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ARTICLE

Pregabalin long-term treatment and assessment of discontinuation in patients with generalized anxiety disorder

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Abstract

Discontinuation effects following cessation of 12 and 24 wk of pregabalin treatment for generalized anxiety disorder (GAD) were evaluated in a placebo- and lorazepam-controlled, randomized, double-blind, multicentre trial conducted in 16 countries. The study design consisted of two 12-wk treatment periods (periods 1 and 2), each followed by a 1-wk taper and two post-discontinuation assessments, one immediately following the taper and one 1-wk post-taper. Patients were assigned to receive an initially flexible dose of pregabalin 450–600 mg/d, pregabalin 150–300 mg/d, or lorazepam 3–4 mg/d for 6 wk; responders continued fixed-dose therapy for 6 additional weeks. Patients entering period 2 continued on the same fixed dose or switched to placebo. Discontinuation effects were evaluated with the Physician Withdrawal Checklist (PWC) and reported discontinuation-emergent signs and symptoms. Rebound anxiety was measured with the Hamilton Anxiety Rating Scale. GAD symptoms improved with all treatments and improvements were maintained over 12 and 24 wk. Low levels of discontinuation symptoms were evident in all treatment groups. For patients who received active treatment during both periods, mean (95% confidence interval) increases on the PWC from last visit on active treatment to the second post-discontinuation assessment were: pregabalin 450–600 mg/d: 2.8 (1.6–3.9), pregabalin 150–300 mg/d: 1.7 (0.7–2.8), lorazepam 3–4 mg/d: 2.2 (1.0–3.5). Rates of rebound anxiety were also low at both 12 and 24 wk (0–6%). This suggests that risk of discontinuation symptoms and rebound anxiety are low for pregabalin after 12 and 24 wk of treatment.

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Introduction

Generalized anxiety disorder (GAD) is a chronic and disabling condition with an estimated 12 month prevalence of ~2% in Europe (Lieb et al., 2005) and ~3% in the United States (Kessler et al., 2005). The probability of full recovery from GAD is less than 40%, and among individuals whose symptoms remit, there is a high likelihood of recurrence (Yonkers et al., 1996; Rodriguez et al., 2006). Functional impairments in those with pure GAD (without comorbidity) is comparable to pure major depressive disorder and other mood disorders and, if not successfully treated, disability is similar to that seen in chronic medical illnesses (Kessler et al., 1999, 2001; Wittchen et al., 2000; Grant et al., 2005; Hoffman et al., 2008).

A variety of treatment options currently exist for GAD, including selective serotonin reuptake inhibitors, serotonin-noradrenaline reuptake inhibitors, benzodiazepines and tricyclic antidepressants (Baldwin et al., 2011). In Europe, as well as in some countries outside Europe, another option is pregabalin, which has been approved for the treatment of GAD in adults and is now included as a first-line treatment option in guidelines from the World Federation of Societies of Biological Psychiatry (Bandelow et al., 2008). The efficacy and safety of pregabalin for the treatment of GAD has been demonstrated in multiple short-term (4 to 8 wk) clinical trials (Feltner et al., 2003; Pande et al., 2003; Pohl et al., 2005; Rickels et al., 2005; Montgomery et al., 2006; Kasper et al., 2009).

Given the chronicity of GAD, the safety and efficacy of long-term pharmacotherapy is of particular clinical relevance. Whereas short-term efficacy trials evaluate the

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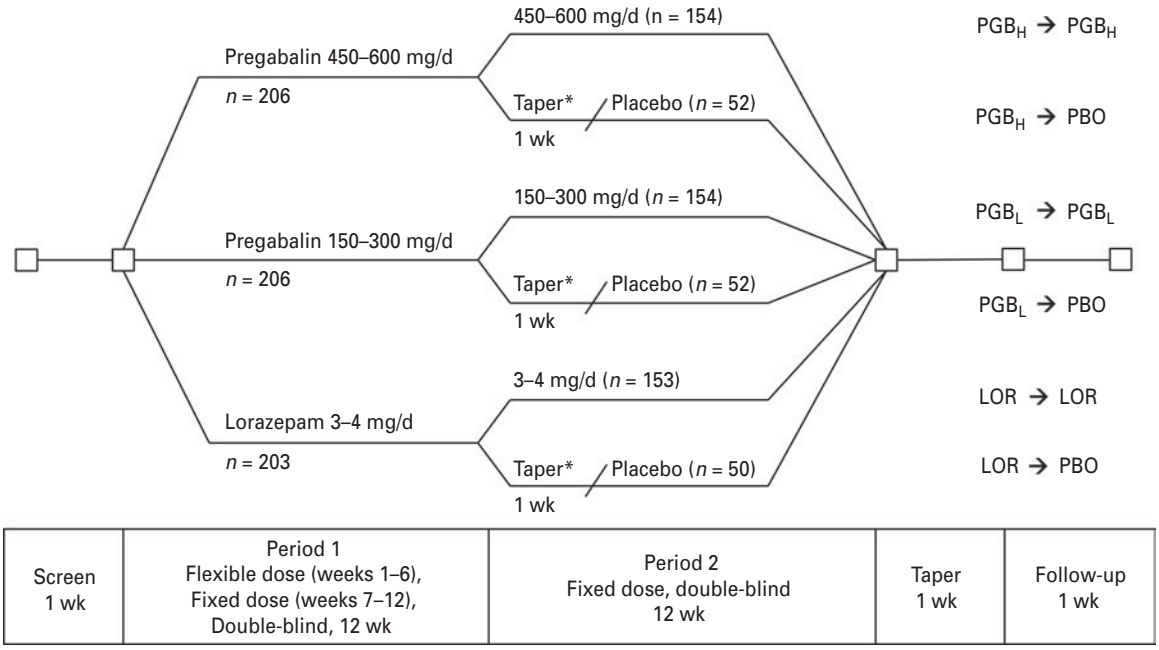

