Pregabalin for the treatment of generalized anxiety disorder: an update

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Abstract: A previous review summarized what was then known about the potential role of pregabalin in the treatment of patients with generalized anxiety disorder (GAD): this review provides an update on its pharmacological properties and presumed mechanism of action, the liability for abuse, and efficacy and tolerability in patients with GAD. Pregabalin has a similar molecular structure to the inhibitory neurotransmitter gamma amino butyric acid (GABA) but its mechanism of action does not appear to be mediated through effects on GABA. Instead, its anxiolytic effects may arise through high-affinity binding to the alpha-2-delta sub-unit of the P/Q type voltage-gated calcium channel in “over-excited” presynaptic neurons, thereby reducing the release of excitatory neurotransmitters such as glutamate. The findings of randomized controlled trials and meta-analyses together indicate that pregabalin is efficacious in both acute treatment and relapse prevention in GAD, with some evidence of an early onset of effect, and broad efficacy in reducing the severity of psychological and physical symptoms of anxiety. It also has efficacy as an augmenting agent after non-response to antidepressant treatment in GAD. Continuing vigilance is needed in assessing its potential abuse liability but the tolerability profile of pregabalin may confer some advantages over other pharmacological treatments in the short term for treatment in patients with GAD.

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Clinical features and epidemiology of generalized anxiety disorder

Generalized anxiety disorder (GAD) is characterized by excessive and inappropriate worrying that is persistent (lasting more than a few months) and not restricted to particular circumstances. Patients have physical anxiety symptoms and key psychological symptoms, including restlessness, difficulty concentrating, irritability, muscle tension, and disturbed sleep. Patients with GAD have the same concerns about health, family, relationships, work, and finances as non-anxious controls but have a greater number of worries over minor matters. However, most patients present with other symptoms; many complain of poor sleep and difficulty in relaxation, but recurrent headaches and various aches and pains are also common. Some patients present repeatedly to health professionals, with pressing but long-standing physical symptoms that prove to be “medically unexplained”.

GAD is common in community and clinical settings. A review of the findings of epidemiological studies in Europe suggests a 12-month prevalence of 1.7%–3.4%, and a lifetime prevalence of around 4.3%–5.9%. It is probably the most common anxiety disorder among the elderly population. GAD is usually regarded as a chronic illness,
which fluctuates in severity over time. It typically emerges gradually\(^4\) and the onset of the full syndromal disorder is later than in other anxiety disorders. Outcome studies in community samples suggest a reasonable prognosis; for example, a 22-year follow-up study of individuals meeting criteria for GAD found that less than 20% had persistent GAD.\(^5\) However, longitudinal studies in treatment-seeking patients generally suggest a prolonged and fluctuating course of illness.\(^6\)

GAD is one of the more common mental disorders seen in primary medical care, and is associated with increased use of health services.\(^7\) Comorbidity with major depression or other anxiety disorders is exceedingly common.\(^1\) GAD and major depression have a similar degree of functional impairment\(^8,9\) but patients with comorbid major depression and GAD have a more severe and prolonged course of illness and greater impairment.\(^10\) GAD is also common among patients with “medically unexplained” chronic pain,\(^11\) chronic physical ill-health,\(^12\) and excessive worrying, and GAD may worsen the outcome of cardiovascular disease.\(^13\)

**Presumed neuropsychobiology of generalized anxiety disorder**

GAD in adult life is associated with an excess of traumatic experiences and undesirable life events during childhood.\(^14\) Like other anxiety disorders, GAD is associated with behavioral inhibition in childhood, which is the tendency to be timid or shy in novel situations.\(^15\) GAD shares a common heritability with major depression\(^16\) and with the personality trait of “neuroticism”.\(^17,18\) The 5-hydroxytryptamine (5-HT; serotonin) transporter gene-linked polymorphic region short/short genotype is more frequent in patients with GAD,\(^19\) and variations in two sub-types of the glutamic acid decarboxylase gene may increase the susceptibility to anxiety disorders, including GAD.\(^20,21\) However, investigations of potential disturbances in the principal neurotransmitters noradrenaline (norepinephrine), 5-HT, and gamma aminobutyric acid (GABA) in GAD have tended to produce either inconsistent or unreplicated findings.

