Role of pregabalin in the treatment of generalized anxiety disorder

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Abstract: Generalized anxiety disorder (GAD) is a common, typically persistent, and disabling condition that is often not recognised, or treated in an evidence-based manner. Current pharmacological and psychological treatment approaches have a number of drawbacks, including a delay in onset of clinical effect, varying relative efficacy against psychological or somatic symptoms of anxiety, potentially troublesome adverse effects, and discontinuation symptoms on stopping treatment. Pregabalin is a structural analog of the inhibitory neurotransmitter gamma amino butyric acid (GABA) but is thought to exert its anxiolytic effects through binding in a state-dependent manner to the alpha-2-delta sub-unit of voltage-gated calcium channels in "over-excited" pre-synaptic neurones, reducing release of excitatory neurotransmitters such as glutamate and substance P. At fixed doses of 200 mg/day or greater, it has consistent proven efficacy in acute treatment of DSM-IV-defined GAD, with some evidence of an early onset of clinical effect, and of efficacy across psychological and somatic anxiety symptom clusters. A pregabalin dosage of 450 mg/day is efficacious in the prevention of relapse. There is at present no published direct comparison with an SSRI. The current known adverse effect profile and studies in healthy volunteers together suggest that pregabalin may have some tolerability advantages over benzodiazepines and venlafaxine, at least in short-term treatment.

Keywords: generalized anxiety disorder, efficacy, tolerability, pregabalin

GAD: clinical features, epidemiology and presumed neuropsychobiology

Generalized anxiety disorder (GAD) is characterized by excessive and inappropriate worrying that persists (lasting 6 months or more) and is not restricted to particular circumstances. DSM-IV-TR diagnostic criteria for GAD (APA 2000) require that anxiety and worry are accompanied by at least 3 of 6 key symptoms (restlessness, fatigue, difficulty concentrating, irritability, muscle tension, and disturbed sleep). ICD-10 research diagnostic criteria give greater prominence to the presence of somatic complaints, and at least one symptom of 'autonomic arousal' is essential for diagnosis (WHO 1994).

However defined, GAD is certainly common: for example, a recent review of epidemiological studies in Europe reported 12-month and lifetime prevalence estimates of 1.5% and 5.1%, respectively (Lieb et al 2005). It is among the most common mental disorders in primary care, and is associated with increased use of health services; but is often not recognised, possibly because only a minority present with anxiety symptoms (Ormel et al 1990). Patients with significant co-existing depressive symptoms have a more severe and persistent course of illness and greater associated functional impairment (Kessler et al 1999), but a greater chance of being recognized as having mental health problems (Wittchen et al 2002).

GAD has an uncertain neuropsychobiology. Genetic studies suggest that GAD and major depression have a common genetic basis, and that environmental factors

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influence their manifestation (Kendler et al 1992). Changes in serotonin (5-hydroxytryptamine, 5-HT), noradrenaline, and gamma amino butyric acid (GABA) are probably important in the treatment response, and disturbances in these neurotransmitters may underpin the pathophysiology of the untreated condition. For example, administration of m-CPP (a non-specific $5HT_1$ and $5HT_2$ agonist) has been found to increase anxiety (Germine et al 1992); blunting of the growth hormone response to clonidine (an alpha-2 adrenoceptor agonist) suggests decreased alpha-2 adrenergic receptor sensitivity (Abelson et al 1991); and imaging studies demonstrate decreased binding of a radiotracer ligand for $GABA_A$ receptors in the left temporal pole (Tiihonen et al 1997). Patients show a specific "cognitive bias" with increased attention to threat-related information and misinterpretation of ambiguous stimuli as threatening, and this bias has been shown to diminish with cognitive-behaviour therapy (CBT) and after selective serotonin reuptake inhibitor (SSRI) treatment (Mogg et al 1995, 2004).

