

REVIEW

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Generalized Anxiety Disorder in Adults: Focus on Pregabalin

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Abstract: Generalized anxiety disorder (GAD) is a chronic illness which impacts significantly on an individual's functioning and quality of life. Pregabalin is a novel structural analogue of the inhibitory neurotransmitter GABA, acting to reduce calcium ion flow through the $\alpha_2\delta$ subunit of pre-synaptic voltage-dependent calcium channels. Pregabalin has been used in treatment of GAD in a total of eight published controlled trials. In each trial, pregabalin has demonstrated a superiority over placebo, with response rates of over 40% in all studies, including patients on lower doses. One study has provided preliminary evidence for the efficacy of pregabalin in treatment of GAD in older adults. Pregabalin is generally well tolerated, with the most common adverse events being dizziness and somnolence. Adverse effects are generally mild-to-moderate, and transient. Pregabalin has low abuse potential. Limitations of the current literature are discussed, and directions for future research are proposed.

Keywords: pregabalin, generalized anxiety disorder, anxiety disorder, anxiety, anxiolytics

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Introduction

Generalized anxiety disorder (GAD) is a psychiatric disorder characterised by clinically significant excesses in worry and anxiety. Worry is subjectively experienced as difficult to control, and is accompanied by a constellation of other anxiety symptoms such as restlessness, fatigability, concentration difficulties, irritability, excess muscle tension, and disturbances of sleep. The individual must experience the symptoms on more days than not, for a period of at least six months, and symptoms must cause clinically significant impairment in functioning.¹

GAD is a chronic illness² that impacts significantly on quality of life,³ life satisfaction, and subjective well-being.⁴ GAD leads to significant functional impairment⁵ and increased health service utilization.⁶ GAD affects approximately 6.2% of the population during their lives, and 2.6% in any one year.⁷

Research into GAD has increased over the past three decades, reflecting improvements in the understanding and treatment of the condition.⁸ Despite this, levels of relapse remain high, suggesting the need for further research into conceptualization and treatment of the condition.⁹

GAD as a diagnostic entity has experienced significant changes over the last three decades. Earlier diagnostic systems such as DSM-III specified that mood disorders and other anxiety disorders effectively 'trumped' GAD, meaning that a diagnosis of comorbid GAD was not made.¹⁰ The DSM-III-R permitted diagnosis of GAD as a comorbid condition when other anxiety or mood disorders were also present.¹¹ The current edition of the DSM places considerably greater importance in worry and anxiety that are excessive and uncontrollable as a hallmark diagnostic feature of the illness.¹ Additionally, the description of GAD in the World Health Organization International Classification of Diseases reflects a different conceptualisation of the disorder, in which excessive uncontrollable worry is not required, and some anxiety disorders such as panic disorder and OCD preclude a comorbid GAD diagnosis.^{12,13}

Several biological factors have been implicated in the pathology of GAD. Genetic factors are thought to play a role, and may also explain the observed comorbidity between GAD and mood disorders.¹⁴ Structures such as the locus ceruleus, the hypothalamic-pituitary-adrenocortical axis, as well

as neurotransmitters such as serotonin, noradrenaline, and γ -aminobutyric acid (GABA) have all been investigated in the pathology of GAD.^{15,16}

GABA is the primary inhibitory neurotransmitter in the central nervous system, acting to modulate the effects of other excitatory neurotransmitters such as serotonin, noradrenaline, acetylcholine, and glutamate. Over half of the synapses in the brain are modulated by GABA, and the GABA receptor complex has been the target of sedative/hypnotic agents such as barbiturates and benzodiazepines.^{17,18}

A range of pharmacological interventions have previously been used in the treatment of GAD, including benzodiazepines, antidepressants, buspirone, and hydroxyzine.^{19,20} Recently, the novel pharmacological agent pregabalin has also been investigated as an alternative drug treatment for GAD. This article briefly describes pregabalin, and then provides the reader with a review of the empirical research into its efficacy in the treatment of GAD. Limitations to the current corpus of research are highlighted, and avenues for future research are suggested.

Mechanism of Action, Metabolism, and Pharmacokinetic Profile

Mechanism of action

Pregabalin is a structural analogue of the inhibitory neurotransmitter GABA.²¹ Despite this, pregabalin does not bind with GABA_A or GABA_B receptor complexes, and so exerts no significant direct GABAergic effect. Pregabalin does not influence GABA reuptake or metabolism. The minimal metabolism undergone by pregabalin does not produce any active metabolites.¹²

In contrast to previous anxiolytic medications such as benzodiazepines, pregabalin does not bind with the post-synaptic GABA_A receptor complex, instead binding with the $\alpha_2\delta$ subunit of pre-synaptic voltage-dependent calcium channels.²²⁻²⁵ In binding with these calcium channels, pregabalin reduces flow of calcium through the ion channel, in turn reducing release of other stimulating neurotransmitters such as glutamate and noradrenaline into the synapse.^{21,25,26}

Pharmacokinetic profile

Metabolism of pregabalin in the body is minimal, with approximately 92% of the substance excreted renally in an unchanged state.²⁷ Metabolites are clinically inactive.²¹



Renal dysfunction can affect clearance of the drug, with the elimination of pregabalin being directly proportional to creatinine clearance rate.²⁸

Pregabalin does not bind to proteins in serum, and does not alter CYP450 functioning. Metabolism and elimination are not altered by drugs which inhibit CYP450 enzymes.²¹

After a single dose in a fasting state, pregabalin plasma levels reach a peak within 0.7 to 1.5 hours.^{21,27,29} When taken with food, peak plasma levels are delayed until 2.6 to 3 hours after administration.^{27,29}

Peak plasma concentration increases linearly with dose, with an oral bioavailability of over 90%.²⁹ When taken with food, peak concentration is reduced by approximately 31%. The half-life for a single dose is 4.6 to 6.8 hrs, while in multiple doses the compound's half-life is changed to 5.5 to 6.7 hours.²⁷ Over multiple doses, steady state plasma concentrations are reached in 1 to 2 days.²¹

Efficacy

A total of eight published studies were identified for use in the current review, through Pubmed searches with 'PREGABALIN AND (GAD OR ANXIETY)' as the search term. Of these, seven³⁰⁻³⁶ were double-blind, randomized controlled trials, and an eighth study³⁷ was a double-blind study of the efficacy of pregabalin in preventing relapse following an open label treatment phase. Table 1 presents a summary of each of the eight efficacy studies, including sample characteristics, treatment conditions, and efficacy outcome measures.

The treatment phases of these eight studies involved administration of pregabalin over four,^{27,30,32} six,^{33,34} or eight^{32,35,37} weeks. Most studies used a fixed dose method.^{27-30,37} One study used flexible dosing for six weeks, followed by a two week fixed dosing phase,³⁵ and one allowed flexible dosing for the entire treatment period.³⁶ Pregabalin doses across the eight studies ranged from 150 mg to 600 mg per day, administered in either two or three divided doses.

All seven RCTs were of high quality when evaluated against the Jadad scale³⁸ for quality of controlled trials. All had random allocation of patients, double-blind administration of the intervention, and clear reporting of withdrawals/dropouts broken down by treatment intervention group.