Fig. 1. Study design. *Discontinuation symptoms were evaluated both at the end of the 1 wk taper (week 13) and at a follow-up visit 1 wk later (week 14). PGB_H, pregabalin high dose (450–600 mg/d); PGB_L, pregabalin low dose (150–300 mg/d); LOR, lorazepam 3–4 mg/d; PBO, placebo.

degree of early treatment response and initial tolerability, long-term trials evaluate the ability of anxiolytic treatments to sustain initial response and achieve symptomatic remission. Additional important goals of long-term trials include evaluating the optimal duration of treatment and the degree to which medication discontinuation is associated with symptoms and/or anxiety recurrence.

When pregabalin is discontinued, a taper of at least 1 wk is recommended to minimize discontinuation symptoms (Pfizer Inc, New York, NY, USA). To evaluate such potential discontinuation effects and to determine maintenance of treatment response following discontinuation of a drug, double-blind placebo-substitution studies are indicated.

Only a few double-blind placebo-substitution studies have been conducted in the treatment of GAD. These include studies of paroxetine (Stocchi et al., 2003), escitalopram (Allgulander et al., 2006), duloxetine (Davidson et al., 2008) and venlafaxine (Rickels et al., 2010). Despite the extensive literature on the short-term efficacy of high potency benzodiazepines in the treatment of GAD (Mitte et al., 2005) and the continued common use of benzodiazepines in the treatment of GAD (Baldwin et al., 2012), no double-blind placebo-substitution studies have been published in which patients have been prospectively treated with a benzodiazepine for GAD. However, studies have recruited patients reporting long-term naturalistic use of benzodiazepines, or who have documented benzodiazepine dependence. These studies report high rates of discontinuation symptoms with long-term (>6 months) use of benzodiazepines, particularly if discontinuation is abrupt (Rickels et al., 1983, 1988, 1990).

The goal of the current study was to evaluate the frequency and severity of discontinuation and rebound symptoms associated with short- (12 wk) and long- (24 wk) term treatment with two doses of pregabalin in patients with moderate-to-severe GAD who responded to 6 wk of acute treatment. To evaluate discontinuation symptoms relative to previous studies of discontinuation or withdrawal symptoms, the study design also included a group of patients who received an established comparator drug (lorazepam) as active control. Secondary aims of the study were to characterize descriptively the long-term safety and efficacy of pregabalin, the latter in terms of the maintenance of improvement among patients who respond to short-term treatment with pregabalin.

Experimental procedures

Study design

This was a 24-wk placebo- and lorazepam-controlled, randomized, double-blind, multicentre trial for the evaluation of the discontinuation effects of pregabalin in the treatment of GAD. The study consisted of an initial screening and baseline assessment followed by two consecutive 12-wk treatment periods (Fig. 1). Eligible patients were randomly assigned at baseline to a sequence of treatments during treatment period 1 and treatment period 2: (1) pregabalin high dose followed by pregabalin high dose, (2) pregabalin high dose followed by placebo, (3) pregabalin low dose followed by pregabalin low dose, (4) pregabalin low dose followed by placebo,

(5) lorazepam followed by lorazepam, or (6) lorazepam followed by placebo. The randomized scheme was structured for a 1:1:1 ratio assignment based on the treatment period 1 group (pregabalin high dose, pregabalin low dose, lorazepam); 25% of patients from each medication group were randomized to discontinue active medication after treatment period 1 and receive placebo during treatment period 2. The allocation of 25% of patients to placebo and 75% to continued treatment was done so that discontinuation effects after both 12-wk and 24-wk exposure to pregabalin could be evaluated. The expectation was that it would be more difficult to retain patients for 24 wk, so a larger percentage was allocated to continue active treatment in treatment period 2.

Treatment period 1 was 12 wk in duration. At week 6, responders, defined as patients with a Clinical Global Impressions-Improvement (CGI-I) (Guy, 1976) score of 1 or 2, continued with treatment for an additional 6 wk; non-responders exited the study. The CGI-I was used to identify non-responders because the CGI-I most closely captures a clinical decision-making process by a psychopharmacologist. At the end of week 12, 75% of patients in each group continued on to treatment period 2 with the same treatment. The other 25% of patients in each group were tapered to placebo so that discontinuation symptoms could be evaluated. Following the double-blind taper, these patients received double-blind placebo in treatment period 2 (12 wk). The patients who continued with active medication during treatment period 2 underwent a 1-wk double-blind taper beginning at week 25 (taper of treatment period 2) to evaluate discontinuation symptoms. Any patients who were discontinued from active medication at any other point during the study also underwent a 1-wk double-blind taper off treatment to evaluate discontinuation symptoms.

The study was conducted from 13 May 2009 to 2 April 2012, at 60 centres in 16 countries (Argentina, Austria, Costa Rica, Croatia, Czech Republic, Finland, Greece, Guatemala, Indonesia, Lithuania, Mexico, Russian Federation, Serbia, Slovenia, Spain and Turkey). At all centres, the study protocol was approved by an Institutional Review Board or Ethics Committee. Written informed consent was obtained from all patients. The study was conducted according to the principles of the Declaration of Helsinki and Good Clinical Practice Guidelines and is registered on Clinicaltrials.gov (NCT00624780).