Current treatment approaches in GAD

In acute treatment, systematic reviews and randomized placebo-controlled trials indicate that CBT, some SSRIs (escitalopram, paroxetine, and sertraline), some serotonin-noradrenaline reuptake inhibitors (SNRIs) (duloxetine and venlafaxine), some benzodiazepines (alprazolam and diazepam), the $5\text{-}HT_{1A}$ partial agonist buspirone, the antipsychotic trifluoperazine, and the antihistamine hydroxyzine are all efficacious (Baldwin et al 2005). Most comparator-controlled studies reveal no differences in efficacy between active compounds (Mitte 2005), although escitalopram appeared superior to paroxetine on some outcome measures in a recent large multi-centre placebo controlled study (Baldwin et al 2006), and psychological symptoms of anxiety are traditionally thought to respond better to antidepressant drugs than to benzodiazepines (Baldwin and Polkinghorn 2005).

In longer-term treatment, some randomized controlled trials indicate that continuing an SSRI or SNRI is associated with an increase in overall response rates, up to 24 weeks (Montgomery et al 2002; Bielski et al 2004); and placebo-controlled relapse prevention studies reveal an advantage for staying on SSRI treatment, after initial response, for up to 6 months (Stocchi et al 2003; Allgulander et al 2006). The comparative efficacy of psychological and pharmacological treatments is currently uncertain, as is the advantage or otherwise of combining them together, compared with either treatment, when given alone. Little is known about the management of patients with GAD who do not respond to first-line treatment, although the second-generation antipsychotic drugs olanzapine and risperidone have both been found efficacious, in small placebo-controlled SSRI augmentation studies (Brawman-Mintzer et al 2005; Pollack et al 2005).

There is still much room for improvement in the treatment of GAD, as the availability of CBT is restricted and the "ideal" anxiolytic drug does not yet exist (see Table 1). For example, SSRIs and the SNRI venlafaxine have proven efficacy in acute and long-term treatment of GAD, but treatment-emergent adverse effects such as sexual dysfunction are common, and discontinuation symptoms can be troublesome with paroxetine and venlafaxine. Benzodiazepines may promptly reduce symptom severity, but their limited efficacy in treating depressive symptoms and associated risks such as drowsiness and the development of dependence in predisposed individuals lead to recommendations that they are restricted to patients who have not responded to other approaches (Bandelow et al 2002; Baldwin et al 2005).

Pregabalin – summary of pharmacological properties

The mechanism of action of pregabalin (the s-enantiomer of 3-isobutylgaba) is thought to be different to that of all other known anxiolytic drugs. Although a structural analog of the inhibitory neurotransmitter gamma amino butyric acid (GABA), it has no clinically significant effects at $GABA_A$ or $GABA_B$ receptors, and is not converted into either GABA

Table 1 Properties of the "ideal" anxiolytic drug

Effectiveness considerations	Acceptability considerations
Effective across full range of anxiety disorders	Once-daily dosage
Effective across the spectrum of symptom severity	Minimal adverse effects
Effective across age range	Minimal interference with everyday life
Effective in achieving remission in acute treatment	No development of tolerance
Effective in preventing relapse of symptoms	No withdrawal symptoms
Rapid onset of action	Suitable in physically ill patients
Effective in treating co-existing depression	Free from interactions
Cost-effective	Safe in overdose

or a GABA agonist. It does not act as an antagonist at glutamate receptors and has no effects on reuptake of 5-HT (Kavoussi 2006). Instead, it binds in a state-dependent manner to the alpha-2-delta sub-unit of voltage-gated calcium channels of "over-excited" pre-synaptic neurones, thereby changing the conformation of the channel and reducing the release of excitatory neurotransmitters such as glutamate and substance P: the consequent reduced stimulation of post-synaptic neurones is thought responsible for its anxiolytic, anticonvulsant, and analgesic effects (Stahl 2004). This proposed mechanism of action is supported by the findings of pre-clinical studies in animal models, which indicate that binding to alpha-2-delta receptors is needed for pregabalin to exert its anxiolytic-like effects (Taylor 2004).