Reductions in anxiety symptoms

The first published randomized controlled trial of the use of pregabalin in treatment of GAD was published in March 2003 by Pande and colleagues.³¹ This double-blind study reported on a cohort of 276 adults with GAD who were treated over a four week period. Diagnosis of GAD was made by a psychiatrist using a diagnostic interview and the Mini International Neuropsychiatric Interview (MINI),³⁹ according to DSM-IV criteria.¹ Patients were randomly assigned to treatment with 50 mg tid pregabalin, 200 mg tid pregabalin, 2 mg tid lorazepam, or a placebo control condition. All patients began treatment with a score of at least 20 on the Hamilton Anxiety Rating Scale (HAM-A), and low levels of depressive symptoms. In addition, clients with comorbid Axis I or severe Axis II diagnoses or drug/alcohol problems were excluded. Patients in all active treatment conditions demonstrated greater reduction in anxiety symptoms, as measured by the HAM-A, than those in the placebo control condition, with a mean drop in HAM-A score of 9.24, 10.25, and 11.96 for the low-dose pregabalin, high-dose pregabalin, and lorazepam groups, respectively (see Figure 1). Significant reductions compared to placebo were also observed for the somatic anxiety and psychic anxiety subscales of the HAM-A.

The authors defined treatment responders as those who demonstrated a 50% reduction in HAM-A total score over the course of the treatment trial. According to this criterion, 46% of those taking 600 mg/day of pregabalin were treatment responders, compared with 27% of placebo control patients, and 61% of the lorazepam comparison group (see Figure 2). The authors reported that response rates were not significantly different between the 150 mg/day pregabalin group and the placebo control group, although they did not report responder rates for the low-dose pregabalin group.

In the same year, Feltner et al.³⁰ published a study using an identical methodology, and similar sample size of 271 adults diagnosed with DSM-IV GAD and low levels of depression symptoms. Diagnosis was made by a psychiatrist following clinical assessment, a screening clinical assessment involving physical and laboratory investigations, and the MINI. Treatment conditions were identical to those of the Pande et al.³¹ study. Similarly to the previous results, the high dose (200 mg tid) of pregabalin resulted in a



Table 1. Randomized controlled trials of pregabalin for generalized anxiety disorder.

| | Sample | Method | Outcome |
|-----------------------------|--|--|---|
| Pande et al ³¹ | <p>N = 276</p> <ul style="list-style-type: none"> Adults. Diagnosis of GAD. Initial HAM-A \geq 20, Covi \geq 9. Initial RDS \leq 7. Excluded patients with other Axis I disorders (except dysthymia, specific phobia, social phobia, somatization disorder) Excluded patients with severe Axis II disorders Excluded patients with drug or alcohol abuse/dependence Excluded patients with significant suicide risk. | <p>Double-blind, fixed dose.</p> <p>No other medications permitted except zolpidem.</p> <p>Randomized to:</p> <ul style="list-style-type: none"> n = 68: PGB (50 mg tid) n = 68: PGB (200 mg tid) n = 62: LRZ (2 mg tid) n = 64: PBO <p>Treatment Phases</p> <ol style="list-style-type: none"> Lead-in: 1 week Treatment: 4 weeks Taper: 1 week | <p>HAM-A</p> <ul style="list-style-type: none"> All active treatments superior to PBO. PGB (200 mg tid) equivalent to LRZ (2 mg tid). PGB (50 mg tid) inferior to LRZ (2 mg tid). PGB (200 mg tid) equivalent to PGB (50 mg tid). <p>HAM-A Psychic Anxiety</p> <ul style="list-style-type: none"> PGB (200 mg tid) superior to PBO PGB (50 mg tid) equivalent to PBO LRZ (2 mg tid) superior to PBO HAM-A Somatic Anxiety <ul style="list-style-type: none"> All active treatments superior to PBO HAM-D All active treatments superior to PBO HAM-A PGB (200 mg tid) superior to PBO. PGB (50 mg tid) equivalent to PBO. LRZ (2 mg tid) superior to PBO. PGB (200 mg tid) equivalent to LRZ (2 mg tid). PGB (50 mg tid) equivalent to LRZ (2 mg tid). PGB (200 mg tid) equivalent to PGB (50 mg tid). <p>HAM-A Psychic Anxiety</p> <ul style="list-style-type: none"> PGB (200 mg tid) superior PBO HAM-A Somatic Anxiety PGB (200 mg tid) superior PBO HAM-A |
| Feltner et al ³⁰ | <p>N = 271</p> <ul style="list-style-type: none"> Adults. Primary diagnosis of GAD. Initial HAM-A \geq 20, Covi \geq 9. Initial RDS \leq 7. Excluded patients with other Axis I disorders (except dysthymia, specific phobia, social phobia, somatization disorder) Excluded patients with severe Axis II disorders Excluded patients with drug or alcohol abuse/dependence Excluded patients with significant suicide risk. | <p>Double-blind, fixed dose.</p> <p>No other medications permitted except zolpidem.</p> <p>Randomized to:</p> <ul style="list-style-type: none"> n = 70: PGB (50 mg tid) n = 66: PGB (200 mg tid) n = 68: LRZ (2 mg tid) n = 67: PBO <p>Treatment Phases</p> <ol style="list-style-type: none"> Lead-in: 1 week Treatment: 4 weeks Taper: 1 week | <p>HAM-A</p> <ul style="list-style-type: none"> All active treatments superior to PBO HAM-D All active treatments superior to PBO HAM-A PGB (200 mg tid) superior to PBO. PGB (50 mg tid) equivalent to PBO. LRZ (2 mg tid) superior to PBO. PGB (200 mg tid) equivalent to LRZ (2 mg tid). PGB (50 mg tid) equivalent to LRZ (2 mg tid). PGB (200 mg tid) equivalent to PGB (50 mg tid). <p>HAM-A Psychic Anxiety</p> <ul style="list-style-type: none"> PGB (200 mg tid) superior PBO HAM-A Somatic Anxiety |
| Rickels et al ³² | <p>N = 454</p> <ul style="list-style-type: none"> Adults. Diagnosis of GAD. Initial HAM-A \geq 20, Covi \geq 9. Initial RDS \leq 7. Excluded women who were pregnant or not using contraception. Excluded patients with current or past bipolar disorder, schizophrenia, schizoaffective, psychotic or factitious disorders, dementia, or seizure disorders. Excluded patients with current (not previous) depressive disorder, social anxiety disorder, panic disorder, PTSD, eating disorders, alcohol or substance disorders. | <p>Double-blind, fixed dose.</p> <p>No other medications permitted except zolpidem.</p> <p>Randomized to:</p> <ul style="list-style-type: none"> n = 91: PGB (100 mg tid) n = 90: PGB (150 mg tid) n = 89: PGB (200 mg tid) n = 93: APZ (0.4 mg tid) n = 91: PBO <p>Treatment phases</p> <ol style="list-style-type: none"> Lead-in: 1 week Treatment: 4 weeks Taper: 1 week | <p>HAM-A</p> <ul style="list-style-type: none"> All active treatments superior to PBO. HAM-A Psychic Anxiety All active treatments superior to PBO. HAM-A Somatic Anxiety PGB (100 mg tid) superior to PBO. PGB (150 mg tid) equivalent to PBO PGB (200 mg tid) superior to PBO. APZ (0.4 mg tid) equivalent to PBO <p>HAM-D</p> <ul style="list-style-type: none"> All active treatments superior to PBO. CGI Improvement Scale All active treatments superior to PBO. |