Hyperventilation is a well-known component of the bodily response to perceived danger, possibly because exhalation of carbon dioxide (CO\(_2\)) induces a respiratory alkalosis which may partly compensate for a metabolic acidosis arising from rising levels of lactate due to increased physical activity. Rebreathing air enriched with 35% CO\(_2\) does not induce panic attacks in patients with GAD\(^22\) nor does intravenous infusion of sodium lactate,\(^23\) contrary to the effects of these challenges in panic disorder. However, inhaling air enriched with 7.5% CO\(_2\) increases subjective and autonomic symptoms both in healthy volunteers and in patients with GAD.\(^24\) Some treatments that have been found efficacious in GAD (for example paroxetine and lorazepam) can reduce the emergence of anxiety following CO\(_2\) inhalation,\(^25\) though not all evidence is consistent.\(^26\)

A series of investigations has shown that individuals with GAD scan the environment for cues suggesting threat;\(^27\) develop worrying in an attempt to solve problems;\(^28\) may use worrying to avoid physical symptoms of anxiety;\(^29\) find it hard to tolerate uncertainty or ambiguity;\(^30\) and “worry about worrying”;\(^31\) A functional MRI study found evidence of increased anticipatory activity in the dorsal amygdala after cues indicating forthcoming aversive and neutral pictures, suggesting an “overall enhanced anticipatory emotional responsiveness in GAD” (that is, preparing for difficult challenges ahead).\(^32\) Investigations of the processing of emotional information suggest that GAD is associated with specific biases for mood-congruent information.\(^33\) Patients with GAD seem prepared to attend to threatening stimuli, and detect threats rapidly and effectively,\(^34\) but also tend to misinterpret ambiguous information as being indicative of threat.\(^35\) Intriguingly, these cognitive biases reduce with successful psychological or pharmacological treatment.\(^36,37\)

**Current pharmacological treatments for generalized anxiety disorder**

The findings of systematic reviews\(^38,39\) and the results of randomized placebo-controlled trials of acute treatment of patients with GAD together provide substantial evidence for the efficacy of many antidepressant drugs, including most selective serotonin reuptake inhibitors (SSRI; citalopram, escitalopram, paroxetine, and sertraline) and the serotonin-norepinephrine reuptake inhibitors (SNRI; duloxetine and venlafaxine) and also for imipramine, trazodone, and agomelatine.\(^40\) Other compounds with efficacy in placebo-controlled acute treatment studies include some benzodiazepines (alprazolam, diazepam, and lorazepam),\(^41\) buspirone,\(^42\) some antipsychotic drugs (quetiapine and trifluoperazine)\(^43\) and the antihistamine hydroxyzine.\(^44\) Beta-blockers are often used in primary medical care settings to manage physical symptoms of anxiety but placebo-controlled evidence of efficacy in acute treatment of patients with GAD is minimal.\(^45\) The findings of randomized placebo-controlled relapse-prevention studies in patients who have previously responded to acute treatment of varying lengths reveal a significant advantage for staying on active medication (including agomelatine, duloxetine, escitalopram, paroxetine, quetiapine, venlafaxine, and vortioxetine), when
compared to switching to placebo, for periods of between 6–18 months.\textsuperscript{46}

In Europe and the US, pregabalin is licensed for the treatment of peripheral and central neuropathic pain, and as an adjunctive therapy in patients with focal epileptic seizures with or without secondary generalization. In the US, pregabalin is also licensed for the treatment of fibromyalgia, whereas in Europe there is no license for fibromyalgia but it is licensed for the treatment of GAD, reflecting its proven efficacy in short-term and long-term treatment.