Absorption of pregabalin in the fasting state is rapid, peak plasma levels occurring within an hour of single or multiple dosing, steady-state levels being achieved after 24–48 hours; when given with food, absorption is slower but its extent is unchanged. It does not bind to plasma proteins, and being highly lipophilic, readily crosses the "blood–brain barrier". Elimination is primarily (92%) through renal excretion of the parent compound, and dosage therefore needs to be reduced in patients with renal impairment (Randinitis et al 2003). The UK Summary of Product Characteristics (SPC) for pregabalin (May 2006) states that dosage in patients with compromised renal function must be individualized according to measured creatinine clearance. Pregabalin has no active metabolites, does not inhibit or induce cytochrome (CYP) P450 enzymes, and its pharmacokinetic properties are not altered by CYP-enzyme inhibitors.

Efficacy of pregabalin in short-term and long-term treatment of GAD

The potential efficacy of pregabalin in DSM-IV defined GAD was examined through a program of 7 multi-center, parallel-group, randomized, placebo-controlled trials (see Table 2). Three initial 4-arm fixed-dose 5-week studies (comparing pregabalin 150 mg/day or 600 mg/day, lorazepam 6 mg/day, vs placebo) produced mixed results on the primary outcome measure, namely change from baseline to study end-point in mean total score on the Hamilton Rating Scale for Anxiety (HAM-A) (Hamilton 1959). In one study (Pande et al 2003) (n=276), the intention-to-treat, last-observation-carried-forward analysis (ITT, LOCF) indicated that both doses of pregabalin and lorazepam were superior to placebo, the change in HAMA score being –9.2 ($p<0.05$) and –10.3 ($p<0.01$) with pregabalin 150 mg/day and 600 mg/day, respectively, and –12.0 with lorazepam ($p<0.001$), compared with –6.8 with placebo. In a second study (Pande et al 2000), neither pregabalin nor lorazepam were significantly superior to placebo. In the third (Feltner et al 2003) (n=271), both pregabalin 600 mg/day ($p<0.01$) and lorazepam ($p<0.05$) were superior to placebo, whereas pregabalin 150 mg/day was not, the change in HAMA scores being –13.2 (pregabalin 600 mg/day) and –11.6 (lorazepam), compared with –9.3 with placebo.

The two positive studies are supported by the findings of 2 further multi-center, parallel-group, randomized, placebo-controlled trials, in which the efficacy of fixed doses of pregabalin was compared with that of alprazolam or venlafaxine (immediate-release formulation). The first (Rickels et al 2005) (n=454) compared 3 fixed-doses of pregabalin (300 mg, 450 mg, or 600 mg, per day) and alprazolam 1.5 mg/day with placebo, with significantly greater reductions on the same primary outcome measure for all four "active" arms: –12.3 with pregabalin 300 mg/day ($p<0.0005$ vs placebo), –11.0 with 450 mg/day ($p<0.05$), –11.8 with 600 mg/day ($p<0.005$), and –10.9 with alprazolam ($p<0.05$), compared with –8.4 with placebo. In the second (Montgomery et al 2006) (n=421), 2 doses of pregabalin (400 mg/day and 600 mg/day) and venlafaxine (in its immediate release formulation) 75 mg/day were all significantly superior to placebo (change in HAMA score from baseline to study end-point: pregabalin 400 mg/day, –14.7; 600 mg/day, –14.1; venlafaxine, –14.1; placebo, –11.6). An additional fixed-dose study, without an active comparator (Pohl et al 2005) (n=341), demonstrated that 3 differing daily dosages of pregabalin (200 mg/day [bid], 400 mg/day [bid], and 450 mg/day [tid]) had similar efficacy, compared with placebo, the change in HAMA score being –9.3 with placebo, and –12.4, –12.9, and –12.4 with pregabalin 200 mg/day, 400 mg/day, and 450 mg/day, respectively.

A single multi-center, parallel-group, flexible-dose, randomized, placebo-controlled study in elderly patients (65 years or older, n=273) has been performed (Khan et al 2006). At study endpoint, pregabalin (mean maximal dose 270 mg/day) was significantly superior ($p<0.05$) to placebo, the change in mean HAMA score from baseline to endpoint being –12.8 and –10.7, respectively.