| | | |
|--|--|--|
| <p>Pohl et al³³</p> <ul style="list-style-type: none"> • Excluded patients with significant medical disorders. • Excluded patients with significant suicide risk. • Excluded patients undergoing psychotherapy for GAD, unless stable with treatment for >3 months. <p>N = 344</p> <ul style="list-style-type: none"> • Adults. • Diagnosis of GAD. • Initial HAM-A \geq 20, Covi \geq 9. • Initial RDS \leq 7. • Excluded patients with "most&quot; other Axis I disorders except dysthymia or specific phobia. • Excluded patients with significant suicide risk. • Excluded patients with significant medical illness. • Excluded patients with prior exposure to pregabalin. | <p>Double-blind, fixed dose. No other medications permitted. Randomized to:</p> <ul style="list-style-type: none"> • n = 78: PGB (100 mg bid) • n = 89: PGB (200 mg bid) • n = 88: PGB (150 mg tid) • n = 86: PBO <p>Treatment phases</p> <ol style="list-style-type: none"> 1. Lead-in: 1 week 2. Treatment: 6 weeks 3. Taper: 1 week <p>Double-blind, fixed dose. No other medications permitted except zolpidem.</p> <p>Randomized to:</p> <ul style="list-style-type: none"> • n = 97: PGB (200 mg bid) • n = 110: PGB (300 mg bid) • n = 113: VLF (37.5 mg bid) • n = 101: PBO <p>Treatment phases</p> <ol style="list-style-type: none"> 1. Lead-in: 1 week 2. Treatment: 6 weeks 3. Taper: 1 week | <p>HAM-A</p> <ul style="list-style-type: none"> • All active treatments superior to PBO. • No significant difference between bid and tid dosing. <p>HAM-A Psychic Anxiety</p> <ul style="list-style-type: none"> • All active treatments superior to PBO. <p>HAM-A Somatic Anxiety</p> <ul style="list-style-type: none"> • All active treatments superior to PBO. <p>HAM-D</p> <ul style="list-style-type: none"> • All active treatments superior to PBO <p>HAM-A</p> <ul style="list-style-type: none"> • All active treatments superior to PBO. <p>HADS-A</p> <ul style="list-style-type: none"> • All active treatments superior to PBO. <p>HAM-D</p> <ul style="list-style-type: none"> • All active treatments superior to PBO. |
| <p>Montgomery et al³⁴</p> <ul style="list-style-type: none"> • Excluded patients with significant medical disorders. • Excluded patients with significant suicide risk. • Excluded patients with Axis I disorders except dysthymia or specific phobia, or somatization disorder. • Excluded patients with borderline, avoidant or antisocial personality disorders. • Excluded patients with relevant medical conditions. • Excluded patients with seizure disorders. • Excluded patients with alcohol or substance disorders in past six months. • Excluded women who were pregnant or not using contraception. • Excluded patients with significant suicide risk. • Excluded patients undergoing psychotherapy for GAD. • Excluded patients with previous exposure to pregabalin. <p>N = 421</p> <ul style="list-style-type: none"> • Adults. • Primary diagnosis of GAD. • Initial HAM-A \geq 20, Covi \geq 9. • Initial RDS \leq 7. | <p>Double-blind. Dose fixed after 6 weeks. No other psychotropic medications permitted. Randomized to:</p> <ul style="list-style-type: none"> • n = 177: PGB (150–600 mg) • n = 96: PBO <p>Treatment Phases</p> | <p>HAM-A</p> <ul style="list-style-type: none"> • PGB superior to PBO. <p>HAM-A Psychic Anxiety</p> <ul style="list-style-type: none"> • PGB superior to PBO. <p>HAM-A Somatic Anxiety</p> <ul style="list-style-type: none"> • PGB superior to PBO. <p>SCL-90-R Anxiety Subscale</p> |
| <p>Montgomery et al³⁵</p> <ul style="list-style-type: none"> • Excluded patients with significant medical disorders. • Excluded patients with significant suicide risk. • Excluded patients with Axis I disorders except dysthymia or specific phobia, or somatization disorder. • Excluded patients with borderline, avoidant or antisocial personality disorders. • Excluded patients with relevant medical conditions. • Excluded patients with seizure disorders. • Excluded patients with alcohol or substance disorders in past six months. • Excluded women who were pregnant or not using contraception. • Excluded patients with significant suicide risk. • Excluded patients undergoing psychotherapy for GAD. • Excluded patients with previous exposure to pregabalin. <p>N = 273</p> <ul style="list-style-type: none"> • Adults aged 65 years and older. • Diagnosis of GAD. • Initial HAM-A \geq 20, MMSE \geq 24. • Excluded patients with current or past schizophrenia, schizoaffective, psychotic, or bipolar disorders. | <p>Double-blind. Dose fixed after 6 weeks. No other psychotropic medications permitted. Randomized to:</p> <ul style="list-style-type: none"> • n = 177: PGB (150–600 mg) • n = 96: PBO <p>Treatment Phases</p> | <p>HAM-A</p> <ul style="list-style-type: none"> • PGB superior to PBO. <p>HAM-A Psychic Anxiety</p> <ul style="list-style-type: none"> • PGB superior to PBO. <p>HAM-A Somatic Anxiety</p> <ul style="list-style-type: none"> • PGB superior to PBO. <p>SCL-90-R Anxiety Subscale</p> |

(Continued)



Table 1. (Continued)

| | Sample | Method | Outcome |
|-----------------------------|---|--|--|
| Feltner et al ³⁷ | <ul style="list-style-type: none"> Excluded patients with current depression, social anxiety (generalized), panic disorder, obsessive-compulsive disorder, post-traumatic stress disorder, eating disorder, delirium, dementia, amnesic disorder, alcohol or substance disorders. Excluded patients with current borderline or antisocial personality disorder Excluded patients with significant medical disorders. Excluded patients undergoing psychotherapy for GAD unless stable for >3 months. Excluded patients with significant suicide risk. Excluded patients with depression symptoms predominating over anxiety symptoms. <p>N = 624</p> <ul style="list-style-type: none"> Adults. Diagnosis of GAD for ≥1 year. Excluded patients with current seizure disorder. Excluded patients with current or past schizophrenia, or bipolar, psychotic or factitious disorder. Excluded patients with any clinically significant Axis I disorder in past six months. Did not exclude patients with dysthymia, depression NOS, or specific phobia. Excluded patients with significant suicide risk. Excluded pregnant or lactating women. Excluded patients undergoing psychotherapy for GAD, unless ongoing for 3 months. | <p>Open label treatment, followed by double-blind relapse prevention.</p> <p>No other psychotropic medications permitted.</p> <p>All patients treated with PGB 150 mg tid during open label treatment phase. In relapse prevention phase, patients who were responders (HAM-A ≤ 11, 50% reduction in HAM-A from baseline) during the open label treatment phase were randomized to:</p> <ul style="list-style-type: none"> n = 168: PGB (150 mg tid) n = 170: PBO <p>Treatment Phases</p> <ol style="list-style-type: none"> Lead-in: 1 week Open label acute treatment: 8 weeks Relapse prevention: 24 weeks <p>Double-blind, flexible dose. No other medications permitted except zolpidem or zopiclone. Randomized to:</p> <ul style="list-style-type: none"> n = 121: PGB (300–600 mg/day) n = 125: VLF (75–225 mg/day) n = 128: PBO | <ul style="list-style-type: none"> PGB superior to PBO. HAM-D PGB superior to PBO. <p>Time to Relapse (HAM-A ≥ 20 and meeting diagnostic criteria for GAD, or CGI rating of 'much worse' or 'very much worse')</p> <ul style="list-style-type: none"> PGB superior to PBO in preventing/slowing relapse HAM-A PGB superior to PCB during relapse prevention phase in maintaining gains from open-label phase. HAM-D PGB superior to PCB during relapse prevention phase in maintaining gains from open-label phase. <p>HAM-A</p> <ul style="list-style-type: none"> PGB superior to PBO. VLF equivalent to PBO. HADS Anxiety Subscale PGB superior to PBO. GA-VAS PGB equivalent to PBO. |
| Kasper et al ³⁸ | <p>N = 374</p> <ul style="list-style-type: none"> Adults. Diagnosis of GAD. Initial HAM-A ≥ 20, HAM-A Somatic Anxiety ≥ 10, HAM-A Psychic Anxiety ≥ 10. Excluded women who were pregnant or not using contraception. Excluded patients with current or past schizophrenia, psychotic, or bipolar disorders. | <p>Double-blind, flexible dose. No other medications permitted except zolpidem or zopiclone. Randomized to:</p> <ul style="list-style-type: none"> n = 121: PGB (300–600 mg/day) n = 125: VLF (75–225 mg/day) n = 128: PBO | <p>HAM-A</p> <ul style="list-style-type: none"> PGB superior to PBO. VLF equivalent to PBO. HADS Anxiety Subscale PGB superior to PBO. GA-VAS PGB equivalent to PBO. |



