lenox-Smith et al., 2003; Hartford et al., 2007; Nicolini et al., 2008), and four were fixed-dose studies (Davidson et al., 1999; Rickels et al., 2000; Allgulander et al., 2001; Hackett et al., 2003), with sample sizes ranging from 81 to 185 per arm. Four of the placebo-controlled trials also included an active comparator. In one fixed-dose study (Davidson et al., 1999), endpoint improvement in the Hamilton Anxiety Rating Scale (HAM-A) total score was not significantly different from placebo on the 75 and 150 mg doses of VXR, or on the buspirone comparator. In a second fixed-dose study with a high placebo response rate, diazepam was significantly superior to placebo, but neither dose of VXR was different from placebo on HAM-A total score (Hackett et al., 2003). In two recent three-arm, flexible-dose, duloxetine comparator studies (Hartford et al., 2007; Nicolini et al., 2008), VXR showed significant improvement compared with placebo. Finally, VXR and duloxetine showed noninferiority in an a priori pooled analysis of data from two placebo-controlled trials (Allgulander et al., 2008). In a secondary analysis, VXR showed significant endpoint improvement in the HAM-A total score versus placebo.

PGB is a new anxiolytic with potent antinociceptive (Sonnett et al., 2006) and antiepileptic (Hamandi and Sander, 2006) efficacy, as well as efficacy in treating fibromyalgia (Crofford et al., 2005). Structurally, PGB is an alkylated analogue of GABA, however, unlike GABA it has no direct or indirect GABAergic activity. In contrast to the benzodiazepines, which bind to a modulatory site on the GABA-receptor complex to augment the inhibitory effects of GABA, available data suggest that PGB acts presynaptically to inhibit excitatory neurotransmission (Dooley et al., 2002; Fink et al., 2002; Taylor et al., 2007). PGB binds to the $\alpha_2\beta_6$ subunit of N-type and P/Q-type calcium channels, resulting in a reduction of calcium influx in response to an action potential. As a result of the inhibition of the inward calcium current, there is a significant reduction in the ability of synaptic vesicles to fuse with the presynaptic membrane, and release neurotransmitter, thus propagating the action potential.

The efficacy of PGB in GAD has been confirmed based on the results of seven large, placebo-controlled trials (Feltner et al., 2003; Pande et al., 2003; Pohl et al., 2005; Rickels et al., 2005; Montgomery, 2006; Montgomery et al., 2006; Montgomery et al., 2008). Six of these trials were fixed-dose, and one trial (in the elderly) was flexible dose, representing a combined total of 15 PGB treatment arms, with sample sizes ranging from 66 to 177 per arm. Overall, PGB showed significant efficacy when compared with placebo. The 150-mg dose level, however, only achieved significance in one of three studies, and thus PGB seems to have a dose–response curve between 150 and 300 mg, whereas no dose–response relationship is evident between 300 and 600 mg (Bech, 2007). In contrast, a clear dose–response relationship has not been shown for VXR across its approved dosage range of 75–225 mg/day (Wyeth, 2007).

The primary objective of this study was to evaluate the efficacy of PGB and VXR compared with placebo in the treatment of GAD. The secondary objectives were to evaluate the onset of anxiolytic activity in PGB compared with both placebo and VXR; to evaluate the ability of PGB to improve the QoL and functioning in patients with GAD; to evaluate the ability of PGB to improve insomnia, pain, and depressive symptoms commonly seen in patients with GAD; and finally, to evaluate the tolerability and safety of PGB and VXR.

**Methods**

**Study design**

This was an 8-week, double-blind, placebo-controlled study of PGB and VXR for the treatment of GAD patients who met *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV) criteria. After a 1-week, open-label, lead-in period, study patients were randomized to 8 weeks of double-blind, parallel-group treatment with flexible doses of either PGB, venlafaxine, or placebo. PGB treatment was started at a dose of 150 mg twice daily for the first week; thereafter, PGB dosing was flexible, based on clinical response and tolerability, in the range of 300–600 mg/day, administered twice daily. VXR treatment was started at a dose of 75 mg/day (administered in the morning, with matching placebo in the evening) for the first week. Thereafter, VXR dosing was flexible, in the range of 75–225 mg/day, administered in the morning (with matching placebo in the evening). Patients were randomized to one of the three treatment groups based on a computer-generated randomization list.

The study was conducted at 47 investigational sites in Belgium, Canada, France, Ireland, Italy, The Netherlands, Spain, and Sweden. The protocol was approved at each site by the appropriate institutional review board, and written informed consent was obtained from each patient before enrolment.