Study treatments

Following the European product label recommendations for pregabalin (Pfizer Inc., 2009), treatment was initiated with a 150 mg/d starting dose in both the low- and high-dose pregabalin groups. The lorazepam starting dose was 2 mg/d. Upward dose escalation occurred during the first 3 wk. Following dose escalation, patients received pregabalin 450–600 mg/d (high dose), pregabalin 150–300 mg/d (low dose) or lorazepam 3–4 mg/d, with flexible-dose treatment within the specified ranges during the first 6 wk based on tolerability and clinical improvement. Patients who showed a clinical response (CGI-I score of 1 or 2) at week 6 continued treatment; those who had a CGI-I score >2 at week 6 were discontinued from the study. During the second half of treatment period 1, patients were maintained on a fixed-dose treatment at the final dosage achieved during the initial 6-wk flexible dosage phase. Study drug was administered twice per day (in equal doses) and was blinded using a double-dummy method. Patients entering treatment period 2 either continued on the same fixed dose or switched to placebo, according to the randomization scheme.

The 1-wk double-blind taper schedule was generally consistent with product labelling and was intended to minimize the risk that patients could potentially experience severe drug discontinuation symptoms. Any patients experiencing severe discontinuation symptoms during the taper periods and up to 7 d afterwards could be provided with a more gradual 'rescue' taper, extending the taper to 4 wk while maintaining the blind. This same taper schedule and rescue taper protocol was used for all patients, regardless of when treatment was discontinued.

Study population

Eligible patients, recruited from the clinic population, clinic referrals or from advertisements, were aged 18 to 65 yr with a primary diagnosis of GAD at baseline. Additional inclusion criteria were a Hamilton Anxiety Rating Scale (HAM-A) (Hamilton, 1960) total score $\geqslant 14$ and a Hamilton Rating Scale for Depression (HAM-D) (Hamilton, 1959) item 1 score $\leqslant 2$ at both screening and baseline visits (the baseline assessment occurred ~4–10 d following screening). Patients with a current or past diagnosis of any other Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV Axis I disorder (American Psychiatric Association, 2000) besides GAD were excluded (with the exception of current or past diagnosis of depression not otherwise specified, specific phobia, somatization disorder, nicotine or caffeine abuse/dependence or past history of major depressive disorder, social phobia, panic disorder or eating disorder). Individuals were also excluded from the study if they reported daily ($\geqslant 5$ d/wk) use of benzodiazepines for treating GAD during the 3 months prior to screening, a history of failed treatment with any benzodiazepine (determined by a judgment of the clinical investigator who took into account reported dosage and duration) or any reported prior exposure to pregabalin. Those individuals taking a benzodiazepine for less than 5 d/wk could be included if they stopped taking the benzodiazepine 2 wk prior to baseline. No benzodiazepine use was allowed during the study. Additional exclusion criteria were pregnancy/lactation, suicide risk, current use of psychotropic

medication that could not be discontinued prior to baseline, positive urine test results at screening for potential drug abuse or illegal drugs, positive alcohol breathalyzer test at screening or any serious or unstable medical condition assessed at screening.

Assessment of discontinuation symptoms

The primary measure of discontinuation symptoms was the Physician Withdrawal Checklist (Rickels et al., 1990). The PWC is a 20-item physician-rated interview (total score range 0–60) that measures the presence of anxiolytic drug discontinuation-related signs and symptoms in the following areas: gastrointestinal, mood, sleep, motor, somatic, perception and cognition. The PWC was administered at baseline and weeks 12, 13, 14, 24, 25 and 26. The 13- and 14-wk assessments and the 25- and 26-wk assessments corresponded to the end of the 1-wk taper and 1 wk after completing the taper for treatment periods 1 and 2, respectively, and were conducted to evaluate discontinuation symptoms by calculating change in PWC total scores from last visit on active treatment (week 12 or 24) to these post-discontinuation visits.

The incidence of spontaneously reported treatment-emergent adverse events occurring during the discontinuation weeks (i.e. from the first day of the first taper dose through the last available visit in either the taper week or the week following taper) was examined as a secondary measure of Discontinuation-Emergent Signs and Symptoms (DESS). These adverse events were evaluated for the taper of treatment periods 1 and 2. DESS were defined as newly developed adverse events or worsening of existing adverse events reported during the taper periods.

The HAM-A total score was used to evaluate rebound anxiety. This was defined as a HAM-A total score higher during the discontinuation assessments (weeks 13, 14, 25 and 26) compared with baseline.

Efficacy measures

The primary efficacy measure was the HAM-A. Secondary efficacy measures consisted of the CGI-I and Clinical Global Impression-Severity (CGI-S) scales (Guy, 1976). The HAM-A and CGI-S were administered by trained clinicians (study investigators) at baseline and weeks 3, 6, 9, 12, 13, 14, 15, 18, 21, 24, 25 and 26. The CGI-I, also administered by trained clinicians, was obtained weekly from weeks 1 to 6, and then at weeks 9, 12, 13, 14, 15, 18, 21, 24, 25 and 26.

Safety measures

Safety was evaluated through blood chemistry, haematology and urinalysis (assessed at baseline and week 26) and by vital signs (assessed at baseline and weeks 1, 3, 6, 9, 12, 13, 14, 24, 25 and 26). Spontaneously reported or observed adverse events (all-causality and treatment-related) were recorded at each study visit. All adverse events were categorized in terms of their severity by the treating clinician. Study discontinuation owing to adverse events was also specified as a measure of safety/tolerability.

