Pregabalin for the treatment of generalized anxiety disorder: a novel pharmacologic intervention

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Pregabalin is the first anxiolytic pharmacologic alternative for the treatment of generalized anxiety disorder (GAD) to be introduced in more than 10 years. GAD is a significant psychiatric condition with lifetime prevalence rates ranging between 5.7 and 6.4%. It causes significant impairment in quality of life and functional abilities equivalent to those associated with major depression. Randomized, controlled trials confirm that pregabalin is superior to placebo and comparable with lorazepam, alprazolam and venlafaxine for the treatment of patients with moderate-to-severe GAD. The onset of anxiolytic activity for pregabalin is apparent within 1 week following initiation of treatment, which is more rapid than that obtained with paroxetine and venlafaxine. Additionally, pregabalin has demonstrated potential for the prevention of relapse of GAD. Recently, the efficacy, safety and tolerability of pregabalin were also shown in a placebo-controlled study with elderly patients. Safety and tolerability profiles are favorable, with transient dizziness and somnolence of mild-to-moderate severity being the most commonly reported adverse events. Pregabalin has minimal potential for drug–drug interactions and does not provoke a clinically significant withdrawal response. Furthermore, pregabalin has low potential for abuse and dependence, unlike other classes of medications used for the treatment of GAD. Clinicians may consider the use of pregabalin in lieu of benzodiazepines as an alternative therapy for their patients with GAD.

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CONTENTS

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Generalized anxiety disorder (GAD) is a significant psychiatric condition characterized by a diverse array of psychic and somatic symptoms, including excessive and persistent worry that persists for 6 months or longer but is not associated with specific phobic situations, combined with autonomic, musculoskeletal, gastrointestinal and respiratory symptoms [1,2]. Current diagnostic criteria for GAD require prolonged feelings of anxiety and worry accompanied by at least three of six key symptoms (restlessness, fatigue, impaired concentration, irritability, muscle tension and disruptions in patterns of sleep) [1].

GAD has a 12-month prevalence of approximately 3.1% in the USA [3]. Lifetime prevalence rates range between 5.7 and 6.4% in the USA and Europe, respectively [4,5]. The point-prevalence rate in primary care practice settings is estimated to be 4% (subjects met all Diagnostic and Statistical Manual of Mental Disorders [DSM]-IV criteria for GAD), with an additional 1.3% meeting all DSM-IV threshold criteria except for the 6-month duration of symptoms [6]. Women are estimated to be at a two-to-threefold higher risk of developing GAD than men [4,5]. European data suggest that GAD is among the most commonly observed psychiatric disorders in primary care practices, with point-prevalence rates of 21.7% for generalized anxiety symptoms only, 1.3% for GAD of 1–5-month duration and 4.0% for GAD of 6-month or more duration [6].

GAD is a chronic disorder characterized by older age at onset compared with other DSM-IV conditions, such as other anxiety disorders and mood disorders [5]. Kessler and

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colleagues reported lifetime prevalence rates for GAD increasing from 4.1% in the cohort aged 18–29 years to 6.8% in those aged 30–44 years to 7.7% in those aged 45–59 years [5]. A study of anxiety disorders in older populations (55–85 years of age) residing in Europe revealed the highest 6-month prevalence of 11.5% for persons aged 65–74 years followed by 6.9% of those 75–85 years and 4.0% of those between the ages of 55–64 years [7]. It has been reported that as many as 66% of persons with GAD have a comorbid diagnosis [2], including major depression (38.6%), panic disorder (22.6%), social anxiety disorder (23.2%) or specific phobia (24.5%) [8].

A diagnosis of GAD is typically predictive of significant impairments in role functioning, social life, work productivity and quality of life [2,9]. The median time between onset of symptoms and treatment seeking is 14 years, owing in part to low detection rates of GAD in primary care medical environments [10]. Full remission of GAD was confirmed in only 38% of patients evaluated in a 5-year follow-up study, and less than 50% achieved partial remission [11].

The pathophysiology of GAD is not yet completely understood. Family and twin studies of GAD provided evidence for familial aggregation and at least a modest role of genetics [12]. There is evidence to suggest that disturbances in the neurotransmission of serotonin (5-hydroxytryptamine [5-HT]), norepinephrine and GABA and changes in cholecystokinin and corticotropin-releasing factors play a contributing role in the etiology of GAD [13]. Specifically, there is evidence to suggest that GAD is associated with impairments of the benzodiazepine receptor system, noradrenergic abnormalities and overstimulation of the 5-HT system, with additional research underway to clarify the neurobiologic causes of GAD [13].

Overview of the market

The clinical management of GAD relies on pharmacologic interventions combined with behavioral or psychotherapeutic interventions [14]. Historically, benzodiazepines have been the preferred pharmacologic intervention for GAD. Current treatment guidelines for GAD emphasize the role of selective serotonin reuptake inhibitors (SSRIs), selective serotonin–norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs) and the 5-HT_{1A} agonist buspirone, rather than benzodiazepine anxiolytics [14–16]. This is largely due to the common comorbidity of GAD with depression and to the side effects typically associated with benzodiazepines as a class, including drowsiness, potential for abuse and dependence and withdrawal symptoms [17].