**Patient selection**

Patients were recruited from clinic referrals and from advertisements in local media. Male and female outpatients ages 18–65 years were eligible for study entry if they met DSM-IV-Text Revision criteria for a primary diagnosis of GAD based on a structured Mini International Neuropsychiatric Interview (M.I.N.I. Plus; version 5.0.0; Sheehan et al., 1997), and if their HAM-A total score was $\geq 20$ at both the screening and baseline visits. The HAM-A psychic and somatic anxiety factors
also were required to be $\geq 10$ at both the screening and baseline visits. Women of childbearing potential were required to have a negative serum $\beta$-human chorionic gonadotropin pregnancy test and be practicing a medically accepted form of birth control.

Patients were excluded if they presented with any of the following: (i) a current or past DSM-IV diagnosis of bipolar disorder, schizophrenia, or any other psychotic disorder; (ii) a DSM-IV diagnosis in the past 6 months of MDD, dysthyemic disorder, obsessive-compulsive disorder, posttraumatic stress disorder, an eating disorder, or alcohol or substance dependence and/or abuse; (iii) a 17-item Hamilton Depression Rating scale (HAM-D) total score $\geq 15$; (iv) a history of seizure disorder (except febrile seizures in childhood); (v) any clinically significant acute or unstable medical condition; (vi) a positive urine drug screen (for benzodiazepines, ethanol, amphetamine, barbiturates, cocaine, opiates, cannabinoids, phencyclidine); (vii) creatinine clearance rates $\leq 60$ ml/min; (viii) concurrent psychotherapy for GAD (psychotherapy not targeting GAD symptoms was permitted if initiated $>3$ months before study enrolment); (ix) use of concomitant psychotropic medications within 2 weeks of the baseline visit (5 weeks for fluoxetine; except, zopiclone or zolpidem were permitted on two nights, as needed, during the 1-week washout period); (x) current suicide risk based on the clinical judgment of the investigator; (xi) previous treatment with either PGB or VXR; and (xii) lactating women.

**Efficacy measures**

The primary efficacy measure was the 14-item, investigator-rated HAM-A total score (Hamilton, 1959), which was completed at screen baseline, day 4 (telephone assessment), and at each assessment visit during double-blind treatment. Secondary investigator-rated measures consisted of: (i) the seven-item HAM-A psychic anxiety factor score; (ii) the seven-item HAM-A somatic anxiety factor score; (iii) the Clinical Global Impression (CGI) Severity scale (completed at baseline and all post-baseline assessment visits; Guy, 1996); (iv) the CGI Improvement scale (completed at every post-baseline visit; Guy, 1996); and (v) the 17-item HAM-D (completed at screen, baseline, and weeks 1, 4, and 8; Hamilton, 1960).

Secondary patient-rated scales consisted of: (i) the 14-item Hospital Anxiety and Depression Scale (HADS; Zigmond and Snaith, 1983) total score, and the seven-item anxiety (HADS-A) and seven-item depression (HADS-depression) subscale scores (completed at baseline, and weeks 4 and 8); (ii) the 100 mm Global Anxiety Visual Analogue Scale (GA-VAS; completed at screen and baseline, day 4 (telephone assessment), and at all assessment visits); (iii) Daily Pain Rating Scale [Dworkin et al., 2005; a single-item that rates pain severity on an 11-point numerical scale; completed at screen and baseline, day 4 (telephone assessment), and at all assessment visits]; (iv) QoL, Enjoyment, and Satisfaction Scale (Endicott et al., 1993; completed at baseline, and weeks 4 and 8); (v) the EuroQoL health status profile questionnaire (EQ-5D; Brooks, 1996; completed at baseline, and weeks 1, 3, 4, 6, and 8); (vi) the EuroQoL visual analogue scale (completed at baseline, and weeks 4 and 8); (vii) the Sheehan Disability Scale (SDS; Sheehan et al., 1996) total score and Work (SDS-work), Family (SDS-family), and Social (SDS-social) subscale scores (completed at baseline, and weeks 2, 4, and 8); and (viii) the 12-item Medical Outcomes Study Sleep Scale (MOS-Sleep; Hays et al., 2005), and its seven subscale scores and nine-item sleep problems index (completed at baseline, and weeks 4 and 8).