The single 6-month relapse-prevention study of pregabalin (Smith et al 2002) (n=338), in which patients

Table 2 Randomized controlled trials of pregabalin in acute treatment of GAD

Study	Treatments	N	Change in HAMA (LOCF, ITT)	Response[a] (%) (LOCF, ITT)
Pande et al 2003	Placebo	69	–6.82	28
	Pregabalin 150 mg/day	69	–9.24*	Not stated. (NS)
	Pregabalin 600 mg/day	70	–10.25**	47*
	Lorazepam 6 mg/day	68	–11.96***	57*
Pande et al 2000	Placebo		No significant difference in efficacy for any treatment versus placebo	
	Pregabalin 150 mg/day			
	Pregabalin 600 mg/day			
	Lorazepam 6 mg/day			
Feltner et al 2003	Placebo	67	–9.27	42.4
	Pregabalin 150 mg/day	70	–10.89	47.8
	Pregabalin 600 mg/day	66	–13.17**	49.2
	Lorazepam 6 mg/day	68	–11.62*	56.3
Rickels et al 2005	Placebo	91	–8.4	31
	Pregabalin 300 mg/day	91	–12.2***	61***
	Pregabalin 450 mg/day	90	–11.0*	44
	Pregabalin 600 mg/day	89	–11.8**	51**
	Alprazolam 1.5 mg/day	93	–10.9*	45*
Montgomery et al 2006	Placebo	101	–11.6	42
	Pregabalin 400 mg/day	97	–14.7**	56*
	Pregabalin 600 mg/day	110	–14.1*	59*
	Venlafaxine 75 mg/day	113	–14.1*	61**
Pohl et al 2005	Placebo	86	–9.3	34
	Pregabalin 200 mg/day	78	–12.4**	56**
	Pregabalin 400 mg/day	89	–12.9***	55**
	Pregabalin 450 mg/day	88	–12.4**	59**
Khan et al 2006 (elderly patients)	Placebo	96	–10.7	Not reported
	Pregabalin 150–600 mg/day (mean maximal 270 mg/day)	177	–12.8 *	

[a]Response defined as Clinical Global Impression of Improvement score of 1 ("very much improved") or 2 ("'much improved").
*p<0.05, **p<0.01, ***p<0.001, all vs placebo. NS not significant.
Abbreviations: HAMA, Hamilton Rating Scale for Anxiety; ITT-LOCF Intention-to-treat, last-observation-carried forward.

who had responded to 8 weeks of open-label treatment were randomly allocated to either continue with pregabalin 450 mg/day or to switch to then continue with placebo, demonstrates that it was superior to placebo ($p<0.0001$) in preventing a relapse of anxiety symptoms.

To summarize, 5 out of 6 fixed-dose studies of pregabalin in the acute treatment of GAD demonstrate that a range of daily doses (150 mg, 300 mg, 400 mg, 450 mg, and 600 mg) can be efficacious. The maximum significant difference between pregabalin (300 mg/day) and placebo on the primary outcome measure (HAMA) of 3.9 (Rickels et al 2005) is certainly clinically relevant, as is the difference of 3.9 with 600 mg/day (Feltner et al 2003), but in some of the other studies, the differences between pregabalin and placebo have uncertain relevance. There is no clear evidence of a dose-response relationship, and no evidence that pregabalin is superior in efficacy to 2 commonly used benzodiazepines. No comparison of pregabalin with an SSRI appears to have been undertaken, and there is as yet no evidence of maintenance of effect of pregabalin over periods longer than 6 weeks, other than in the relapse-prevention study.

Tolerability of pregabalin

The UK SPC for pregabalin states that it was well tolerated in clinically relevant doses in conventional safety studies in animals. An increased incidence of retinal atrophy commonly observed in aged albino rats was seen after long-term exposure to doses 5 or more times greater than the mean human exposure at the maximum recommended dose. Similarly, the increased incidence of haemangiosarcoma in mice subject to higher exposures is thought to derive from platelet changes (and associated endothelial cell proliferation) that are not present in rats or in humans, based on short-term and limited long-term clinical data.