**Preclinical properties and presumed mechanism underlying the anxiolytic effects of pregabalin**

Since the previous review,\textsuperscript{47} there have been considerable advances in the understanding of the presumed mechanism of action of pregabalin underlying its anxiolytic effects. Pregabalin is a branched chain amino acid, similar in structure to leucine and GABA. However, it does not appear to bind to the GABA receptor, or to any binding site allosterically linked to GABA, or to the GABA transporter, or to enzymes involved in the synthetic or metabolic pathways of GABA.\textsuperscript{48}

It is absorbed rapidly after oral administration and achieves maximal plasma concentrations within 1-hour: absorption is dependent upon active transport with the L-type amino acid transporter 1 (LAT1) and is linear with proportional increases in plasma levels across the dose range.\textsuperscript{49}

Pregabalin shows high affinity binding to the Type 1 and Type 2 proteins of the $\alpha_2\delta$ subunit of the P/Q type of voltage-gated calcium channel. These channels consist of four protein subunits: the $\alpha_2\delta$ subunit comprises a $\delta$ protein which anchors the subunit to the plasma membrane, linked by a disulphide bond to the $\alpha_2$ protein which contains the pregabalin binding site. The $\alpha_2\delta$ subunit is a glycosylphosphatidylinositol (GPI)-anchored protein\textsuperscript{50} linked to a lipid raft membrane microdomain which appears sensitive to the physiological state of the cell.\textsuperscript{51}

Standardized receptor-binding assays have shown that pregabalin has no significant binding to a wide range of receptor sites; conversely, a broad range of anxiolytics and antidepressant drugs have no affinity for the $\alpha_2\delta$-1 or $\alpha_2\delta$-2 calcium channel subunits.\textsuperscript{52} Autoradiography and immunostaining studies indicate that pregabalin is mainly bound to $\alpha_2\delta$-1 subunits in the cortex, olfactory bulb, hypothalamus, amygdala, and hippocampus, but to $\alpha_2\delta$-2 subunits in the cerebellum.\textsuperscript{53,54}

As with other anxiolytic drugs, administration of pregabalin has been shown to attenuate the activation of the left anterior insula and left amygdala in response to emotionally charged visual stimuli in healthy volunteers.\textsuperscript{55} Pregabalin is also efficacious in the treatment of patients with GAD,\textsuperscript{56} and social anxiety disorder.\textsuperscript{57} These anxiolytic effects of pregabalin are presumed to be mediated through its actions on the $\alpha_2\delta$-1 subunit, which leads to reductions in the availability and effects of excitatory neurotransmitters, including glutamate. High-affinity $\alpha_2\delta$ ligands exert potent effects in animal models of anxiety;\textsuperscript{58} pregabalin has no anxiolytic-like effects in transgenic mice with specific point mutations in the voltage-gated calcium channel $\alpha_2\delta$ Type 1 protein, whereas anxiolytic-like effects are preserved in mice with a point mutation in the $\alpha_2\delta$-2 protein.\textsuperscript{59}

A range of studies have indicated that through its effects on calcium channels, pregabalin administration reduces the release of glutamate;\textsuperscript{60} furthermore, pregabalin administration may reduce the synthesis of excitatory synapses\textsuperscript{60} and may block the trafficking of new voltage-gated calcium channels to the cell surface.\textsuperscript{61}

**Evidence base for pregabalin in the treatment of GAD**

Our previous review noted that it was not possible to make definitive statements about the potential role of pregabalin in the overall management of patients with GAD as no placebo-controlled trial with an SSRI as active comparator had been published, the effect of pregabalin on depressive symptoms in patients with GAD was not established, little was known about its longterm tolerability and patient acceptability, and no data was available regarding its use as a second-line treatment in patients who had not responded to previous interventions.\textsuperscript{47}

The randomized double-blind placebo-controlled evidence base supporting the use of pregabalin in GAD has steadily expanded, and currently comprises six short term (4–6 week) fixed-dose studies;\textsuperscript{62–67} two short-term (8-week) flexible-dose studies, one in elderly patients,\textsuperscript{68} the other in younger patients;\textsuperscript{69} a single long-term (6-month) fixed dose relapse prevention study;\textsuperscript{70} and a short-term (8-week) flexible-dose study in patients who had not responded to previous treatment with either an SSRI or SNRI antidepressant (Table 1).\textsuperscript{71}