**Safety and tolerability measures**

Blood chemistry, hematology, urinalysis, and physical examination were carried out at the screen and week 8 visits (or at the last visit, if the patient was discontinuing prematurely). Vital signs and weight were obtained at every study visit. Spontaneously reported or observed adverse events were recorded, regardless of causality, in terms of time of onset, severity, and outcome. Use of concomitant medications was recorded in terms of daily dose, stop and start dates, and reason for use.

Treatment-related sexual dysfunction was evaluated using the male and female versions of the Changes in Sexual Functioning Questionnaire (CSFQ-male; CSFQ-female; Clayton et al., 1997), which were completed at baseline, and weeks 4 and 8.

**Statistical analyses**

On the basis of data from previous PGB GAD studies, it was estimated that a sample size of 130 patients per treatment group would have 90% power to detect a 3-point difference in HAM-A total score as significant on a two-sided test with a type I error rate of 0.05.

All statistical analyses were performed using SAS statistical package (version 8) (SAS Institute, Cary, North Carolina, USA, 2000) on the intent-to-treat population consisting of all randomized patients who received at least one dose of study medication.

The primary analysis was a comparison of endpoint change in HAM-A total score between PGB and placebo based on an analysis of covariance model with center and baseline as covariates, and utilizing tests for center by treatment and treatment by baseline interactions. In addition, the two active treatment groups were compared with placebo using Dunnett’s test. A mixed-effects model repeated-measures (MMRM) analysis was also carried out post hoc on the HAM-A total score, and psychic and
somatic anxiety factor scores. All other secondary efficacy outcomes were analyzed with an analysis of covariance model as described above.

All efficacy analyses were two sided with \( \alpha = 0.05 \). Hierarchical testing was used to control overall type I error at \( \alpha = 0.05 \). The hierarchy of hypotheses tests used in the primary tests and key secondary analyses were applied at the \( \alpha = 0.05 \) level for each hypothesis test.

**Results**

Four-hundred-sixty-six patients provided informed consent and were recruited into the study, of which 374 (80.3%) met eligibility criteria at baseline and agreed to be randomized to 8 weeks of study treatment (Fig. 1). The intent-to-treat sample, used in both safety and efficacy analyses, consisted of 374 patients. No significant baseline differences were observed in the demographic or clinical characteristics of patients assigned to each treatment group (Table 1).

**Anxiolytic efficacy**

Treatment with PGB resulted in significant improvement compared with placebo on the primary endpoint, least squares (LS) mean change in HAM-A total score at last observation carried forward endpoint (Table 2). The endpoint difference in HAM-A change score in the VXR treatment group was not significantly different from placebo. A post-hoc, MMRM analysis confirmed that there was a significant improvement on PGB, but not VXR, compared with placebo across the 8 weeks of study treatment (Fig. 2). Post-hoc, MMRM analyses also found significant improvement on PGB compared with placebo on both the HAM-A psychic anxiety factor (Fig. 3), and the HAM-A somatic anxiety factor (Fig. 4). Treatment

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**Table 1** Baseline clinical and demographic characteristics of patient sample

<table>
<thead>
<tr>
<th></th>
<th>Pregabalin N=121</th>
<th>Venlafaxine-XR N=125</th>
<th>Placebo N=128</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female (%)</td>
<td>64</td>
<td>58</td>
<td>61</td>
</tr>
<tr>
<td>Age, mean ± SD (years)</td>
<td>39.5 ± 11.9</td>
<td>42.6 ± 11.8</td>
<td>40.2 ± 12.1</td>
</tr>
<tr>
<td>White (%)</td>
<td>71</td>
<td>70</td>
<td>72</td>
</tr>
<tr>
<td>Weight, mean ± SD (kg)</td>
<td>72.5 ± 17.9</td>
<td>72.6 ± 14.6</td>
<td>74.4 ± 14.6</td>
</tr>
<tr>
<td>Time since first diagnosis of GAD, mean (years)</td>
<td>3.1</td>
<td>4.0</td>
<td>4.6</td>
</tr>
<tr>
<td>HAM-A, LS mean ± SE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total score</td>
<td>27.6 ± 0.4</td>
<td>27.4 ± 0.4</td>
<td>26.8 ± 0.8</td>
</tr>
<tr>
<td>Psychic factor score</td>
<td>14.4 ± 0.3</td>
<td>14.0 ± 0.3</td>
<td>13.8 ± 0.3</td>
</tr>
<tr>
<td>Somatic factor score</td>
<td>13.3 ± 0.3</td>
<td>13.0 ± 0.3</td>
<td>12.9 ± 0.3</td>
</tr>
<tr>
<td>HAM-D-17, LS mean ± SE</td>
<td>11.5 ± 0.2</td>
<td>11.5 ± 0.2</td>
<td>11.5 ± 0.2</td>
</tr>
</tbody>
</table>

GAD, generalized anxiety disorder; HAM-A, Hamilton Anxiety Rating Scale; HAM-D, Hamilton Depression Rating scale; LS, least square.