Pooled analysis of tolerability data from the six acute efficacy studies in younger patients suggests that pregabalin is generally well tolerated (Kavoussi 2006). The most

frequently reported adverse events were dizziness (30%, vs 8% for placebo) and somnolence (29%, vs 11% for placebo). Both are described as "very common" (i.e., occurring in more than 1 in 10 patients in the UK SPC for pregabalin), but in the clinical trial database it was uncommon for patients to stop double-blind treatment because of these adverse events (dizziness: pregabalin 3%, somnolence: pregabalin 4%). Across the dose range, study patients dropped out of treatment with pregabalin or placebo in similar proportions (11% and 9%, respectively), less so than with the active comparators (alprazolam 1.5 mg/day, 13%; venlafaxine 75 mg/day, 20%; lorazepam 6 mg/day, 35%). Similar findings are seen in the single study in the elderly (Khan et al 2006), in which 10.7% and 9.4% of patients dropped out due to adverse events with pregabalin and placebo, respectively.

In the clinical trial database, pregabalin treatment was not associated with clinically significant effects on heart or respiratory rate, blood pressure, or changes on the ECG. Weight gain of clinical significance (≥7% increase from baseline) was more frequent (4%) than with placebo (1.4%). Overdoses of pregabalin in approximately 100 patients were not associated with unexpected adverse events or medically important consequences.

Concerns regarding use of benzodiazepines in the treatment of patients with anxiety disorders have focused on their deleterious effects on psychomotor function, the risk of tolerance during long-term use, and the possibility of distressing withdrawal symptoms after stopping treatment. Potential similar concerns regarding pregabalin have been addressed, to some extent.

Short-term (3-day) placebo-controlled studies of the effect of pregabalin on cognitive and psychomotor function in healthy volunteers (n=24) indicate that unlike the comparator alprazolam (3 mg/day), pregabalin (450 mg/day) was not associated with significant impairments in performance in the Hicks Choice Reaction Time Test, the Sternberg Memory Correct Response Test, or the Brake Reaction Time Test (Hindmarch et al 2002). The UK SPC for pregabalin advises that patients should not drive, operate complex machinery, or engage in other potentially hazardous activities until they know whether the medication affects their abilities to perform these tasks. A cross-over polysomnographic study, again in healthy volunteers, indicates that both pregabalin and alprazolam significantly increased total sleep time and sleep efficiency, compared with placebo, whereas the proportion of slow-wave (restorative) sleep was significantly increased with pregabalin, but reduced with alprazolam (Hindmarch et al 2005). No similar studies in clinical samples have been reported.

Although pre-clinical studies in animal models indicate that pregabalin has neither a benzodiazepine- or morphine-like discriminative stimulus, and is not self-administered in a sustained manner, some evidence of drug "likeability" was seen in human recreational drug abusers (Kavoussi 2006). The pooled database provides no evidence of the development of craving, misuse, or dependence; and an acute treatment study (Pande et al 2003) showed that significantly fewer withdrawal symptoms occurred after stopping pregabalin than did so after stopping lorazepam.

To summarize, analysis of the acute treatment study pooled database suggests that pregabalin is better tolerated than some other compounds known to be efficacious in the treatment of GAD, namely venlafaxine, alprazolam, and lorazepam. The comparative tolerability of pregabalin and an efficacious SSRI is not established. The findings of pre-clinical studies and investigations in non-abusing healthy volunteers provide some encouragement, but it is currently uncertain whether problems sometimes seen during longer-term treatment with benzodiazepines might also occur during prolonged treatment with pregabalin.

How close is pregabalin to the "ideal" anxiolytic drug?

When compared with other treatment approaches, pregabalin could in theory have certain relative advantages, relating to the speed of onset of efficacy, the breadth of efficacy, and the absence of particular adverse events seen during treatment with SSRIs or benzodiazepines. Possible disadvantages relate to the adverse effects and potential risks described previously, and to the uncertain efficacy of pregabalin in relieving depressive symptoms.