Statistical methods

Sample size determination was based on an expected discontinuation rate of 50% by the end of treatment period 1. A sample size of 75 patients per group was calculated based on an estimation of the true mean change from baseline to within 2.0 units of the PWC (assuming a standard deviation of 7.8 units) using a 95% confidence interval (CI) with 90% coverage probability.

The primary sample for analyses of discontinuation symptoms and efficacy included all randomized patients who had at least one discontinuation week or efficacy assessment, and who were not major protocol violators. The primary safety sample was defined as all randomized patients who received at least one dose of study medication.

To evaluate potential discontinuation effects, one sample analysis was conducted, consisting of mean changes (and associated 95% CI) in the PWC total scores from the visit prior to the start of tapering to the end of weeks 1 and 2 of each taper period (weeks 13 and 14 for treatment period 1; weeks 25 and 26 for treatment period 2). DESS events and the percent of patients with rebound anxiety were summarized by treatment group and for each of the 2 wk following the initiation of the tapers. Efficacy of continued treatment was evaluated descriptively for each treatment group in terms of mean changes (and 95% CIs) in the HAM-A and CGI-S from baseline to week 12 and baseline to week 24. CGI-I scores at weeks 12 and 24 (last observation carried forward) were similarly evaluated. Safety analyses consisted of reporting the proportion of patients with treatment-emergent adverse events for each treatment.

Results

Patient characteristics and disposition

A total of 816 patients were screened for the study (Fig. 2). Of those screened, 615 patients met study entry criteria and were randomized to one of two pregabalin dose ranges: 450–600 mg/d (n=206) or 150–300 mg/d (n=206); or lorazepam 3–4 mg/d (n=203). A total of 615 patients received at least one dose of study treatment and constituted the safety sample. There were 463 (75.3%) patients who completed treatment period 1 and 366 (59.5%) who completed treatment period 2. Among patients who discontinued treatment period 1 early or entered the taper period following treatment period 1, a rescue taper was used for four patients assigned to pregabalin 450–600 mg/d, six patients assigned to pregabalin 150–300 mg/d and two patients assigned to lorazepam

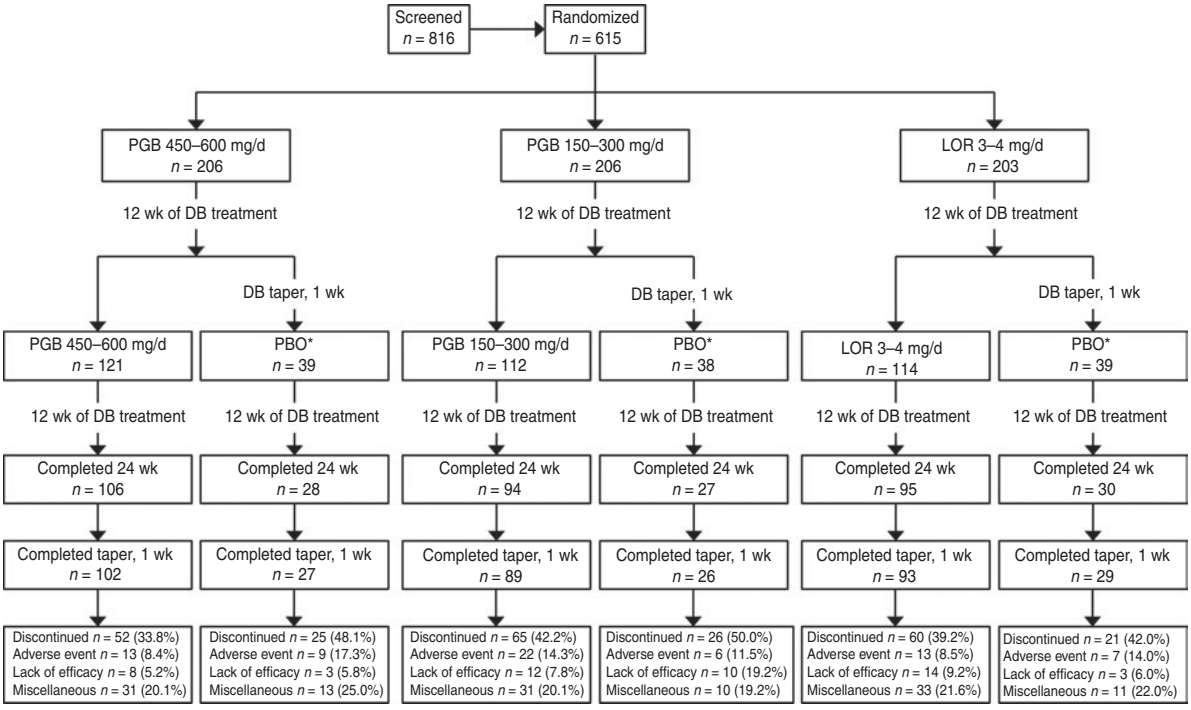

Fig. 2. Patient disposition. *Represents the number of patients who received placebo after completing 12 wk of treatment. A larger number of patients were randomized at baseline to receive placebo at the end of period 1 in the pregabalin 450–600 mg group (n=52), the pregabalin 150–300 mg group (n=52), and the lorazepam 3–4 mg group (n=50); however, the number who actually received placebo was smaller owing to premature discontinuation. DB, double-blind; PGB, pregabalin; LOR, lorazepam 3–4 mg/d; PBO, placebo.