Taken together, these studies demonstrate that pregabalin is efficacious in both acute treatment and relapse prevention. Its relative efficacy in acute treatment when compared to other medications is not firmly established, though an analysis of randomized controlled trials which found an overall mean effect size of 0.39, also found some differences between medication class: pregabalin, 0.50; SNRI, 0.42;
The relative efficacy of pregabalin and antidepressant drugs in preventing relapse in patients with GAD, when compared to antidepressant drugs, is uncertain. There have been few studies of the further management of patients with GAD who had not responded to first-line interventions. The findings of small randomized placebo-controlled augmentation studies suggest that augmentation of antidepressants with antipsychotic drugs (olanzapine, quetiapine, and risperidone) may be beneficial, though the evidence for quetiapine augmentation is inconsistent and uncertain for ziprasidone augmentation. However, the findings of a recent large randomized placebo-controlled augmentation study demonstrate that the addition of pregabalin to SSRI or SNRI antidepressant drugs is superior to continued treatment with antidepressants alone.

**Onset of effect and dose-response relationships**

An early onset of effect in reducing anxiety symptoms is considered beneficial in treating patients with anxiety disorders, but the findings of randomized controlled trials tend to indicate that a few weeks pass before antidepressants are superior to placebo. Pregabalin has been found superior to placebo in reducing anxiety in patients prior to undergoing dental or orthopedic procedures, with an onset of effect within a few hours. In GAD, an assessment of the potential early efficacy of pregabalin has not been reported, although a large, placebo-controlled, flexible-dose trial which included...
an assessment of efficacy at day 4 of treatment found that pregabalin was superior to both venlafaxine XL and placebo at day 4.40

For many medications, it is uncertain how long treatment should continue in the absence of signs of improvement, before concluding that a response is unlikely. However, the findings of post hoc analyses of data from randomized double-blind placebo-controlled studies with duloxetine41 and escitalopram42 suggest that response is unlikely if there is no onset of clinical effect within 4 weeks of starting treatment. A post hoc analysis of randomized controlled trial data with pregabalin indicates that an onset of overall clinical effect within the first 2 weeks is associated with a 5.3-fold odds ratio of responding to treatment, whereas only one quarter of patients who show no onset of clinical effect by the second week will have responded to treatment at study endpoint.83

Dose-response relationships for antidepressants in the treatment of patients with GAD are not established, and for pregabalin, the evidence is mixed. Meta-analysis of the findings from randomized controlled trials found no evidence for a dose-response curve for daily dosages between 200–600 mg, although a 150 mg daily dosage was associated with a slower onset of efficacy.84 However, a dose-response effect was observed when comparing the lowest dose (150 mg/d) to the 200–600 mg dosing range. For the 150 mg/d dose of pregabalin, there was a somewhat lower short-term improvement in both the Hamilton Rating Scale for Anxiety (HAM-A)85 total score, and in the HAM-A sleep item.84 A post hoc analysis of the effects of pregabalin in reducing severity of psychological and physical anxiety symptoms indicates a 150 mg daily dosage may be suboptimal, whereas no dose-response effect was observed within a daily dosage range of between 300–600 mg.36

**Effects of pregabalin in reducing depressive symptoms, somatic symptoms, and sleep disturbance**

Coexisting depressive symptoms and comorbid depressive disorders are common in patients with a primary diagnosis of GAD. Many clinicians choose an antidepressant when treating patients with comorbid conditions, hoping that a single medication will prove effective in reducing both anxiety and depressive symptom severity. In the clinical trial program with pregabalin patients in which those with severe depressive symptoms were excluded from participation, but those with depressive symptoms of mild or moderate intensity were potentially suitable, a post hoc analysis in the subgroup of patients with more severe depressive symptoms (HAM-D ≥15) found that pregabalin treatment was effective in reducing depressive symptoms, across the dosing range of 150–600 mg.87 Furthermore, findings from the flexible-dose comparison of pregabalin (300–600 mg/day) and venlafaxine-XL (75–225 mg/day) indicate that pregabalin treatment was associated with a significantly greater reduction in HAM-D total score, when compared to placebo (P = 0.018).89