Baldwin and Polkinghorn completed a comprehensive computerized literature search for the period 1980–2003 to assess evidence for the efficacy of then-current pharmacologic treatments for GAD, including SSRIs (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline), venlafaxine, benzodiazepines, imipramine, pregabalin, 5-HT_{1A} agonists (buspirone and flesinoxan), hydroxyzine, propranolol and trifluoperazine [18]. They concluded that some TCAs and benzodiazepines have established efficacy for the treatment of GAD. Specifically, benzodiazepines have rapid onset of anxiolytic effect and were effective for short-term therapy, but these benefits were offset by side effects and risks associated with abuse, dependence and withdrawal. The efficacy of SSRIs and venlafaxine has been established in placebo-controlled trials [18]. Both paroxetine and venlafaxine have been approved by the US FDA for the treatment of GAD, and escitalopram has been approved in European countries. These pharmacologic interventions are not associated with the risks of dependence and abuse associated with benzodiazepines, but they have a slower onset of action [19].

Promising results from a number of randomized, placebo-controlled trials with pregabalin have demonstrated its efficacy for the treatment of partial seizures, neuropathic pain syndromes and GAD. In GAD, pregabalin has demonstrated a comparatively more rapid onset of effect than that reported for SSRIs and venlafaxine and a low risk of abuse or dependence, unacceptable adverse events and withdrawal symptoms [19].

A summary of the efficacy and speed of onset for several pharmacologic interventions currently available for the treatment of GAD is presented in TABLE 1 [20–30].

Introduction to pregabalin

Pregabalin, $C_8H_{17}NO_2$, is described chemically as (*S*)-3-(aminomethyl)-5-methylhexanoic acid, and it is a structural analog of GABA. It does not, however, affect $GABA_A$, $GABA_B$ or benzodiazepine receptor sites [31–33,101]. Pregabalin evoked anxiolytic properties in two rodent models of anxiety including the elevated x-maze and conflict test and has also demonstrated analgesic and anticonvulsant effects in animal models [34–36].

Pharmacodynamics

Pregabalin anxiolytic effects are attributed to its potent binding to the α_2-δ subunit protein of voltage-gated N- and P/Q-type calcium channels in CNS tissues [37], and it has recently been demonstrated that binding at this site is essential to the anxiolytic, analgesic and antiepileptic effects of pregabalin [32,35,36]. Such binding reduces calcium influx at nerve terminals and modulates the release of neurotransmitters, including glutamate, noradrenaline, substance P and calcitonin gene-related peptide, from pathologically excited neurons [38–42].

Pregabalin does not exacerbate GABA-mediated responses nor does it affect GABA reuptake or GABA transaminase inhibition. It does not appear to alter rat brain GABA concentration, augment $GABA_A$ responses in cultured neurons or exert acute effects on GABA uptake or degradation [31,33]. However, it has been shown that prolonged exposure to pregabalin increases both the density of GABA transporter protein and the speed of functional GABA transport in cultured neurons [101].

Pharmacokinetics & metabolism

Administration of pregabalin in a fasting state is associated with rapid absorption, with T_{max} achieved within 1.5 h following both single and multiple oral dosing [101]. Oral bioavailability of pregabalin generally exceeded 90% and was independent of

Table 1. Qualitative comparison of efficacy across key outcomes for classes of drugs used to treat generalized anxiety disorder.

Class	Examples	Onset of effect	Symptom efficacy			Ref.
			Psychic	*Somatic*	*Depression*	
Benzodiazepines	Diazepam, alprazolam	<7 days	Moderate	Marked	Some	[20,21]
TCAs	Imipramine	~3 weeks	Marked	Some	Marked	[20]
SSRI, SNRI	Venlafaxine-XR, paroxetine, escitalopram	2–3 weeks	Marked	Some	Marked	[22–25]
Azapirones	Buspirone	~3 weeks	Marked	Some	Moderate	[26,27]
α_2-δ modulators	Pregabalin	≤7 days	Marked	Marked	Moderate	[28–30]

SSRI: Selective serotonin reuptake inhibitor; SNRI: Serotonin–noradrenaline reuptake inhibitor; TCA: Tricyclic antidepressant; XR: Extended release.
Adapted from [52].

dose, with steady-state plasma levels attained within 24–48 h following administration. At doses of 75–900 mg, the C_{max} of pregabalin increased linearly, as did the area under the plasma concentration–time curve [101]. The rate of absorption of pregabalin is somewhat slowed when taken with food: C_{max} is decreased by approximately 25–30%, and T_{max} is delayed to approximately 3 h. This characteristic has no clinically meaningful effect, and pregabalin can be taken with or without food [101].

The recommended therapeutic dosage of pregabalin is 150–600 mg/day administered in two or three divided doses. Initiation of treatment for GAD can begin with a 75 mg/day dosage that is increased to 300 mg/day after 1 week. Dosage may be increased, based on individual patients' response, by 150 mg/day at 1-week intervals up to the maximum recommended daily dosage of 600 mg.

The primary route of elimination of pregabalin is renal, with 80–100% of the administered dose recovered as unchanged parent drug in urine [43,44]. Urinary excretion is largely independent of dose, and the elimination half-life of pregabalin in healthy volunteers is approximately 6 h [101]. Elimination of pregabalin does not vary by gender or race, but may be decreased for older persons who might have age-related changes in renal function.