3–4 mg/d. Among those who discontinued treatment period 2 early or entered the taper period following treatment period 2, a rescue taper was used for six patients who received pregabalin 450–600 mg/d throughout both treatment periods, zero patients who received pregabalin 450–600 mg/d during treatment period 1 and placebo during treatment period 2, five patients who received pregabalin 150–300 mg/d throughout both treatment periods, six patients who received pregabalin 150–300 mg/d during treatment period 1 and placebo during treatment period 2, eight patients who received lorazepam 3–4 mg/d throughout both treatment periods and two patients who received lorazepam 3–4 mg/d during treatment period 1 and placebo during treatment period 2.

Patients in the study sample had a mean age of ~42 yr (range 18–65); 60.8% of patients were female and 82.4% were white (Table 1). The mean duration since the onset of GAD symptoms was ~2.3 yr (range 0–36.6). Patients in the six treatment groups in treatment period 2 did not differ significantly on available baseline characteristics or median treatment duration.

Table 1. Baseline characteristics and treatment duration (treatment period 1 group)

	Pregabalin (450–600 mg/d) (n=206)	Pregabalin (150–300 mg/d) (n=206)	Lorazepam (3–4 mg/d) (n=203)
Male, *n* (%)	87 (42.2)	73 (35.4)	81 (39.9)
Race, *n* (%)			
White	176 (85.4)	165 (80.1)	166 (81.8)
Black	0 (0)	0 (0)	1 (0.5)
Asian	14 (6.8)	22 (10.7)	22 (10.8)
Other	16 (7.8)	19 (9.2)	14 (6.9)
Age, yr			
Mean (S.D.)	42.4 (11.5)	40.5 (12.3)	42.6 (11.2)
Range	18–64	18–65	19–65
Duration of illness, yr			
Mean (S.D.)	2.2 (4.4)	2.1 (4.3)	2.4 (4.3)
Range	0–28	0–28	0–37
Treatment duration, d			
Median (S.D.)	139.4 (55.1)	133.2 (58.3)	136.7 (59.4)
Range	1–233	2–216	4–216

S.D., standard deviation.

Discontinuation symptoms and rebound anxiety

Increases in PWC total scores from the last visit in treatment period 1 to the first and second weeks following taper were small (Table 2). Similarly, in the groups who remained on active treatment throughout both treatment periods, small increases in PWC scores were apparent from the last visit of the second treatment period to the first and second weeks following the initiation of the taper of treatment period 2. Mean change on the PWC

Table 2. Discontinuation symptoms following treatment period 1 (weeks 1 to 12) and treatment period 2 (weeks 13 to 24): mean change in PWC

Mean change[a] (95% CI) in PWC, *n*	Pregabalin (450–600 mg/d)	Pregabalin (150–300 mg/d)	Lorazepam (3–4 mg/d)
Discontinuation symptoms following treatment period 1[b]			
Week 1 after initiating taper[c]	*n*=58	*n*=52	*n*=49
	1.9 (−0.1, 3.8)	1.4 (0.2, 2.7)	2.3 (0.4, 4.2)
Week 2 after initiating taper[c]	*n*=54	*n*=49	*n*=44
	2.1 (0.4, 3.7)	2.0 (0.5, 3.6)	1.6 (−0.3, 3.6)
Discontinuation symptoms following treatment period 2[d]			
Week 1 after initiating taper[c]	*n*=109	*n*=93	*n*=99
	1.7 (0.7, 2.6)	1.1 (0.4, 1.9)	3.0 (1.7, 4.4)
Week 2 after initiating taper[c]	*n*=106	*n*=84	*n*=93
	2.8 (1.6, 3.9)	1.7 (0.7, 2.8)	2.2 (1.0, 3.5)

[a] Change is measured from the last visit during the respective treatment period to the week 1 and week 2 visits following taper initiation after each treatment period.
[b] Includes all patients who discontinued between weeks 9–15, or who switched to placebo at the end of week 12, and had a corresponding assessment in the 2 wk following initiation of the taper.
[c] The taper period was 1 wk long.
[d] Includes all patients who either completed the study or discontinued after week 15, and had a corresponding assessment in the 2 wk following taper initiation.
PWC, Physician Withdrawal Checklist, total score; CI, confidence interval.

among the patients who received placebo during treatment period 2 was also small.

Among the subgroup of patients who discontinued active treatment at the end of treatment period 1, DESS were reported by a total of 21 (36.2%) who received pregabalin 450–600 mg/d, 17 (32.7%) who received pregabalin 150–300 mg/d and 17 (32.7%) who received lorazepam 3–4 mg/d during the 2 wk following the initiation of the taper of treatment period 1 (Table 3). Anxiety, headache, insomnia and nausea were the only DESS that occurred in ⩾5% of patients in any treatment group during treatment period 1. In the 2 wk following the initiation of the taper of treatment period 2, DESS events were reported by 22.3–31.2% of patients receiving any active medication during both treatment periods (Table 3), and by 13.3–31.0% of those receiving placebo during treatment period 2. Anxiety, headache and insomnia were the only DESS that occurred in ⩾5% of patients in any of the treatment groups during treatment period 2.

The incidence of rebound anxiety was low across active treatment groups in patients who discontinued active treatment after treatment period 1 (range 1.9–5.2%) and also in patients who discontinued active treatment after treatment period 2 (range 0–6%) (Table 4).