Pain and somatic symptoms, some of which can seem “medically unexplained”, are common complaints among patients with GAD, and are often the reasons leading to medical consultation. Pregabalin is licensed for the treatment of neuropathic pain and fibromyalgia, itself characterized by often perplexing somatic symptoms, and a post hoc analysis of clinical trial data has found that it is effective in reducing the severity of cardiovascular, respiratory, muscular, and gastrointestinal symptoms in GAD.86 Many patients with GAD are also troubled by persistent insomnia and other forms of sleep disturbance. In a pooled analysis of the clinical trial database with pregabalin, in which 54% of patients reported moderate-to-severe insomnia at baseline, treatment with pregabalin was associated with a significant reduction in sleep disturbance, across the dosing range of 300–600 mg/day.88 Pregabalin was found superior to both placebo and venlafaxine XL in reducing sleep disturbance within the context of a double-blind flexible-dose study89,90 in younger patients and treatment with pregabalin was associated with a significant improvement in sleep in elderly patients.89

**Tolerability and safety of pregabalin**

In our previous review47 we noted that the increased incidence of hemangioma seen in mice subject to higher exposures to pregabalin was thought to derive from platelet changes (and associated endothelial cell proliferation) that are not present in rats or in humans. Further analysis of genotoxicity, tumor incidence and tumor genetics indicates that pregabalin can act as a single-species (mice), single tumor-type (hemangiosarcoma) non-genotoxic carcinogen.91 Knowledge of the mechanism of hemangioma induction has increased, and it is now thought that increased bicarbonate, and dysregulated erythropoiesis, macrophage activation, and increased angiogenic growth factors may all be important.91 Pregabalin appears to induce hypoxia and endothelial cell proliferation in a species-specific manner, but these effects can be inhibited by vitamin E, presumably due to its antioxidant and antiangiogenic properties.92 Based on an extensive dataset, a recent review concluded that the findings...
seen in mice are not relevant to humans at the clinical dose of pregabalin, and that use of pregabalin does not pose an increased risk for hemangiosarcoma in humans.93

The findings of randomized controlled trials indicate that treatment with pregabalin is generally well-tolerated, across the daily dosing range of 150–600 mg. In the clinical trial database the majority of adverse events were recorded as being mild-to-moderate in severity, though dizziness and somnolence were rated as “severe” by more than 2% of patients. A similar proportion of patients withdrew from further participation due to an adverse event (pregabalin 11.3%; placebo 9.3%).94 Most adverse events have an onset in the first week of treatment, and tend to have remitted within 3 weeks. Little is known about the relative tolerability of pregabalin when compared to other treatments; however, the adverse event profile of pregabalin differs to that of venlafaxine XL, pregabalin being associated with more prominent dizziness and vertigo, and venlafaxine XL with more prominent nausea,95 and a pooled analysis of studies that included a benzodiazepine indicates that treatment with pregabalin is more likely to be associated with dizziness, and benzodiazepine treatment more likely to be associated with somnolence and incoordination. The findings of a more recent mixed treatment comparison suggest that the tolerability of pregabalin in acute treatment is probably better than that of comparator medications.96

The potential for weight gain is a common concern among patients undergoing long-term treatment with antidepressant or anxiolytics drugs. In our earlier review we noted that weight gain of potential clinical significance (ie, more than 7% increase) was present in 4% of patients undergoing treatment with pregabalin, compared to 1.4% of those allocated to placebo. As a recent meta-analysis of the clinical trial database for pregabalin across four clinical areas (mental disorder, drug-resistant partial epilepsy, fibromyalgia, and neuropathic pain) indicates that the adverse event profile is similar in all four areas,97 it seems reasonable to examine changes in weight during pregabalin treatment for other conditions. In the clinical trial database of studies in post-herpetic neuralgia or neuropathic pain, weight gain was reported in 3.8%–7.0% of Western patients but 11.7%–13.4% of Japanese patients, perhaps due to their lower mean body weight;96 and in the clinical trial database for studies in fibromyalgia, weight gain was significantly more frequent with pregabalin (0.97%) than placebo (0.22%).97