Pregabalin does not inhibit or induce cytochrome P450 enzymes, and these enzymes do not alter the pharmacokinetics of pregabalin. Therefore, pregabalin may be combined with SSRIs and other antidepressants, which may often be necessary in GAD patients with comorbid depression. Additionally, pharmacokinetic studies of patients with partial seizures who were on stable monotherapy with one of four antiepileptic drugs (carbamazepine, phenytoin, lamotrigine or valproate) demonstrated that addition of pregabalin 600 mg/day for 1 week resulted in no clinically meaningful pharmacokinetic drug–drug interactions. Pregabalin T_{max} and elimination half-life were similar to those observed in studies of healthy volunteers [45]. Bockbrader and colleagues have reported that pregabalin has minimal drug–drug interactions with other compounds including lorazepam, oxycodone and ethanol [46]. In a related study, pregabalin did not significantly alter the effectiveness of an oral contraceptive to prevent ovulation, and concomitant use of an oral contraceptive did not interfere with the plasma concentration of pregabalin [47]. Pregabalin clearance is directly proportional to creatinine clearance (CL_{cr}); thus, dosage reduction should be considered in patients with compromised renal function (e.g., CL_{cr} < 60 ml/min). To achieve similar plasma drug concentrations in patients with impaired renal function, it is recommended that pregabalin dosages be decreased by approximately 50% for each 50% decline in CL_{cr} [44].

Clinical efficacy of pregabalin for GAD

The efficacy of pregabalin for treatment of GAD has been studied in eight randomized, double-blind, placebo-controlled trials, five of which have been fully published to date [14,28–30,48]. A total of six trials evaluated responses to acute treatment for intervals of 4–6 weeks and included comparisons of different dosages of pregabalin with placebo, lorazepam, alprazolam or venlafaxine, and all relied on change from baseline to end point in the Hamilton Anxiety Rating Scale (HAM-A) as the primary outcome measure for efficacy [14,28–30,48,49]. One trial studied the effects of pregabalin in elderly patients over 8 weeks of treatment [50], and one trial evaluated relapse prevention over a 6-month treatment period [51]. These Phase II and III clinical trials evaluated almost 3000 patients with DSM-IV and confirmed clinical diagnoses of GAD based on validated, reliable anxiety scales, such as the HAM-A, the Clinical Global Impression – Improvement Scale (CGI-I) or the Covi Anxiety Scale. Although pregabalin is not an antidepressant, and patients with major depression were excluded from the GAD studies, depression scales, such as the Hamilton Depression Rating Scale (HAM-D) or the Raskin Depression Scale, were used in some of the trials. To assess abuse potential, the Physician Withdrawal Checklist was used.

A HAM-A score of at least 20 was a key criterion for study inclusion as well as no evidence of current comorbid depression, another DSM-IV anxiety disorder or alcohol or substance abuse. The acute-treatment trials followed a standard design of a 1-week washout period followed by initiation of the appropriate dosage of the assigned medication, and a 1-week taper upon completion of the treatment interval of 4–6 weeks. Pregabalin dosages ranged from 50 to 600 mg/day administered either twice or three-times daily (TABLE 2).

Among the earliest evaluations of pregabalin, Feltner and colleagues described a double-blind, fixed-dose, parallel-group, placebo- and active-controlled (lorazepam), multicenter, 4-week study that compared patients treated with pregabalin 150 or 600 mg/day three-times daily, placebo or lorazepam 6 mg/day three-times daily followed by a 1-week double-blind taper [14]. Significant improvements in HAM-A scores were observed for pregabalin 600 mg/day (-13.2 points) versus the placebo group (-9.3; p = 0.0013; FIGURE 1). The statistically significant efficacy of pregabalin 600 mg/day was evident after 1 week, the first time point measured. Early discontinuation of study participation owing to adverse events was significantly higher in the lorazepam group (35%) compared with the pregabalin 600 mg/day treatment group (21%; p = 0.01) [12]. These results were confirmed by a study that compared the effect of pregabalin 150 mg/day, pregabalin 600 mg/day and lorazepam 6 mg/day with placebo [48]. After 1 week of treatment, pregabalin 600 mg/day and lorazepam significantly reduced HAM-A scores compared with placebo, and these significant improvements were maintained at end point (comparison of lorazepam with pregabalin 150 mg/day favored lorazepam). Additionally, both pregabalin 600 mg/day and lorazepam significantly improved both the psychic and somatic subscales of the HAM-A. As in the trial reported by Feltner, more lorazepam-treated patients (41.2%) discontinued the study early than did pregabalin-treated patients (28.6% of 600 mg/day group; 10.1% of 150 mg/day group; and 27.5% of the placebo group) [35]. A third acute-treatment trial comparing pregabalin with lorazepam and placebo showed that whilst pregabalin 600 mg/day demonstrated numerical superiority to lorazepam and placebo, neither pregabalin nor lorazepam treatment groups separated statistically from placebo on the primary efficacy measure [49].

Rickels and colleagues compared three dosages of pregabalin (300, 450 or 600 mg/day) with alprazolam (1.5 mg/day) or placebo for a 4-week, double-blind treatment interval followed by a 1-week taper period [28]. All three dosages of pregabalin and alprazolam achieved significant reductions after 1 week of treatment in HAM-A total score, HAM-A psychic score, HAM-A items 1 (anxiety/worry) and 2 (tension) and CGI-I scores compared with placebo. Significant reductions in the HAM-A total scores were observed in the pregabalin 300 and 600 mg/day groups at week 1 compared with alprazolam ($p < 0.05$). Pregabalin 300 and 600 mg/day were associated with significant improvement, compared with placebo, in the HAM-A somatic factor score at both week 1 and end point, while alprazolam was not [28].