Efficacy

Substantial improvements in anxiety and illness severity were observed in all three treatment groups at the end of treatment period 1 (Table 5). Mean HAM-A changes from baseline to week 12 (LOCF) ranged from −16.0 to −17.4 across treatment groups. For patients continuing into treatment period 2, improvements in anxiety symptoms were maintained for those who remained on active medication during treatment period 2 as well as for patients who switched from active drug to placebo for treatment period 2 (Table 5). Mean HAM-A changes from baseline to week 24 (LOCF) ranged from −14.9 to −19.0 over the six treatment groups. Results for CGI-S and CGI-I scores also showed that improvements during the initial 12-wk treatment period were maintained over the course of the second 12-wk treatment period, both for patients who remained on active drug and for those switched to placebo (Table 5).

Safety

Among patients assigned to receive active drug for 24 wk, treatment-emergent adverse events were reported by 78.6% (121/154) who received pregabalin 450–600 mg/d, 78.6% (121/154) receiving pregabalin 150–300 mg/d and 75.2% (115/153) of patients receiving lorazepam. Severe adverse events occurred in 17.5% (27/154) of patients treated with pregabalin 450–600 mg/d, 13.6% (21/154) treated with pregabalin 150–300 mg/d and 14.4% (22/153) treated with lorazepam. The most common adverse events reported were headache, dizziness, insomnia and somnolence (Table 6). Discontinuations owing to adverse events at any time while on active drug over the course of 6 months occurred for 8.4% of patients receiving pregabalin 450–600 mg/d, 14.3% receiving pregabalin 150–300 mg/d and 8.5% receiving lorazepam. One death occurred

Table 3. Discontinuation emergent signs and symptoms (DESS) occurring in ⩾5% of patients after 12 and 24 wk of treatment

DESS[a] during 2 wk following taper[b] initiation after treatment period 1[c]

	PGB_H (n=58)	PGB_L (n=52)	LOR (n=52)
Patients with DESS, *n* (%)	21 (36.2)	17 (32.7)	17 (32.7)
Anxiety	3 (5.2)	0 (0.0)	2 (3.8)
Dizziness	3 (5.2)	0 (0.0)	0 (0.0)
Headache	3 (5.2)	4 (7.7)	1 (1.9)
Insomnia	6 (10.3)	4 (7.7)	10 (19.2)
Nausea	4 (6.9)	3 (5.8)	2 (3.8)

DESS[a] during 2 wk following taper[b] initiation after treatment period 2[d]

	$PGB_H \rightarrow PGB_H$ (n=109)	$PGB_H \rightarrow$ PBO (n=30)	$PGB_L \rightarrow PGB_L$ (n=94)	$PGB_L \rightarrow$ PBO (n=29)	LOR→LOR (n=100)	LOR→PBO (n=30)
Patients with DESS, *n* (%)	34 (31.2)	4 (13.3)	21 (22.3)	9 (31.0)	28 (28.0)	4 (13.3)
Anxiety	7 (6.4)	1 (3.3)	4 (4.3)	0 (0.0)	8 (8.0)	0 (0.0)
Headache	5 (4.6)	(0.0)	3 (3.2)	2 (6.9)	2 (2.0)	(0.0)
Insomnia	13 (11.9)	1 (3.3)	8 (8.5)	2 (6.9)	6 (6.0)	2 (6.7)

[a] DESS adverse events are a subset of Treatment Emergent Signs and Symptoms and are defined as those spontaneously reported adverse events that developed or existed prior to but worsened during the 2 wk following taper initiation (i.e. weeks 13 and 14 for those who discontinued at week 12 and weeks 25 and 26 for those who discontinued at week 24).
[b] The taper period was 1 wk long.
[c] All patients who discontinued between weeks 9–15, or who switched to placebo at the end of week 12, and had a corresponding discontinuation week assessment.
[d] All patients who either completed the study or discontinued after week 15, and had a corresponding assessment in the 2 wk following taper initiation.
DESS, discontinuation-emergent signs and symptoms; PGB_H, pregabalin high dose (450–600 mg/d); PGB_L, pregabalin low dose (150–300 mg/d); LOR, lorazepam 3–4 mg/d.

Table 4. Rebound anxiety after treatment periods 1 and 2

	Pregabalin (450–600 mg/d)	Pregabalin (150–300 mg/d)	Lorazepam (3–4 mg/d)
Rebound anxiety[a] during 2 wk following taper[b] initiation, *n*/*N* (%)			
After treatment period 1[c]	3/58 (5.2)	1/52 (1.9)	2/48 (4.2)
After treatment period 2[d]	4/109 (3.7)	0/94 (0)	6/100 (6.0)

[a] Rebound anxiety is defined as a Hamilton Anxiety Rating Scale total score greater than the baseline score during either of the 2 wk following taper initiation.
[b] The taper period was 1 wk long.
[c] All patients who discontinued between weeks 9–15, or who switched to placebo at the end of week 12, and had a corresponding assessment in the 2 wk following taper initiation.
[d] All patients who either completed the study or discontinued after week 15, and had a corresponding assessment in the 2 wk following taper initiation.

during the study. The patient had been randomized to receive pregabalin 150–300 mg/d in both treatment groups. The cause of death was reported as metastasis of unknown origin and was not considered related to the study drug. The patient also had infectious disease of unknown origin at the time of death.

No clinically meaningful changes in laboratory test values were evident for patients in any of the treatment groups. A similarly small proportion of patients had vital signs that met the criteria for abnormality (e.g. increased systolic blood pressure), but none of the values were considered to be of clinical concern.