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**Fig. 1**

Flow diagram. DB, double-blind; ITT, intent-to-treat.
with VXR was not associated with significant improvement compared with placebo in either HAM-A factor.

Treatment with PGB was associated with significant endpoint improvement on one of the two secondary patient-rated measures of anxiety (HADS-A; Table 2), but not on the other, the GA-VAS. VXR showed trend levels of significance on the HADS-A ($P > 0.07$), but was nonsignificant on the GA-VAS. In addition, PGB-treated patients showed significantly greater improvement compared with placebo-treated patients on both the CGI Improvement and CGI Severity measures (Table 2). In contrast, patients treated with VXR did not show efficacy on these two global measures. The proportion of patients who met HAM-A responder criteria ($\geq 50\%$ reduction from baseline) was significantly higher on PGB compared with both placebo and VXR ($59\%$ vs. $46\%$, Cochran-Mantel-Haenszel; $P = 0.05$, and $44\%$, Cochran-Mantel-Haenszel; $P = 0.05$).

### Early onset of anxiolytic efficacy

An a priori study objective was to evaluate the time of onset of anxiolytic efficacy. Treatment with PGB was associated with significantly greater improvement...
in HAM-A total score than both placebo and VXR, respectively, on day 4 (by phone assessment: \(-5.3 \pm 0.5\) vs. \(-3.4 \pm 0.5\); \(P = 0.008\); and vs. \(-2.94 \pm 0.6\); \(P = 0.001\)); and on day 7 (\(-7.9 \pm 0.6\) vs. \(-5.4 \pm 0.6\); \(P = 0.002\); and vs. \(-5.6 \pm 0.6\); \(P = 0.005\)). Twenty percent or greater improvement from baseline in HAM-A total score was achieved on day 4 by significantly more patients treated with PGB (36.3%) compared with VXR (18.3%; \(P = 0.008\)) or placebo (20.3%; \(P = 0.002\)).

On an MMRM analysis, treatment with PGB resulted in greater early improvement, on day 4, compared with VXR and placebo on the HAM-A psychic factor score (\(-3.51 \pm 0.48\) vs. \(-2.57 \pm 0.50\); \(P = 0.02\); and vs. \(-2.13 \pm 0.49\); \(P = 0.0003\)), and on the HAM-A somatic anxiety factor score (\(-3.69 \pm 0.52\) vs. \(-3.02 \pm 0.54\); \(P = 0.12\); and vs. \(-2.54 \pm 0.54\); \(P = 0.008\)).

On the patient-rated GA-VAS, treatment with PGB was associated with significantly greater improvement than both placebo and VXR, respectively, on day 4: \(-11.3 \pm 1.6\) vs. \(-4.3 \pm 1.6\); \(P = 0.002\); and vs. \(-5.2 \pm 1.6\); \(P = 0.01\); and on day 7: \(-15.3 \pm 1.8\) vs. \(-5.2 \pm 1.8\); \(P < 0.0001\); and vs. \(-8.6 \pm 1.8\); \(P = 0.01\).
**Secondary symptom measures: insomnia, depression, pain**

PGB-treated patients showed significantly greater endpoint improvement than placebo-treated patients on both the four-item MOS-Sleep Disturbance Scale, and the nine-item MOS-Sleep problems index (Table 2). The effect of VXR on sleep measures was similar to placebo.

In this study sample, HAM-D and Daily Pain Rating scores were relatively low at pretreatment baseline. On the 17-item HAM-D total score, the PGB group showed significantly greater endpoint improvement than placebo, whereas VXR did not (Table 2). No difference was found between PGB or VXR and placebo on the Daily Pain Rating Scale (Table 2).

**Quality of life and functioning**

The treatment effect of PGB and VXR on patient-rated QoL and functioning was modest and only intermittently significant. At endpoint, PGB-treated patients showed significant improvement compared with placebo on the SDS, but not on any of the three QoL measures (Table 2). In contrast, patients treated with VXR showed significant improvement compared with placebo on the Quality of Life, Enjoyment, and Satisfaction Scale, but not on the SDS, or the other two QoL scales (Table 2).