Pregabalin also demonstrated greater efficacy for the treatment of GAD when compared with venlafaxine in a 6-week, multicenter, randomized, double-blind, placebo-controlled trial [29]. Patients received either pregabalin 400 or 600 mg/day, venlafaxine 75 mg/day or placebo. While both dosages of pregabalin and venlafaxine significantly reduced HAM-A scores compared with placebo, the onset of effect was noted at week 1 for the pregabalin groups compared with week 2 for those treated with venlafaxine [29]. Pregabalin at both dosages significantly improved the HAM-A psychic factor score compared with placebo at both week 1 and end point, while venlafaxine was associated with significant improvement in HAM-A psychic factor score only at end point. Additionally, in a *post hoc* comparison, the improvement seen at week 1 in psychic factor score was significantly greater (p = 0.007) than that observed in the venlafaxine group. Pregabalin 400 mg/day was associated with a significant improvement at both week 1 and end point in the HAM-A somatic factor score, and at week 1, both pregabalin groups were significantly superior to venlafaxine in a *post hoc* comparison for improvement of HAM-A somatic factor score. Furthermore, rates of discontinuation of study participation owing to adverse events were highest for those treated with venlafaxine (20.4%) compared with 13.6% of those in the pregabalin 600 mg/day group, 9.9% for the placebo group and 6.2% for the pregabalin 400 mg/day group. This difference was statistically significant for the venlafaxine group compared with the pregabalin 400 mg/day group ($p < 0.01$) [29].

Pohl and colleagues confirmed that three dosages of pregabalin (200 mg/day twice daily, 400 mg/day twice daily or 450 mg/day three-times daily) resulted in significant improvements in mean HAM-A total scores at last observation carried forward compared with placebo. All three dosages were also associated with improvements at end point in both HAM-A psychic and somatic factor scores. Pairwise comparisons of twice and three-times daily dosing revealed no significant differences in HAM-A total score at end point [30].

Montgomery and colleagues evaluated the efficacy of pregabalin for the treatment of GAD in patients 65 years and older [50]. They reported significant reductions from baseline in mean HAM-A total score in patients treated with pregabalin (-12.84 standard error of the mean [SEM] ± 0.70) compared with placebo (-10.65 SEM ± 0.89; p = 0.0437). The positive effect of pregabalin on mean total HAM-A scores was observed in the pregabalin-treated patients at weeks 2, 4 and 8 compared with placebo [50].

In the trials described previously, current major depressive disorder was an exclusion criterion, and patients tended to have fairly low HAM-D scale scores. However, relative to placebo treatment, there was, in the trials described above, a significantly greater decrease from baseline to end point in the total HAM-D score for patients receiving pregabalin (150–600 mg/day) relative to those receiving placebo. There were two exceptions: in the fully published study by Feltner [14], pregabalin 150 mg/day did not separate from placebo for change in HAM-D, and data on change in HAM-D were not reported for the one unsuccessful trial of pregabalin [49].

Table 2. Summary of clinical trials evaluating the efficacy and safety of pregabalin for treatment of generalized anxiety disorder.

Design	n (ITT population)	Key efficacy measures	Efficacy summary	Ref.
Trial 1				[48]
4-week, double-blind treatment with placebo, pregabalin 150 or 600 mg/day or lorazepam 6 mg/day	PBO = 69	Change from BL to EP (LOCF) in HAM-A total score	All three active treatments statistically significantly superior to PBO	
	150 mg/day = 69	Time to onset of effect	Pregabalin 600 mg/day and lorazepam statistically significantly superior to PBO by week 1, the first time point measured	
	600 mg/day = 70	CGI-I responders	Pregabalin 600 mg/day and lorazepam statistically significantly superior to PBO	
	Lorazepam = 68	≥50% HAM-A responders	Pregabalin 600 mg/day and lorazepam statistically significantly superior to PBO	
Trial 2				[49]
4-week, double-blind treatment with placebo, pregabalin 150 or 600 mg/day or lorazepam 6 mg/day	PBO = 70	Change from BL to EP (LOCF) in HAM-A total score	None of the three active treatments significantly separated from PBO	
	150 mg/day = 71	Time to onset of effect	Pregabalin 600 mg/day was significantly superior to PBO at week 1 and week 2, but this was not sustained through end point	
	600 mg/day = 71	CGI-I responders	None of the three active treatments significantly separated from PBO	
	Lorazepam = 70			
Trial 3				[14]
4-week, double-blind treatment with placebo, pregabalin 150 or 600 mg/day or lorazepam 150 or 600 mg/day	PBO = 67	Change from BL to EP (LOCF) in HAM-A total score	Pregabalin 600 mg/day and lorazepam were statistically significantly superior to PBO	
	150 mg/day = 70	Time to onset of effect	Pregabalin 600 mg/day and lorazepam statistically significantly superior to PBO by week 1, the first time point measured	
	600 mg/day = 66	CGI-I responders	None of the three active treatments significantly separated from PBO	
	Lorazepam = 68	≥50% HAM-A responders	None of the three active treatments significantly separated from PBO	

b.i.d.: Twice daily; BL: Baseline; CGI-I: Clinical Global Impression – Improvement Scale; EP: End point; HAM-A: Hamilton Anxiety Rating Scale; ITT: Intent to treat; LOCF: Last observation carried forward; PBO: Placebo; t.i.d.: Three-times daily.

Table 2. Summary of clinical trials evaluating the efficacy and safety of pregabalin for treatment of generalized anxiety disorder (cont.).