- Excluded patients with depression, dysthymia, obsessive-compulsive disorder, posttraumatic stress disorders, eating disorder, or alcohol/drug use disorder in past six months.
- Excluded patients with initial HAM-D \geq 15.
- Excluded patients with clinically significant medical illness or creatinine clearance \leq ml/min.
- Excluded patients undergoing concurrent psychotherapy for GAD unless duration \geq 3 months.
- Excluded patients with significant suicide risk.
- Excluded patients with previous exposure to PGB or VLF.

- Treatment Phases
1. Lead-in: 1 week
 2. Treatment: 8 weeks
 3. Taper: 1–2 weeks

- HAM-D
- PGB superior to PBO.
 - VLF equivalent to PBO.
- CGI Improvement Scale
- PGB superior to PBO.
 - VLF equivalent to PBO.
- CGI Severity Scale
- PGB superior to PBO.
 - VLF equivalent to PBO.
- MOS Sleep Disturbance Scale
- PGB superior to PBO.
 - VLF equivalent to PBO.
- MOS Sleep Problems Index
- PGB superior to PBO.
 - VLF equivalent to PBO.
- Daily Pain Rating Scale
- PGB, VLF, and PBO all equivalent

Abbreviations: APZ, Alprazolam; CGI, Clinical Global Impressions Scale; Covi, Covi Anxiety Scale; GA-VAS, Global Anxiety Visual Analog Scale; HADS, Hospital Anxiety and Depression Scale; HAM-A, Hamilton Anxiety Rating Scale; HAM-D, Hamilton Depression Rating Scale; LRZ, Lorazepam; MMSE, Mini Mental State Examination; NOS, Not Otherwise Specified; PBO, Placebo; PGB, Pregabalin; RDS, Raskin Depression Scale; SCL-90-R, Symptom Checklist 90 Revised; VLF, Venlafaxine.

reduction in anxiety symptoms (as measured by the HAM-A) which was statistically significantly different to the placebo condition. Patients in the 200 mg tid pregabalin treatment group demonstrated a mean reduction of 13.2 points in HAM-A total scores (see Figure 1). In contrast, low dose pregabalin (50 mg tid) was not significantly different from placebo. There was no difference between either dose of pregabalin and the comparator drug, lorazepam, on anxiety symptoms. Examination of the psychic and somatic subscales of the HAM-A demonstrated that pregabalin (200 mg tid) was significantly more effective in reducing symptoms than the placebo.

Using the same criteria for treatment response as Pande et al.³¹ of a 50% reduction in HAM-A total scores over the four week treatment trial, a total of 59% of those patients on high dose pregabalin, and 52% of those on the lower dose, were classified as responders. In comparison 55% of those on lorazepam, and 44% of those taking the placebo showed the same 50% response rate.

A larger sample of 454 adults with a primary diagnosis of GAD was used by Rickels et al.³² in a four-week, double-blind study comparing three different doses of pregabalin (100 mg tid, 150 mg tid, and 200 mg tid) with the short-acting benzodiazepine alprazolam, and a placebo control. All patients were diagnosed with GAD using the MINI. In this study, all three of the pregabalin treatment groups, as well as the alprazolam group, showed reductions in HAM-A anxiety symptoms that were superior to those in the placebo control condition. This superiority over the placebo treatment was also observed for all active treatments on the HAM-A psychic anxiety subscale, and for the 100 mg tid and 200 mg tid-pregabalin groups on the HAM-A somatic anxiety subscale. HAM-A total scores fell by more than 50% in 61%, 47%, and 53% of patients from the 100 mg tid, 150 mg tid, and 200 mg tid-pregabalin groups, respectively. Response rates of >50% were seen in 43% of those treated with alprazolam, and 34% of those who were given the placebo.

Pohl et al.³³ expanded on these three previous four-week studies by examining the efficacy of pregabalin in a six-week trial of 344 adults diagnosed with GAD (using the MINI), who also had only low levels of depression symptoms. Additionally, comparisons were made between bid and tid dosing regimens