Table 5. Efficacy measures at baseline, week 12, and week 24

	Treatment groups during treatment period 1		
	PGB_H	PGB_L	LOR
HAM-A total score			
Baseline (95% CI)	*n*=197 25.3 (24.7, 26.0)	*n*=183 24.9 (24.3, 25.4)	*n*=188 24.5 (23.9, 25.1)
Week 12 mean change (95% CI) (LOCF)	*n*=194 −17.4 (−18.5, −16.4)	*n*=180 −16.0 (−17.1, −14.9)	*n*=185 −16.7 (−17.8, −15.5)
CGI-Severity score			
Baseline (95% CI)	*n*=197 4.6 (4.5, 4.7)	*n*=183 4.5 (4.4, 4.6)	*n*=188 4.4 (4.3, 4.5)
Week 12 mean change (95% CI) (LOCF)	*n*=195 −2.3 (−2.5, −2.1)	*n*=181 −2.1 (−2.2, −1.9)	*n*=186 −2.1 (−2.2, −1.9)
CGI-Improvement			
Week 12 mean score (95% CI) (LOCF)	*n*=197 1.9 (1.7, 2.0)	*n*=183 1.9 (1.7, 2.0)	*n*=188 1.9 (1.8, 2.1)

	Treatment groups during treatment period 2					
	$PGB_H \rightarrow PGB_H$ (*n*=117)	$PGB_H \rightarrow$ PBO (*n*=37)	$PGB_L \rightarrow PGB_L$ (*n*=103)	$PGB_L \rightarrow$ PBO (*n*=37)	LOR→LOR (*n*=106)	LOR→PBO (*n*=37)
HAM-A total score						
Baseline (95% CI)	25.6 (25.0, 26.3)	24.6 (23.0, 26.1)	24.8 (24.0, 25.5)	25.1 (23.8, 26.4)	24.7 (23.8, 25.5)	24.1 (22.8, 25.5)
Week 24 mean change (95% CI) (LOCF)	−18.7 (−20.0, −17.3)	−17.5 (−19.8, −15.2)	−18.2 (−19.5, −17.0)	−14.9 (−17.6, −12.3)	−19.0 (−20.4, −17.6)	−17.5 (−20.2, −14.7)
CGI-Severity score						
Baseline (95% CI)	4.7 (4.6, 4.8)	4.5 (4.3, 4.7)	4.5 (4.4, 4.7)	4.5 (4.3, 4.8)	4.4 (4.3, 4.6)	4.5 (4.3, 4.7)
Week 24 mean change (95% CI) (LOCF)	−2.4 (−2.6, −2.2)	−2.3 (−2.7, −1.9)	−2.4 (−2.6, −2.2)	−2.0 (−2.4, −1.6)	−2.5 (−2.7, −2.3)	−2.2 (−2.6, −1.8)
CGI-Improvement						
Week 24 mean score (95% CI) (LOCF)	1.7 (1.6, 1.9)	1.9 (1.6, 2.3)	1.6 (1.4, 1.7)	2.3 (1.8, 2.8)	1.5 (1.3, 1.7)	2.0 (1.6, 2.3)

PGB_H, pregabalin high dose (450–600 mg/d); PGB_L, pregabalin low dose (150–300 mg/d); LOR, lorazepam 3–4 mg/d; HAM-A, Hamilton Anxiety Rating Scale total score; CI, confidence interval; LOCF, last observation carried forward; CGI, Clinical Global Impressions; PBO, placebo.

Table 6. Treatment-emergent adverse events (incidence ⩾5% in any 1 treatment group)

	Treatment group					
Adverse event, *n* (%)	$PGB_H \rightarrow PGB_H$ (*n*=154)	$PGB_H \rightarrow PBO$ (*n*=52)	$PGB_L \rightarrow PGB_L$ (*n*=154)	$PGB_L \rightarrow PBO$ (*n*=52)	LOR→LOR (*n*=153)	LOR→PBO (*n*=50)
Headache	38 (24.7)	13 (25.0)	36 (23.4)	17 (32.7)	33 (21.6)	10 (20.0)
Dizziness	37 (24.0)	17 (32.7)	28 (18.2)	14 (26.9)	20 (13.1)	10 (20.0)
Insomnia	31 (20.1)	15 (28.8)	24 (15.6)	12 (23.1)	23 (15.0)	13 (26.0)
Somnolence	25 (16.2)	7 (13.5)	31 (20.1)	9 (17.3)	35 (22.9)	13 (26.0)
Nausea	17 (11.0)	7 (13.5)	12 (7.8)	8 (15.4)	18 (11.8)	7 (14.0)
Fatigue	16 (10.4)	6 (11.5)	15 (9.7)	11 (21.2)	15 (9.8)	5 (10.0)
Anxiety	15 (9.7)	6 (11.5)	10 (6.5)	1 (1.9)	19 (12.4)	5 (10.0)
Nasopharyngitis	13 (8.4)	2 (3.8)	7 (4.5)	5 (9.6)	8 (5.2)	4 (8.0)
Dry mouth	13 (8.4)	3 (5.8)	5 (3.2)	2 (3.8)	8 (5.2)	4 (8.0)
Disturbance in attention	12 (7.8)	1 (1.9)	3 (1.9)	2 (3.8)	6 (3.9)	1 (2.0)
Diarrhoea	10 (6.5)	3 (5.8)	8 (5.2)	5 (9.6)	9 (5.9)	1 (2.0)
Constipation	10 (6.5)	1 (1.9)	4 (2.6)	2 (3.8)	2 (1.3)	1 (2.0)
Back pain	9 (5.8)	1 (1.9)	1 (0.6)	0	4 (2.6)	2 (4.0)
Influenza	8 (5.2)	3 (5.8)	7 (4.5)	0	7 (4.6)	0
Tension	8 (5.2)	1 (1.9)	4 (2.6)	0	2 (1.3)	1 (2.0)
Sedation	6 (3.9)	2 (3.8)	5 (3.2)	0	10 (6.5)	1 (2.0)
Decreased appetite	6 (3.9)	1 (1.9)	3 (1.9)	4 (7.7)	6 (3.9)	3 (6.0)
Irritability	6 (3.9)	1 (1.9)	4 (2.6)	2 (3.8)	8 (5.2)	1 (2.0)
Paraesthesia	6 (3.9)	0	3 (1.9)	3 (5.8)	5 (3.3)	2 (4.0)
Myalgia	5 (3.2)	4 (7.7)	4 (2.6)	2 (3.8)	9 (5.9)	1 (2.0)
Tremor	5 (3.2)	2 (3.8)	1 (0.6)	3 (5.8)	6 (3.9)	0
Weight increased	5 (3.2)	1 (1.9)	7 (4.5)	3 (5.8)	4 (2.6)	0
Generalized anxiety disorder	4 (2.6)	2 (3.8)	9 (5.8)	2 (3.8)	7 (4.6)	2 (4.0)
Vertigo	4 (2.6)	1 (1.9)	5 (3.2)	4 (7.7)	3 (2.0)	1 (2.0)
Arthralgia	4 (2.6)	1 (1.9)	3 (1.9)	0	3 (2.0)	3 (6.0)
Cough	1 (0.6)	1 (1.9)	2 (1.3)	0	2 (1.3)	4 (8.0)
Abdominal pain	1 (0.6)	1 (1.9)	2 (1.3)	3 (5.8)	1 (0.7)	0