Design	n (ITT population)	Key efficacy measures	Efficacy summary	Ref.
Trial 4				[28]
4-week, double-blind treatment with placebo, pregabalin 300, 450 or 600 mg/day or alprazolam 1.5 mg/day	PBO = 91 300 mg/day = 91	Change from BL to EP (LOCF) in HAM-A total score	All four active treatments statistically significantly superior to PBO	
	450 mg/day = 90	Time to onset of effect	All pregabalin dosages and alprazolam statistically significantly superior to PBO by week 1, the first time point measured	
	600 mg/day = 89	CGI-I responders	Pregabalin 300 and 600 mg/day and alprazolam were statistically significantly superior to PBO	
	Alprazolam = 93	≥50% HAM-A responders	Pregabalin 300 and 600 mg/day were statistically significantly superior to PBO	
Trial 5				[29]
6-week, double-blind treatment with placebo, pregabalin 400 of 600 mg/day or venlafaxine 75 mg/day	PBO = 101	Change from BL to EP (LOCF) in HAM-A total score	All three active treatments statistically significantly superior to PBO	
	400 mg/day = 97	Time to onset of effect	Both pregabalin dosages statistically significantly superior to PBO by week 1, the first time point measured	
	600 mg/day = 110	CGI-I responders	All three active treatments statistically significantly superior to PBO	
	venlafaxine = 113	≥50% HAM-A responders	Pregabalin 400 mg/day and venlafaxine were statistically significantly superior to PBO	
Trial 6				[30]
6-week, double-blind treatment with placebo, pregabalin 200 mg/day (b.i.d.), 400 mg/day (b.i.d.) or 450 mg/day (t.i.d.)	PBO = 86	Change from BL to EP (LOCF) in HAM-A total score	All pregabalin dosages statistically significantly superior to PBO	
	200 mg/day = 78	Time to onset of effect	All pregabalin dosages statistically significantly superior to PBO by week 1, the first time point measured	
	400 mg/day = 89	CGI-I responders	All pregabalin dosages statistically significantly superior to PBO	
	450 mg/day = 88	≥50% HAM-A responders	All pregabalin dosages statistically significantly superior to PBO	

b.i.d.: Twice daily; BL: Baseline; CGI-I: Clinical Global Impression – Improvement Scale; EP: End point; HAM-A: Hamilton Anxiety Rating Scale; ITT: Intent to treat; LOCF: Last observation carried forward; PBO: Placebo; t.i.d.: Three-times daily.

Table 2. Summary of clinical trials evaluating the efficacy and safety of pregabalin for treatment of generalized anxiety disorder (cont.).

Design	n (ITT population)	Key efficacy measures	Efficacy summary	Ref.
Trial 7				[50]
8-week, double-blind treatment with placebo or flexibly dosed pregabalin 150–600 mg/day b.i.d. or t.i.d.	PBO = 96	Change from BL to EP (LOCF) in HAM-A total score	Pregabalin was statistically significantly superior to PBO	
	Pregabalin = 177	Time to onset of effect	Pregabalin was statistically significantly superior to PBO by week 2	
		CGI-I responders	Pregabalin did not statistically significantly separate from PBO	
		≥50% HAM-A responders	Pregabalin did not statistically significantly separate from PBO ($p = 0.071$)	
Trial 8				[51]
8-week, open-label treatment with pregabalin followed by 26-week, double-blind, fixed-dosage treatment with placebo or pregabalin 450 mg/day	PBO = 170	Time to relapse of GAD	Time to relapse was statistically significantly longer for pregabalin treatment group than for PBO	
	450 mg/day = 168	Change from BL to EP (LOCF) in HAM-A total score		
		Change from double-blind BL to endpoint (LOCF) in HAM-A total score	Pregabalin was statistically significantly superior to PBO	
		CGI-I nonresponders	Proportion of nonresponders (patients rated 'very much' or 'much' worse) was statistically significantly greater in the PBO group than the pregabalin group	

b.i.d.: Twice daily; BL: Baseline; CGI-I: Clinical Global Impression – Improvement Scale; EP: End point; HAM-A: Hamilton Anxiety Rating Scale; ITT: Intent to treat; LOCF: Last observation carried forward; PBO: Placebo; t.i.d.: Three-times daily.

A single long-term trial has evaluated the efficacy of pregabalin for the prevention of relapse in GAD. Patients who had a positive response to open-label pregabalin after 8 weeks of treatment were randomized to either 24 additional weeks of a fixed-dose of pregabalin 150 mg three-times daily or placebo. Pregabalin 450 mg/day resulted in remission of GAD in 49.6% of patients. There were no significant differences noted between patients considered to have more severe GAD at baseline (HAM-A score >24; 47.4% remission rate) compared with those who had less severe GAD (HAM-A score ≤24; 51.6% remission rate) [51]. A Kaplan–Meier analysis found that the pregabalin group was associated with a significantly longer time to relapse than placebo (log rank $p < 0.0001$), although attrition rates were high in both groups (36% for pregabalin and 22% for placebo). The high attrition rate in the pregabalin group can, in part, be explained by the