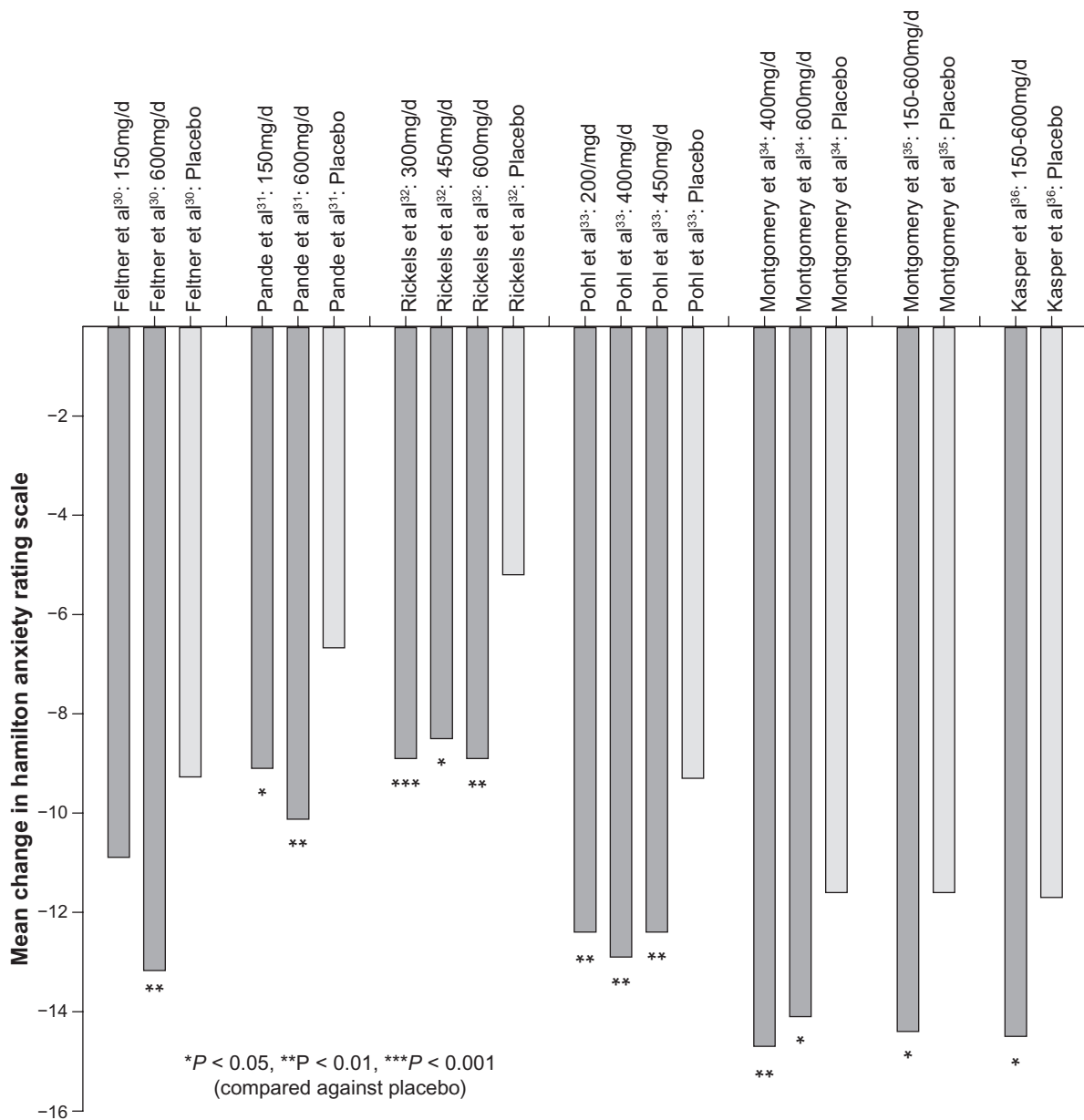


Figure 1. Mean change in Hamilton Anxiety Rating Scale scores for each study and dosage of pregabalin in generalized anxiety disorder.

in this double-blind, fixed dose study. Similarly to earlier studies, these authors found that over six weeks, the three pregabalin doses (100 mg bid, 200 mg bid, 150 mg tid) were all superior to placebo in their ability to reduce HAM-A total scores, as well as the psychic and somatic anxiety subscales. A total of 46% of patients taking pregabalin showed an improvement of >50% on the HAM-A, compared with 34% of those taking the placebo. The authors stated that their results provided support for immediate commencement of patients on effective doses of pregabalin, without the need to gradually titrate from

a lower level. The convenience of bid dosing, without significant increases in adverse events, or decreases in therapeutic efficacy, is also noteworthy.

While all previous investigations of pregabalin had been compared against placebos and benzodiazepines, Montgomery et al³⁴ used the serotonin/noradrenaline reuptake inhibitor venlafaxine as a comparison in a study published in 2006. A cohort of 421 patients diagnosed with DSM-IV GAD using the MINI were entered into the study. In another development from earlier pregabalin studies, these authors also incorporated a self-report measure of anxiety symptoms,

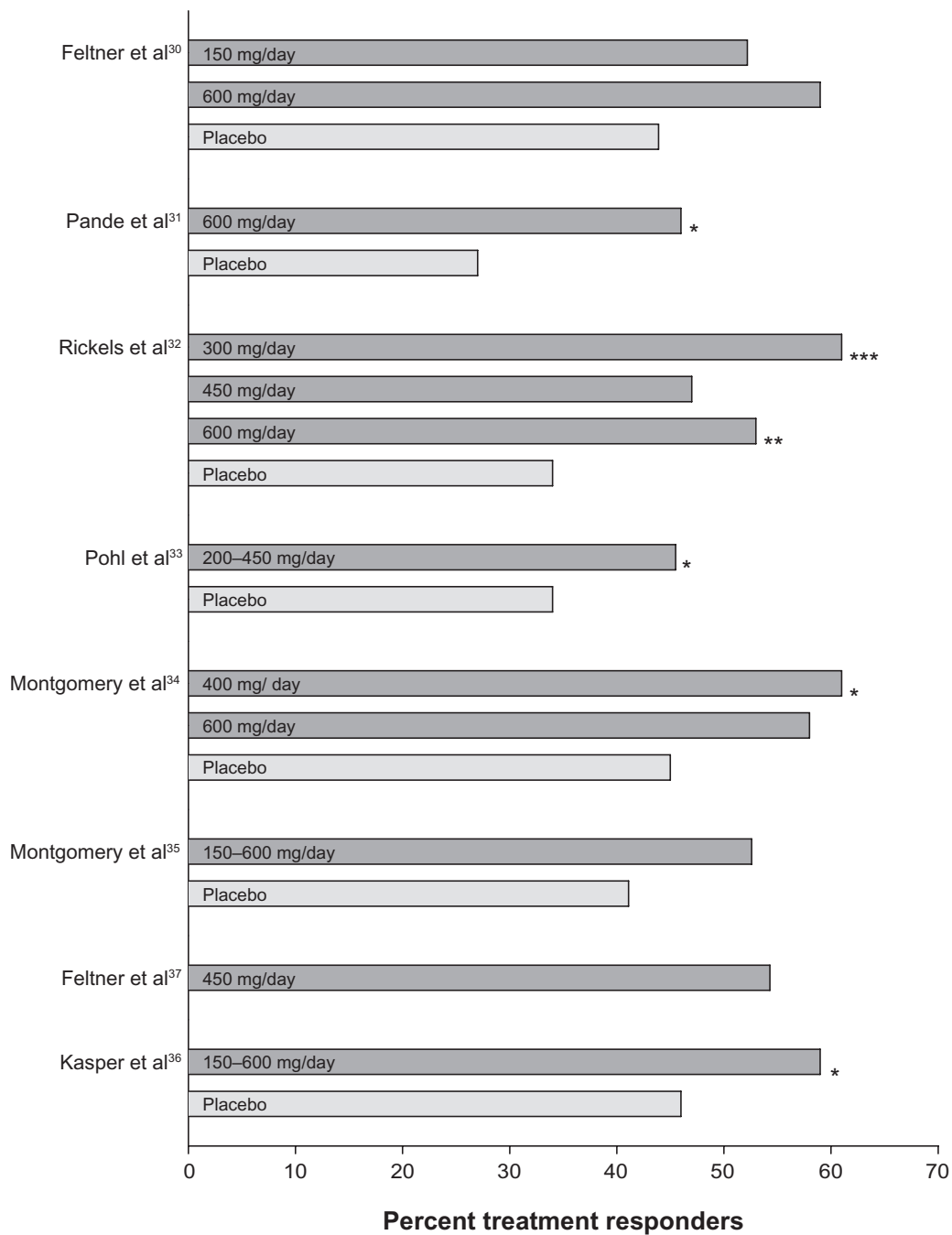


Figure 2. Number of treatment responders for each study and dosage of pregabalin in generalized anxiety disorder. **Note:** * = $P < 0.05$, ** = $P < 0.01$, *** = $P < 0.001$, compared to placebo. Feltner et al³⁷ did not use a placebo control during the initial treatment response phase, so no assessment of statistical significance vs. placebo is available.

the Hospital Anxiety and Depression Scale (HADS) in addition to the clinician-rated HAM-A. The results were consistent with those of previous research in that clinician-rated HAM-A scores demonstrated efficacy of pregabalin in treatment of GAD, although with relatively modest effect sizes of 0.38 and 0.31 for the 400 mg/day and 600 mg/day doses, respectively. Of those patients taking 400 mg/day of pregabalin 61%

showed a drop of at least 50% in their HAM-A scores, while 58% of those on the higher dose of 600 mg/day were classified as responders. In comparison, 62% of those taking venlafaxine and 45% of those receiving the placebo demonstrated a drop of at least 50% in HAM-A score. Subjective patient ratings of their own anxiety symptoms as measures by the HADS anxiety subscale showed similar results with all active



treatments being superior to placebo over the six week double-blind trial. In those taking pregabalin, response rates based on improvement in HADS anxiety score were 61% for the 400 mg/day, and 58% for the 600 mg/day group. In comparison, 62% of those taking venlafaxine, and 45% of those on placebo, were responders as measured by the HADS anxiety scale.