Case reports have described the association of pregabalin treatment with the development of peripheral edema,98–101 peripheral edema and worsened hepatic function,102 and with peripheral edema and pleural effusion.103 However, other potentially causative factors were present in all patients. The exact incidence of edema in patients with GAD is uncertain, although it was significantly more frequent with pregabalin (5.9%) than with placebo (1.6%) in the fibromyalgia clinical trial database97 and occurs in a similar proportion of patients with fibromyalgia or neuropathic pain.95

In our previous review,97 we noted that overdoses of pregabalin in approximately 100 patients had not been associated with unexpected adverse events or medically important consequences. A subsequent case report described the development of complete but transient atrioventricular block following pregabalin overdose.104 However, a review of 42 cases of pregabalin overdose indicates that serious complications are unusual,105 and a case report has described full recovery with general supportive care only, after ingestion of 8.4 grams of pregabalin, which resulted in a serum level of 66.5 mg/L.106

Potential for abuse of and dependence on pregabalin

Our earlier review97 noted that while pre-clinical studies in animal models had indicated that pregabalin had neither a benzodiazepine- or morphine-like discriminative stimulus, and was not self-administered in a sustained manner, some evidence of drug “likeability” had been seen in human recreational drug abusers.107 However, pregabalin does not appear to increase the “likeability” of opiate analgesics.108 “Euphoria” was an adverse event in clinical trials among recreational drug abusers. However, evidence of drug “likeability” had been seen in human recreational drug abusers. Since entering widespread clinical use, reports of pregabalin abuse have appeared, often involving individuals with a history of abuse of other medications.109–113

Discontinuation symptoms were reported after abruptly stopping pregabalin within the randomized controlled trial program; these were more prominent after stopping higher daily doses,63,65 but there were significantly fewer withdrawal symptoms after stopping pregabalin than after stopping lorazepam.62 However, a number of case reports and case series suggest that pregabalin may be beneficial in facilitating withdrawal from benzodiazepines and related compounds.114–117 A switch study in which patients receiving long-term benzodiazepines were randomized to 12 weeks of double-blind treatment with either flexible-dose pregabalin or placebo while the dosage of benzodiazepines was tapered down, followed by a 6-week benzodiazepine-free phase, found that pregabalin was more beneficial (though not significantly
superior) than placebo in enabling patients to become benzodiazepine-free (51.4% versus 37%, respectively; $P = 0.284$). In addition, preclinical studies in animal models indicate that pregabalin reduces alcohol consumption and alcohol-seeking behavior, and reduces the severity of handling-induced seizures in mice withdrawing from alcohol. The evidence that pregabalin facilitates alcohol withdrawal symptoms and the maintenance of abstinence in detoxified patients is encouraging but inconsistent.

**Conclusion**

GAD is a common, distressing, and impairing medical condition that tends to run a chronic or episodic course. A broad range of psychological and pharmacological interventions are available, but many patients do not respond to first-line approaches, and many are troubled by side effects that can limit treatment adherence and increase the risk of relapse. Pregabalin is efficacious in acute treatment and in the prevention of relapse, has comparable efficacy to alternative medications including certain benzodiazepines and the SNRI venlafaxine, and may have tolerability advantages over some comparator treatments. It is efficacious in reducing the severity of psychological and physical symptoms of anxiety, in reducing sleep disturbance, and in reducing the severity of coexisting depressive symptoms, and is also efficacious as a second-line treatment, in patients who have not responded to initial treatment with SSRI or SNRI antidepressants. It has been recommended as a potential first-line treatment in patients with GAD and in psychiatric practice is commonly used both as a first-line treatment and as a second-line treatment either on its own or as an augmentation agent. Because of its beneficial effects in reducing sleep disturbance and somatic symptom severity, it has also been recommended as a first-line treatment for patients with GAD seen in primary care settings. There have been steady advances in understanding of its properties in animal models, and of the molecular and neuropsychological mechanisms thought to underlie its anxiolytic effects. As with all psychotropic medications, continuing vigilance is needed when assessing the potential for the development of tolerance, dependence, discontinuation symptoms, and abuse.

**Disclosure**

The authors report no conflicts of interest in this work.

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