**Tolerability and safety**

The mean maximal daily dose of PGB was 424 ± 118 mg; the proportion of patients using a daily dose of 450 mg (37.2%) was somewhat higher than the proportion of patients using 300 mg (33.1%) and 600 mg (28.9%). The mean maximal daily dose of VXR was 155 ± 60 mg; the proportion of patients using a daily dose of 75 mg (37.6%) was somewhat higher than the proportion of patients using 150 mg (32.0%), 225 mg (29.6%), or 300 mg (0.8%). Both PGB and VXR were well tolerated in the dosage range used in this study. The most frequent adverse events on PGB were dizziness, headache, and nausea; whereas the most frequent adverse events on VXR were nausea, headache, and fatigue (Table 3). The proportion of adverse events reported as severe was significantly higher on VXR (20.0%) compared with placebo (7.8%; Fisher’s exact test, \( P = 0.002 \)), whereas the rate of severe adverse events was intermediate on PGB (9.1%). Consistent with this, the rate of attrition because of adverse events was numerically higher on VXR compared with placebo (17.6 vs. 5.5%), and again was intermediate (12.4%) on PGB.

**Discussion**

This randomized, placebo-controlled trial evaluated the efficacy of flexible doses of PGB and VXR in patients with GAD. The doses achieved in the trial were within
the recommended therapeutic dosing range of both PGB and VXR. Treatment with PGB resulted in significantly greater improvement compared with placebo in the primary outcome, the HAM-A total score. Onset of significant efficacy versus placebo occurred at the first post-baseline assessment, by day 4, and was maintained throughout the 8 weeks of study treatment. Similarly, significant levels of improvement on PGB occurred in both psychic and somatic symptoms of anxiety, with the onset of improvement observed by day 4 on both HAM-A subscales.

To our knowledge, this is the first study to show significant efficacy within the first 4 days of treatment for a nonbenzodiazepine in patients with GAD. The early onset of improvement was clinically significant, with 36% of patients reporting a 20% or greater reduction in HAM-A severity on day 4. Earlier (before day 4) efficacy assessment was not carried out. However, PGB has shown rapid onset of anxiolytic effect (within 3–4 h) in a dental model of anxiety symptoms (Nutt et al., 2008).

As GAD is often comorbid with symptoms of depression, it is important to evaluate the influence of depressive symptoms on the efficacy of PGB. Treatment with PGB was associated with significant improvement in secondary depressive symptoms as measured by the HAM-D. PGB also showed significant efficacy in treating symptoms of insomnia as measured by the MOS-Sleep factors. In contrast, venlafaxine did not show significant efficacy when compared with placebo on either the HAM-D or MOS-Sleep factors. Improvement on PGB in subsyndromic depressive symptoms, using the Bech Melancholia Scale, has been reported in a pooled analysis of earlier GAD studies (Pollack et al., 2003). However, it should be noted that baseline HAM-D scores were relatively low (11.5) in this study, and a comorbid diagnosis of MDD or dysthymic disorder was reason for exclusion. No clinical trial data are available on the efficacy of PGB as a monotherapy in patients with GAD that is comorbid with MDD or dysthymic disorder. The only published data we are aware of that have evaluated the efficacy selective serotonin reuptake inhibitors or serotonin–norepinephrine reuptake inhibitor therapy in GAD comorbid with MDD or dysthymia is a post-hoc subgroup analysis that found significant anxiolytic and antidepressant efficacy for VXR, but not fluoxetine (Silverstone and Salinas, 2001).

A battery of QoL and functioning scales was used in this study to determine whether improvement in anxiety was associated with parallel improvement in patient-centered outcomes. The results were disappointing, perhaps because of several reasons. First, the measures used in this study may not have been sensitive to change in outpatients diagnosed with GAD. For example, the EuroQoL EQ-5D has not been validated for use in psychiatric disorders such as GAD and, in fact, contains items of questionable relevance in this population (e.g. ‘I have some problems walking about’; ‘I am confined to bed’; and ‘I have some problems washing and dressing myself’). Second, the apparent lack of treatment effect on QoL and functional outcomes may be attributable to the fact that at least half of the patients seem to have had minimal anxiety-related impairment in QoL or functioning at baseline. Study entry criteria did not require impairment in QoL or functioning as inclusion criteria, nor was the study powered to detect treatment effects on QoL or functional measures. Finally, it is possible that improvement in QoL and functioning lags behind improvement in anxiety symptomatology, and that a longer treatment period would be required to show efficacy in these outcome domains.