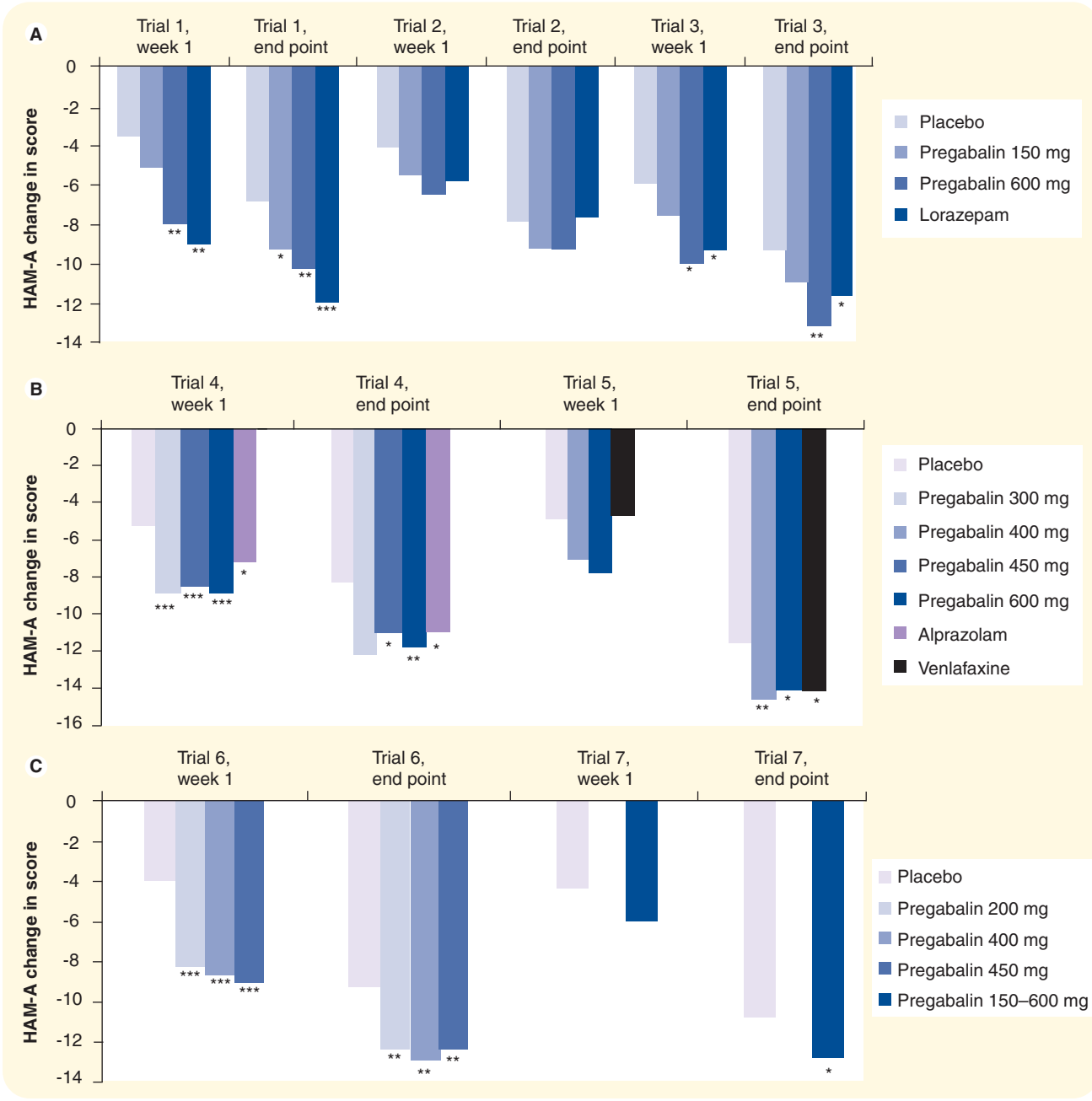

Figure 1. Change in HAM-A from baseline to week 1 and last observation carried forward end point in short-term randomized clinical trials of pregabalin. (A) Comparator trials with lorazepam. (B) Comparator trials with alprazolam and venlafaxine. (C) Comparator trials with placebo only.
Trial 1: [48]; Trial 2: [49]; Trial 3: [14]; Trial 4: [28]; Trial 5: [29]; Trial 6: [30]; Trial 7: [50].
* $p < 0.005$; ** $p < 0.01$; *** $p < 0.001$.
EP: End point; HAM-A: Hamilton Anxiety Rating Scale.

study design, which included an 8-week open-label phase during which pregabalin was dosed flexibly. Patients who responded well during open-label treatment to pregabalin at dosages lower than the 450 mg/day fixed dosage used for double-blind treatment may not have tolerated this higher dosage as well and, thus, may have discontinued double-blind treatment.

Safety & tolerability

Five adverse events were noted significantly more often for patients treated with pregabalin compared with placebo, with an incidence greater than 5%. These were dizziness (31 vs 9%), sedation (29 vs 12%), dry mouth (15 vs 6%), amblyopia (8 vs 2%) and impaired coordination (7 vs 1%). These events were usually rated as mild to moderate in severity and of transient duration. In the trial of pregabalin as treatment of GAD in patients aged 65 years or over [50], the profile of adverse events was similar to that observed in other trials: dizziness was most common, occurring in 20.3% of pregabalin patients (vs 11.5% placebo), followed by somnolence, occurring in 13.0% of pregabalin patients (vs 7.3% placebo).