Generalized anxiety disorder has an increased prevalence in older adults, leading to significant additional disability, service utilization, and reduced quality of life.⁴⁰ In an investigation of the effectiveness of pregabalin in adults over 65 years of age, Montgomery et al.³⁵ compared 177 older adults taking pregabalin with 96 who were given a placebo over an 8 week period. Patients were diagnosed with DSM-IV GAD according to the MINI. This was also the first study of pregabalin in which dosing was flexible (between 150 and 600 mg/day) for the first 6 weeks of the 8 week treatment phase. Anxiety was assessed using the standard clinician-rated HAM-A, as well as the anxiety scale of the Symptom Checklist 90 Revised. As in younger adult samples, pregabalin demonstrated superiority over placebo in terms of overall reduction in anxiety symptoms. Additionally, the number of treatment responders (ie, those with a reduction of >50% in HAM-A scores) was greater in the pregabalin group (53%) than the placebo group (41%). The placebo-controlled effect size for pregabalin in this study was $d = 0.26$.

While those studies already reviewed above have examined the effect of pregabalin on self-reported and clinician-rated anxiety symptoms, Kasper et al.³⁶ examined the effect of the drug on a broader range of outcome measures, including quality of life and functioning, using venlafaxine XR as a comparison. A group of 374 individuals diagnosed with DSM-IV GAD according to MINI were treated as part of the study. As expected by the investigators, pregabalin significantly reduced HAM-A total scores, as well as somatic and psychic anxiety subscale scores, compared with placebo. A total of 59% of those taking pregabalin were treatment responders (with a reduction of at least 50% in HAM-A scores), compared with 44% of those taking venlafaxine, and 46% receiving placebo. Only one of the two self-report measures of anxiety symptoms (the HADS) showed a significant reduction compared

with placebo, while the other measure (the Global Anxiety Visual Analog Scale) was reported to show "trend levels of significance". Pregabalin was associated with reduced levels of sleep disturbance and insomnia compared with placebo, as well as reduced scores on a general measure of pain. Pregabalin led to reduced levels of disability compared with placebo. Despite these improvements in symptoms and functioning, patients taking pregabalin did not show consistent improvement in measures of quality of life. The authors suggested that while these results were disappointing, they may be attributable to the measurement tools used, which may not be sensitive to the quality of life impact of GAD. Alternatively, Kasper et al. suggested that gains in quality of life may lag behind reductions in anxiety symptoms, and so may not have been observable in an eight-week trial of the drug.

Longer-term studies of the efficacy of pregabalin have been slower to appear in the psychiatric literature. To date, only one investigation has reported on the ability of pregabalin to sustain reductions in anxiety symptoms beyond eight weeks. Feltner et al.³⁷ treated a total of 624 adults who had experienced DSM-IV GAD for at least one year, diagnosed according to the MINI. In this study flexible dosing of pregabalin was used over an eight week treatment phase. The 339 responders from this first phase of the study were then randomized to receive either 450 mg of pregabalin each day, or a pill placebo, for a period of 24 weeks. In the relapse prevention phase relapse was defined as the patient being removed from the trial due to any of the following criteria: Increased HAM-A score (≥ 20) with a diagnosis of GAD according to the MINI; two consecutive weekly ratings of 'much worse' or 'very much worse' on the Clinical Global Impressions scale along with a diagnosis of GAD; or a clinical judgment that worsening of anxiety symptoms required immediate intervention. During this double-blind relapse prevention phase, pregabalin was demonstrated to significantly slow/prevent relapse compared to placebo, with 42% of pregabalin patients relapsing compared with 65% of those taking the placebo ($P < 0.0001$). Pregabalin was also associated with better maintenance of treatment effects from the acute phase of the study as measured by the HAM-A. Although this is the sole study examining the longer term efficacy of pregabalin, the results show initial



promise for the use of the drug in preventing relapse in GAD.

Meta-analyses

The first meta-analysis to examine the effect size of pregabalin against other pharmacological agents used in the treatment of GAD was published in 2007.²⁰ This study incorporated only two published pregabalin studies in its analysis. Using this limited sample of studies, the authors reported an uncontrolled effect size of 0.50 for pregabalin, which was superior to all other classes of medication. The authors were tentative in drawing firm conclusions from this limited dataset, however, for a number of reasons. They highlighted the short (six-week) duration of the two pregabalin studies used in their analysis as a limitation of previous studies, stating that it remained unknown whether these early reductions in symptoms would be sustained over longer durations used in studies with other medications.

A more recent analysis⁴¹ has incorporated the outcome data from seven published placebo-controlled studies, including those in the earlier meta-analysis. The overall placebo-controlled effect size for pregabalin in this larger analysis was reduced to Hedges' $g = 0.36$. Furthermore, the effect of pregabalin on psychic anxiety symptoms ($g = 0.35$) was greater than that on somatic anxiety symptoms ($g = 0.24$).

Speed of onset of therapeutic effect

A weakness of antidepressants in the treatment of GAD has been the delay in therapeutic effect, or even short-term increases in anxiety when they are first taken.⁴² Many of the studies of pregabalin's efficacy in the treatment of GAD have examined the speed on onset of the anxiolytic effects of the drug, to assess immediate response which may give pregabalin an advantage over previous agents. The majority of studies report that the anxiolytic effect of pregabalin is rapid, with significant differences from placebo observed within one week ($P < 0.05$ or better).³⁰⁻³⁴ In one study where measurements using the HAM-A were done more frequently, significant anxiolysis compared to placebo ($P < 0.001$) was observed within four days.³⁶ When used in older adults, the therapeutic effect may take longer to occur, with two weeks required to achieve significant difference ($P < 0.05$) in anxiety compared to a pill placebo.³⁵ Although rate

of response in pregabalin and benzodiazepines has not been directly compared, benzodiazepines show similar significant reduction in anxiety symptoms when compared against a placebo after one week of administration.³⁰⁻³² When compared to venlafaxine, pregabalin is associated with a more rapid anxiolytic effect ($P < 0.05$ after 1 week).⁴³

Effect of pregabalin on associated depression symptoms

Depression symptoms are a significant issue for many of those with GAD.⁴⁴ Approximately 39% of those with GAD also have a comorbid major depressive disorder.⁴⁵ The presence of GAD increases the odds of having major depressive disorder or dysthymic disorder by 10.2 and 12.6 times, respectively.⁴⁶ Research examining the relationship between the two diagnoses has also reported that differentiating the symptoms of the two conditions can be difficult.⁴⁷⁻⁴⁹ Although many of the first studies using pregabalin in the treatment of GAD specifically excluded those with high levels of depression symptoms,³⁰⁻³⁴ some studies also have investigated the effect of the drug on mood symptoms during treatment of GAD. A reduction in low-level depression symptoms has been observed in several previous studies.³¹⁻³⁴ This finding was confirmed with a larger scale meta-analysis of earlier efficacy research findings, including for patients with higher levels of depression symptoms.⁵⁰ Furthermore, this meta-analysis suggested that the presence of depression symptoms did not reduce the effectiveness of pregabalin in the treatment of GAD.