The interpretation of the results of this study is complicated by the relatively high placebo response. High placebo response, and inability to show significance, has been reported to occur, even among drugs of proven efficacy in GAD, in approximately 50% of clinical trials (Khan et al., 2002, 2005). In 8-week trials evaluating the efficacy of VXR in GAD, the endpoint HAM-A change score on placebo ranged from −8.1 to −11.7, with three out of seven trials having a high placebo response (> 10-point improvement in HAM-A; [45] Thase, 2006). In this study, the endpoint improvement in the HAM-A total score on placebo was −11.7, identical to the HAM-A change score in the largest previous VXR trial with an active comparator control (diazepam; Hackett et al., 2003). In the previous study, [16]Hackett and colleagues (2003) reported an endpoint improvement on the 150 mg dose of VXR that was similar to what was observed in the current trial (−12.8 vs. −12.0). In both studies, the VXR treatment groups were not significant versus placebo, whereas diazepam (in the study by Hackett and colleagues, 2003) and PGB (in this study) did show significant efficacy versus placebo. In contrast, an earlier placebo-controlled trial of PGB, conducted in European sites similar to this study, did show significant efficacy versus placebo for a lower (75 mg) fixed dose of venlafaxine (Montgomery et al., 2006).

Table 3 Incidence (%) of treatment-emergent adverse events (all-causality, with incidence ≥ 5%)

<table>
<thead>
<tr>
<th></th>
<th>Pregabalin</th>
<th>Venlafaxine-XR</th>
<th>Placebo</th>
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<tbody>
<tr>
<td></td>
<td>N = 121</td>
<td>N = 125</td>
<td>N = 128</td>
</tr>
<tr>
<td>Nausea</td>
<td>12.4</td>
<td>25.6</td>
<td>8.6</td>
</tr>
<tr>
<td>Dizziness</td>
<td>20.7</td>
<td>9.6</td>
<td>6.3</td>
</tr>
<tr>
<td>Headache</td>
<td>17.4</td>
<td>16.0</td>
<td>11.7</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>10.7</td>
<td>12.0</td>
<td>3.9</td>
</tr>
<tr>
<td>Fatigue</td>
<td>9.9</td>
<td>12.8</td>
<td>3.9</td>
</tr>
<tr>
<td>Somnolence</td>
<td>9.1</td>
<td>4.8</td>
<td>2.3</td>
</tr>
<tr>
<td>Insomnia</td>
<td>4.1</td>
<td>9.6</td>
<td>4.7</td>
</tr>
<tr>
<td>Vertigo</td>
<td>13.2</td>
<td>8.0</td>
<td>3.1</td>
</tr>
<tr>
<td>Constipation</td>
<td>4.1</td>
<td>5.6</td>
<td>3.1</td>
</tr>
<tr>
<td>Hyperhidrosis</td>
<td>2.5</td>
<td>8.0</td>
<td>5.5</td>
</tr>
<tr>
<td>Any ‘severe’ adverse event</td>
<td>9.1</td>
<td>20.0</td>
<td>7.8</td>
</tr>
</tbody>
</table>
Various factors have been suggested (Benedetti, 2008; Price et al., 2008) that may increase the likelihood of a high placebo response during a clinical trial, including illness characteristics (shorter duration; low severity; low comorbidity); study design characteristics (higher number of active treatment arms; too many outcome measures, especially as the latter may increase the time of doctor–patient contact resulting in an increase in nonspecific psychotherapy effects); various longitudinal effects (spontaneous remission; regression to the mean); and patient variables (expectancy effects). The specific reasons for the high placebo response observed in this study are uncertain, but we suspect that expectancy effects may have played a role. In particular, the use of a day 4 assessment may have created the impression that the treatment under study might be powerful and rapid in onset. Clinical trials in central nervous system disorders are especially susceptible to this type of subject and observer bias (Benedetti, 2008; Price et al., 2008).

Treatment with both PGB and VXR were generally well tolerated. Treatment with PGB was associated with higher rates of dizziness, whereas treatment with VXR was associated with higher rates of nausea. Overall, the incidence of adverse events rated as severe was significantly higher on VXR than with PGB. No clinically significant, treatment-emergent changes were observed on either drug in vital signs or in laboratory parameters.

In conclusion, this study provides further confirmation of the efficacy of PGB in the treatment of GAD. The onset of significant antianxiety effect for PGB occurred by day 4, with rapid improvement occurring in both psychic and somatic symptoms of anxiety.

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References