Discontinuation rates for pregabalin were 6 and 3% for the 150 and 300 mg/day doses and were not significantly different from placebo (9%) (TABLE 3). However, the discontinuation rate for patients who received pregabalin 600 mg/day was 19%. Notably, attrition rates owing to adverse events were comparable with or higher for patients treated with alprazolam 1.5 mg/day (13%), venlafaxine 75 mg/day (20%) and lorazepam 6 mg/day (35%). Sexual dysfunction was not a common side effect of pregabalin, occurring in only 2.9% of males treated with pregabalin versus 0.7% of these who received placebo [52].

To evaluate the cognitive and psychomotor effects of pregabalin compared with alprazolam or placebo, Hindmarch and colleagues conducted a double-blind, placebo-controlled trial with 24 healthy volunteers that included a variety of psychometric tests [53]. They concluded that pregabalin had no significant detrimental effects on objective psychometric tests including choice reaction time, brake reaction time, rapid visual information processing and Sternberg short-term memory scanning test compared with placebo. However, significant decrements were noted for critical flicker fusion, compensatory tracking time and the subjective line analogue rating scale (LARS). Notably, treatment with alprazolam resulted in significant reductions in performance on all objective measures and the LARS [53]. The investigators concluded that pregabalin exerted a relatively benign effect on the central nervous system.

The effects of pregabalin were also compared with those of alprazolam and placebo in the above trial on quantitative and qualitative measures of sleep using the objective polysomnography and Leeds sleep evaluation questionnaire [54]. Both alprazolam and pregabalin resulted in a significant increase in total sleep time and shorter time to sleep onset compared with placebo. However, pregabalin achieved a significantly higher proportion of slow-wave sleep in the total sleep interval compared with alprazolam and placebo. Both drugs reduced rapid eye movement sleep as a proportion of the total sleep interval compared with placebo.

Expert commentary

The efficacy of pregabalin for treatment of the psychic and somatic symptoms of GAD has been studied in eight randomized, double-blind, placebo-controlled trials. The reported trials used the last observation carried forward (LOCF) method to handle drop-outs. In recent trials, the mixed-models repeated measures analysis was used, as it is assumed to be superior to LOCF in accounting for the bias from subject drop-out [55]. Six of these Phase II and III trials evaluated the responses of almost 3000 patients to acute treatment with pregabalin for intervals of 4–6 weeks and included comparisons of different dosages of pregabalin with placebo, lorazepam or venlafaxine. Pregabalin also demonstrated efficacy and safety for the treatment of GAD in older patients, and it shows promise as a long-term treatment option for the prevention of relapse.

Time to onset of effectiveness occurs within 1 week of initiation of therapy, which represents a meaningful advantage over TCA, SSRI and SNRI drug classes. Importantly, pregabalin demonstrated efficacy for relieving both the psychic and somatic symptoms of GAD, an advantage over antidepressants that may predominantly relieve only psychic symptoms.

Pregabalin has a favorable safety and tolerability profile with only mild-to-moderate side effects that dissipate over time. Neither sexual dysfunction nor gastrointestinal side effects, which

Table 3. Summary of discontinuations from trials of pregabalin as treatment for generalized anxiety disorder.

Trial and dosage groups (n = ITT population)	Cause of discontinuation (n [%])		
	Adverse events	*Lack of efficacy*	*Other reasons*
Trial 1			
Placebo (n = 69)	7 (10.1)	1 (1.4)	11 (15.9)
Pregabalin 150 mg/day (n = 69)	2 (2.9)	2 (2.9)	3 (4.3)
Pregabalin 600 mg/day (n = 70)	14 (20.0)	2 (2.9)	4 (5.7)
Lorazepam (n = 68)	19 (27.9)	1 (1.5)	8 (11.8)

*Includes 12 placebo and 25 pregabalin patients required to withdraw owing to study closure.
ITT: Intent to treat.

Table 3. Summary of discontinuations from trials of pregabalin as treatment for generalized anxiety disorder (cont.).

Trial and dosage groups (n = ITT population)	Cause of discontinuation (n [%])		
	Adverse events	*Lack of efficacy*	*Other reasons*
Trial 2			
Placebo (n = 70)	8 (11.4)	2 (2.9)	7 (10.0)
Pregabalin 150 mg/day (n = 71)	6 (8.5)	4 (5.6)	5 (7.0)
Pregabalin 600 mg/day (n = 71)	19 (26.8)	1 (1.4)	4 (5.6)
Lorazepam (n = 70)	29 (41.4)	2 (2.9)	7 (10.0)
Trial 3			
Placebo (n = 67)	4 (6.0)	3 (4.5)	12 (17.9)
Pregabalin 150 mg/day (n = 70)	5 (7.1)	0	12 (17.1)
Pregabalin 600 mg/day (n = 66)	13 (19.7)	0	7 (10.6)
Lorazepam (n = 68)	24 (35.3)	1 (1.5)	7 (10.3)
Trial 4			
Placebo (n = 91)	9 (9.9)	3 (3.3)	14 (15.4)
Pregabalin 300 mg/day (n = 91)	3 (3.3)	0	7 (7.7)
Pregabalin 450 mg/day (n = 90)	7 (7.8)	1 (1.1)	10 (11.1)
Pregabalin 600 mg/day (n = 89)	12 (13.5)	1 (1.1)	10 (11.2)
Alprazolam (n = 93)	12 12.9)	0	13 (14.0)
Trial 5			
Placebo (n = 101)	10 (9.9)	2 (2.0)	8 (7.9)
Pregabalin 400 mg/day (n = 97)	6 (6.2)	2 (2.1)	8 (8.2)
Pregabalin 600 mg/day (n = 110)	15 (13.6)	2 (1.8)	12 (10.9)
Venlafaxine (n = 113)	23 (20.4)	1 (0.9)	10 (8.8)
Trial 6			
Placebo (n = 86)	7 (8.1)	2 (2.3)	16 (18.6)
Pregabalin 200 mg/day (n = 78)	7 (9.0)	0	16 (20.5)
Pregabalin 400 mg/day (n = 89)	10 (11.2)	2 (2.2)	13 (14.6)
Pregabalin 450 mg/day (n = 88)	11 (12.5)	2 (2.3)	9 (10.2)
Trial 7			
Placebo (n = 96)	9 (9.4)	7 (7.3)	11 (11.5)
Pregabalin (n = 177)	19 (10.7)	7 (4.0)	18 (10.2)
Trial 8			
Placebo (n = 170)	4 (2.4)		34 (20.0)*
Pregabalin 450 mg/day (n = 168)	10 (6.0)		51 (30.4)*