Cost-effectiveness

In addition to efficacy, cost-effectiveness of a new pharmacological agent can influence its prescription and use by consumers. Only one study has so far examined the cost-effectiveness of pregabalin in the treatment of GAD, with these results coming from a Spanish study which reported on the development of a model of 1000 hypothetical patients with GAD.⁵¹ Treatment with pregabalin was compared with treatment using venlafaxine, with outcome measures including HAM-A scores, period of time with minimal levels of anxiety symptoms, and quality adjusted life years (QALYs). The results of the model simulation reported by the authors indicated that pregabalin was expected to yield lower endpoint HAM-A scores,



more weeks with minimal or no anxiety, and similar levels of increased quality of life, compared with venlafaxine. Although pregabalin was associated with lower drug-specific costs, total predicted cost over a single year, including other health service utilisation, was 19% higher than for venlafaxine.

Safety

Adverse events

Pregabalin is generally well tolerated with few adverse events of low severity.⁵⁶ Early controlled trials of pregabalin in treatment of GAD reported that the drug was not associated with clinically significant changes in vital measures such as blood pressure, heart rate, respiratory rate, or other laboratory measures of physiological functioning.³³

The most common adverse events observed in patients with GAD treated with pregabalin are dizziness (31%), sedation (29%), dry mouth (15%), blurred vision (8%), and impaired coordination (7%).¹⁶ In previous trials these adverse events have generally been rated as mild or moderate in severity,^{16,30,31} and tend also to be transient.¹⁶

Pregabalin has not been associated with increased rates of ophthalmological problems compared to placebo, despite concerns regarding its similarity to vigabatrin, a drug associated with adverse events including visual field defects. Even in situations where patients experienced blurred vision, ophthalmological assessment has suggested no evidence of compromised visual acuity.³⁰

The subjective impact of pregabalin on cognitive functioning has been reported in several of the controlled trials of treatment of GAD. Subjective reports of memory problems have been reported with low frequency in two studies (3%³⁰ and 7%³¹), while “abnormal thinking” has been reported in up to 10% of individuals in one flexible-dose study.³⁷ More detailed investigation of the cognitive and psychomotor effects of pregabalin has been conducted by Hindmarch et al.⁵² in a group of 24 healthy volunteers, with a range of neuropsychological and other assessment methods known to be sensitive to administration of other psychoactive medications. In this study pregabalin did not show any effects above those of a placebo on a range of neuropsychological tests measuring reaction time, vigilance, or serial memory. Pregabalin was associated with performance decrements on

CNS arousal, divided attention, and sedation. The authors did not specify whether these impairments were clinically meaningful. It is worth noting, however, that the dose of pregabalin used in this study was 450 mg, which is less than some people may receive in the treatment of GAD. Furthermore, pregabalin was administered over a period of three days, and so this research would have been unable to detect any neuropsychological or psychomotor effects that may emerge with longer periods of administration.

A less favourable result of pregabalin on cognitive performance has been observed more recently in a cohort of 30 healthy volunteers who took a dose of pregabalin titrated up to 600 mg/day, with a total of 12 weeks of administration. In this patient group, impairment was observed on three of six neuropsychological measures—digit symbol, stroop colour word interference, and the controlled oral word association test. The authors used these results to suggest that the mild cognitive impairments observed should be considered in the decision to prescribe pregabalin over an extended period.⁵³

A small number of case reports have documented a potentially more serious adverse effect that may be associated with pregabalin use. Some authors have suggested that peripheral oedema observed in 5–20% of placebo controlled trials may contribute to serious cardiovascular consequences such as exacerbation of heart disease.⁵⁴ The authors report three new cases, and review literature concerning three previous cases of similar exacerbation of cardiac illness by pregabalin. Although none of the cases presented were using pregabalin for the treatment of GAD, the author presents a cautionary note that pregabalin should be used extremely cautiously in patients with existing heart disease.

Abuse potential

Previous treatments for anxiety such as the benzodiazepines have significant potential for tolerance, dependence, and abuse.⁵⁵ Among the characteristics of an ‘ideal’ novel anxiolytic agent are that it should show no development of tolerance or withdrawal, and have low potential for abuse.²¹ Experience with pregabalin to date suggests that it is less likely to lead to these problems than earlier GABA agonists such as the benzodiazepines and barbiturates. Animals do not repeatedly self-administer the drug.⁵⁶ Some reviews



of the clinical and preclinical studies which employed pregabalin have also asserted that there is no clear evidence of misuse, addiction, dependence, or craving.^{21,57}

In contrast, other evidence has suggested that while pregabalin may not present as much risk as other GABA agonists for abuse, the potential for problem use of the drug may still need to be considered. Euphoria has been noted as an adverse event in two of the published controlled trials of the drug, in between 10 and 16.7% of those taking the drug.^{33,37} A recent examination in Sweden of adverse drug reactions register identified a total of 198 cases of abuse or addiction to prescribed medications, with 16 (8.08%) of these concerning pregabalin.⁵⁸ The authors of this report suggest that further research into abuse and dependence of pregabalin in clinical use is necessary before firm conclusions can be drawn concerning the potential for dependence and abuse.

Discontinuance/withdrawal effects

Related to the potential for abuse and dependence, are the withdrawal and discontinuation effects of a drug. In pregabalin studies of the treatment of GAD, the Physician Withdrawal Checklist has often been used to assess the discontinuance symptoms experienced by those taking the drug. Discontinuance effects have been minimal across a range of trials using different lengths of tapering, and different doses of pregabalin. Over a 1 week taper, one study reported that both 150 mg/day and 600 mg/day doses of pregabalin were not associated with a level of discontinuance symptoms that were significantly above placebo, in contrast to a group of individuals taking 6 mg/day of lorazepam.³¹ Other studies have reported the same result for immediate cessation of up to 300 mg/day of pregabalin.^{32,33} In studies that have found discontinuance symptoms greater than placebo, these have involved anxiety/nervousness, irritability, and loss of appetite.^{30,33}

Low frequency and severity of discontinuance effects have also been observed when pregabalin is used to treat GAD in older adults. In a rapid taper of the drug over 1 to 5 days, the only 2 discontinuance experiences that were observed with a higher frequency than placebo were dizziness and insomnia, both seen in only 0.6% of patients compared to none of those previously on placebo.³⁵

Interactions

Another characteristic of the ideal anxiolytic drug is that it demonstrates little or no interaction with other prescribed medications.²¹ Drug interactions with pregabalin are limited by the fact that the drug does not undergo significant hepatic metabolism, and that the drug neither inhibits nor potentiates cytochrome P450 enzymes.^{21,27} Metabolism of pregabalin is not significantly changed by other pharmacotherapy which alters CYP450 functioning.²¹ Pregabalin demonstrates little or no interaction with other GABA agonists such as benzodiazepines or alcohol, and can be combined with SSRIs and other antidepressants.¹⁶ Nor does pregabalin interact significantly with other antiepileptic agents such as carbamazepine, phenytoin, lamotrigine, or valproate.⁵⁹ Pregabalin does not impact on the effectiveness of the contraceptive pill.⁶⁰