Although efficacious in acute treatment of GAD, a few weeks may pass before SSRIs are associated with a marked reduction in symptom severity, in contrast to the earlier onset of action of benzodiazepines. Analyses of the comparator-controlled studies involving alprazolam or venlafaxine indicate that pregabalin (across all doses) is associated with a significantly ($p<0.01$) greater reduction in symptom severity, when compared with placebo, after 1 week of double-blind treatment; this finding is similar to that with alprazolam, whereas it was seen with venlafaxine after only 2 weeks of treatment (Montgomery et al 2003).

Pregabalin is also significantly superior to placebo in relieving both the psychic and the somatic symptom clusters,

as shown through analysis of pooled data from the five "positive" acute efficacy studies (Lydiard et al 2003). This result is in contrast to the lack of efficacy of some benzodiazepines in relieving psychic symptoms, seen in some studies, and to the relative lack of efficacy of certain antidepressants in relieving somatic symptoms, seen in others. A third possible advantage relates to the lack of adverse events commonly seen during SSRI or venlafaxine treatment, such as the emergence of sexual dysfunction or worsened insomnia, but this strength can only be regarded as potential until a suitable head-to-head comparison with an SSRI has been performed.

A potential weakness of pregabalin relates to its uncertain efficacy in reducing depressive symptoms of more than mild intensity. Although it has been found significantly superior to placebo in reducing low levels of depressive symptom severity at baseline in some acute treatment studies (Pande et al 2003; Pohl et al 2005; Rickels et al 2005), some of this apparent effect may have been due to reduction in severity of anxiety and insomnia items included within the Hamilton Rating Scale for Depression (Hamilton 1960). Furthermore, patients with more severe depressive symptoms were excluded from the clinical trial program, and pregabalin has no demonstrated efficacy in major depression. Most GAD patients in more routine clinical samples have significant coexisting depressive symptoms, and recent evidence-based reviews and treatment guidelines (Baldwin and Polkinghorn 2005; Baldwin et al 2005) have recommended the use of antidepressants over non-antidepressant anxiolytics, in GAD patients with coexisting major depressive symptoms.

Conclusions

GAD is common in community and primary care settings, tends to run a chronic course, and is associated with significant occupational impairment. However, it is often not recognized, and even when treated many patients respond poorly or develop troublesome adverse effects. Pregabalin appears to have a novel mechanism of action, and proven efficacy in acute treatment and prevention of relapse. When compared with some existing pharmacological treatments, it may offer some advantages, for example, an earlier onset of clinical effect than that with venlafaxine, and efficacy across the range of psychological and somatic symptoms of anxiety. In addition, the existing clinical trial database indicates that pregabalin is rather better tolerated than venlafaxine, alprazolam, and lorazepam; and limited data suggest that the risk of the development of tolerance or dependence is likely to be lower than that with benzodiazepines.

It is not yet possible to make a definitive decision regarding the potential role of pregabalin in the overall management of patients with GAD. The absence of a placebo-controlled trial with an SSRI as active comparator is a major drawback, when considering the relative strengths and weaknesses of pregabalin compared with existing treatment approaches. Furthermore, as most patients in clinical settings have significant co-existing depressive symptoms, the relative efficacy of pregabalin and an SSRI or SNRI in treating patients with more than mild depressive symptoms needs to be established. Finally, the clinical trial database is too limited to permit more than tentative conclusions regarding long-term tolerability and patient acceptability.

Disclosures

DSB has acted as a consultant to a number of companies with an interest in anxiety and depressive disorders (Asahi, Cephalon, Eli Lilly, GlaxoSmithKline, Lundbeck, Organon, Pfizer, Pharmacia, Pierre Fabre, Roche, Servier, Sumitomo, Wyeth). He holds or has held research grants (on behalf of the University of Southampton) from a number of companies with an interest in anxiety and depressive disorders (Cephalon, Eli Lilly, GlaxoSmithKline, Lundbeck, Organon, Pfizer, Pharmacia, Roche, Wyeth). He has accepted paid speaking engagements in industry-supported satellite symposia at international and national meetings. KA has no interests to declare. Neither DSB nor KA hold shares in any pharmaceutical company. The opinions expressed in this article are those of the authors alone, and should not be construed as representing those of any other person or organization.

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