*Includes 12 placebo and 25 pregabalin patients required to withdraw owing to study closure.
ITT: Intent to treat.

can be profoundly treatment limiting, are common with pregabalin treatment. Discontinuation rates for pregabalin owing to adverse events are comparable with placebo, except for the 600 mg/day dose, the upper end of the recommended dosing range of pregabalin. Additionally, direct comparisons from the pregabalin studies described here show lower rates of attrition for pregabalin than for those associated with benzodiazepines and the SNRI venlafaxine. Effects on the CNS are minimal and less significant than those observed for benzodiazepines, and quality of sleep appears to be improved by pregabalin. The pharmacokinetic composition of pregabalin appears to have minimal potential for drug–drug interactions, an especially important consideration in patients on polypharmacy, and pregabalin has been shown to be both safe and efficacious in elderly populations. There is growing evidence that interdose anxiety, psychomotor impairment and abuse are not challenges for pregabalin. Furthermore, pregabalin does not appear to provoke tolerance or dependence and is not associated with the withdrawal syndromes commonly observed in patients treated with benzodiazepines, SSRIs and SNRIs.

Owing to its well-documented efficacy in these short-term trials, the rapidity of onset of its anxiolytic effect and its safety and tolerability across a large and diverse population, pregabalin appears to be a good choice as first-line treatment of GAD in adults.

Five-year view

Pregabalin offers the first novel pharmacologic intervention for GAD in more than 10 years with strong evidence for its efficacy in resolution of psychic and somatic symptoms coupled with a sound profile for safety and tolerability, and it was recently approved in the EU for treatment of GAD. Postmarketing research should target further elucidating the efficacy of pregabalin in relapse prevention, long-term treatment and special populations (e.g., children, those at high risk of GAD and those with comorbid psychiatric conditions, especially depression), as well as its time to onset of action. Also, because pregabalin was associated with a significant improvement in HAM-D scores, albeit in patients whose depressive symptoms were not severe, investigation of its efficacy as a treatment for depression may be warranted. Once-daily, rather than twice or three-times daily dosing, has the potential to enhance compliance and warrants further evaluation [56]. Pregabalin has a favorable safety profile relative to benzodiazepines with comparable advantage of quick onset that is not achieved with TCA, SSRI and SNRI classes of drugs. There is no potential for interactions with psychopharmacologic agents or other drugs that are metabolized by the cytochrome P450 system. As such, and because its mechanism of action is distinct from that of other anti-anxiety agents, investigation into the possibility of using pregabalin in combination with other agents for patients whose GAD is refractory to treatment might be undertaken. Pregabalin has shown efficacy and good tolerability in patients with GAD in several studies, and it represents a valid therapeutic option in this population.

Disclosure

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Key issues

- Generalized anxiety disorder (GAD) is a significant psychiatric condition characterized by a diverse array of psychic and somatic symptoms, including excessive and persistent worry that persists for 6 months or longer combined with autonomic, musculoskeletal, gastrointestinal and respiratory symptoms.
- Many persons with GAD are not diagnosed with a potentially treatable anxiety disorder or, alternatively, are recognized as having a psychiatric condition, but are either not treated or receive treatment with drugs with unproven efficacy.
- Published clinical trials of selective serotonin reuptake inhibitors (SSRIs), selective serotonin–norepinephrine reuptake inhibitors (SNRIs), benzodiazepines, tricyclic antidepressants, 5-hydroxytryptamine$_{1A}$ agonists, hydroxyzine, propranolol and trifluoperazine have established efficacy for the treatment of GAD, but present challenges with respect to safety, tolerability and speed of onset of action.
- The efficacy of pregabalin for treatment of GAD has been studied in eight randomized, double-blind, placebo-controlled trials, including one that demonstrated efficacy and safety in elderly populations and a second that established a role for pregabalin in the prevention of relapse.
- Pregabalin has comparable and significant efficacy for the improvement of psychic and somatic symptomatology.
- Pregabalin has an acceptable safety and tolerability profile with only mild-to-moderate side effects that dissipate over time. Pregabalin does not appear to provoke tolerance or dependence, nor is it associated with the withdrawal syndromes commonly observed in patients treated with benzodiazepines, SSRIs or SNRIs.
- Time to onset of effectiveness of pregabalin occurs within 1 week of initiation of therapy.

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Website

101 Pfizer Inc. Lyrica® (pregabalin) 25, 50, 75, 100, 150, 200, 225 and 300-mg capsules: prescribing information www.pfizer.com/pfizer/download/uspi_lyrica.pdf

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