PGB_H, pregabalin high dose (450–600 mg/d); PBO, placebo; PGB_L, pregabalin low dose (150–300 mg/d); LOR, lorazepam 3–4 mg/d.

Discussion

The current study is the first to evaluate discontinuation symptoms following long-term (6 month) pregabalin treatment for GAD using a prospective, randomized, double-blind, active control, placebo-substitution design with evaluations at 12 and 24 wk. The results indicate that, for both high- and low-dose pregabalin responders who continued with treatment to 12 or 24 wk, there was a low incidence of discontinuation symptoms as measured by the PWC or by spontaneously reported DESS during a 2-wk discontinuation evaluation at the end of each treatment period. In addition, the incidence of rebound anxiety was low (0–6%) and did not appear to be related to either dose or duration of treatment. The lack of clinically meaningful discontinuation symptoms or rebound anxiety for pregabalin after either 12 or 24 wk of treatment supports the utilization of a 1-wk treatment taper to manage the potential of rebound anxiety and discontinuation symptoms with pregabalin for the treatment of GAD.

No new safety findings regarding pregabalin were evident in this study. There were no notable or unexpected abnormalities in vital signs or laboratory findings during 6 months of treatment with either pregabalin or lorazepam. Both doses of pregabalin were well-tolerated, with minimal dose-related differences in adverse events. However, interpreting the incidence of adverse events is difficult in the absence of a parallel placebo-control group during the initial 12 wk of treatment.

Comparison of the discontinuation results of the current study to other studies in the literature is difficult because the current study used a 4 mg maximum dose of lorazepam, consistent with product labelling and current clinical practice. In contrast, previous studies often used higher (up to 6 mg/d) doses of lorazepam (Cutler et al., 1993; Mandos et al., 1995; Feltner et al., 2003). The lower dose used here may explain why marked discontinuation effects were not observed following a 1-wk taper off lorazepam.

Although this study was designed to assess potential discontinuation symptoms, the efficacy outcome data

also add to the existing literature on the short-term (Feltner et al., 2003; Pande et al., 2003; Pohl et al., 2005; Rickels et al., 2005; Montgomery et al., 2006) and long-term (Feltner et al., 2008) efficacy of pregabalin in GAD. Although the study was not designed or powered for between-drug comparisons (i.e. lack of non-inferiority testing or superiority testing among treatments), it should be noted that the maintenance of response at 24 wk was similar for pregabalin low dose, pregabalin high dose and lorazepam. Further studies are needed to confirm these 24-wk comparative outcomes.

To put the improvements over time for all treatment groups in context, characteristics of the sample population recruited for the current study need to be taken into account. The average duration of GAD symptoms (2–3 yr) for the sample in the current study was considerably less than that reported in many other GAD studies, where the average duration of GAD symptoms ranged from 11 to 14 yr (Rickels et al., 2005; Feltner et al., 2008). Not only did the active treatment groups show maintenance of improvements in the current study, but patients who switched to placebo at 12 wk (following a taper period) also showed maintenance of gains when evaluated at 24 wk. The possibility that individuals with a less chronic history of GAD may fully maintain gains achieved with a short-term (12 wk) course of treatment (i.e. without continuation treatment) has important clinical implications and should be addressed in future studies.

A potential limitation of the current study is that only responders at 6 wk were evaluated for discontinuation effects. This protocol-driven selection of patients may have biased the remaining sample towards low reporting of symptoms. However, this design decision is consistent with clinical guidelines (non-responders, after an adequate period of treatment, would be treated with an alternative agent) (National Institute of Health and Care Excellence (NICE), 2011) and ethical principles for long-term research studies. Also, the sample size, although appropriate for the main objective to assess potential discontinuation symptoms, was not sufficient for between-group comparisons of these events. A larger sample size or different study design is required to adequately test for between-group differences.

In summary, the results of this study showed that pregabalin treatment (450–600 or 150–300 mg/d) for 12 or 24 wk was not associated with clinically meaningful discontinuation symptoms or rebound anxiety following a 1-wk taper.

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Statement of Interest

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