Safety in overdose

Potential for overdose is a concern with any psychiatric medication. Limited published information suggests that pregabalin is relatively safe in overdose. Baldwin & Ajel reviewed approximately 100 cases of pregabalin overdose, and reported that none of these led to significant adverse events or other serious medical complications.²¹

Patient Preference

Assessment of preference of individuals with GAD for treatment with pregabalin has not been directly assessed. Results from controlled trials, however, provide some information as to the acceptability of the drug when used to treat GAD in these studies. Rates of dropout during controlled trials provide one estimate of the acceptability of pregabalin treatment to patients. For patients with GAD on a fixed dose of up to 200 mg of pregabalin, discontinuance rates ranged from 10.1% to 29.5% ($M = 21.3\%$, $SD = 10.0\%$). Doses of between 201 and 400 mg per day yielded discontinuance rates of 11.0% to 28.0% ($M = 18.5\%$, $SD = 8.7\%$), while higher doses of over 400 mg have shown discontinuance rates of 19.9% to 40.5% ($M = 28.0\%$, $SD = 6.4\%$). By way of comparison, 19.9% to 29.0% ($M = 27.0\%$, $SD = 3.2\%$) of individuals taking a placebo pill in pregabalin trials for GAD discontinued.²⁶⁻³³ In pregabalin RCTs that used another drug as an active comparator, 27% of



those taking alprazolam,³² 30% to 33% of those taking venlafaxine,^{34,36} and 41% to 47% of those taking lorazepam^{30,31} did not complete treatment.

Discontinuance rates in the elderly have been similar to those observed for general adult samples. In the single controlled trial of pregabalin treatment in older adults, 24.9% of patients on a six-week flexible dose of pregabalin discontinued before the end of the six week trial (10.7% due to adverse events),

compared with 28.1% of those receiving the placebo (9.4% due to adverse events).³⁵ Figure 3 provides a graphic representation of discontinuance rates from the eight controlled trials of pregabalin use in GAD, compared to those observed for placebo treatment in the same study.

It is important to acknowledge that these discontinuance rates are attributable to a range of causes that may not include unacceptability of the drug to

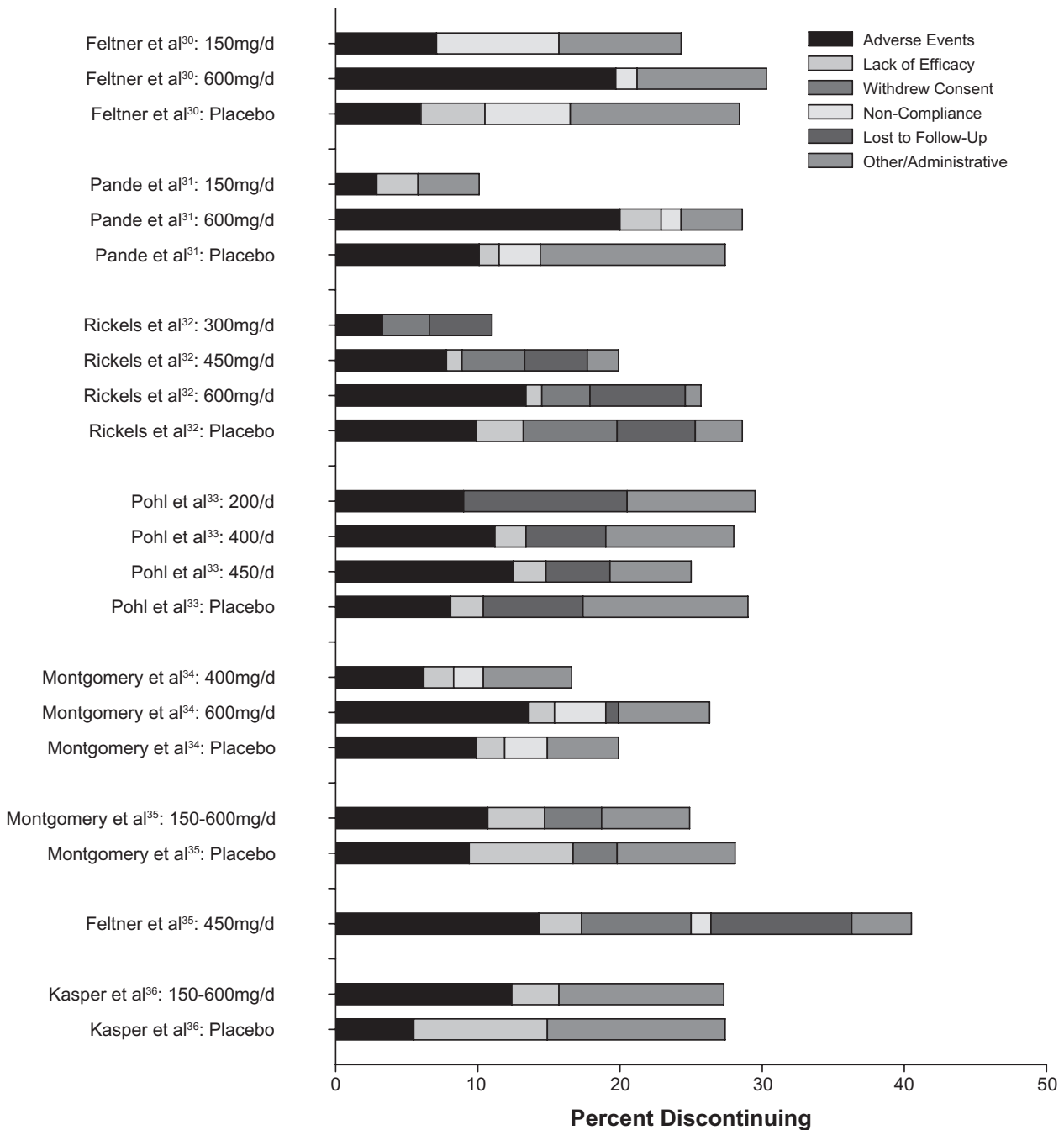


Figure 3. Number of individuals discontinuing pregabalin and placebo treatment.



patients. These rates include causes such as ‘administrative and other’ causes, as well as withdrawn consent, non-compliance, and being lost to follow-up. As such, patient dissatisfaction with pregabalin may be overestimated by these statistics. In his analysis of published pregabalin trials, Kavoussi reported that the most common side effects of pregabalin, dizziness and somnolence, led to discontinuance in 3% and 4% of patients, respectively.⁵⁶

A common side effect of other psychotropic medication is weight gain, which may reduce acceptability of a drug.²⁵ Excessive weight gain is known to lead to noncompliance with prescription of other psychoactive medications.⁶¹ Individuals taking pregabalin have shown comparatively low rates of excessive weight gain in 4 to 8 week clinical trials, with only 4% of those taking pregabalin gaining more than 7%, compared with 1.4% of those taking placebos.²¹ When weight gain is examined over a longer period, however, higher rates are observed. In the single longer-term study of pregabalin in GAD, approximately 13% of those on pregabalin for 24 weeks demonstrated over 7% weight gain.³⁷

Place in Therapy

Prescription of pregabalin

As stated above, pregabalin has demonstrated efficacy over eight published trials in the treatment of GAD. Doses used in these studies have ranged from 150 mg/day to 600 mg/day. In countries such as the United Kingdom where pregabalin has a recognised indication for treatment of GAD, treatment is usually commenced at 150 mg/day (in either 2 or 3 divided doses). If necessary, this dose can then be increased to 300 mg after 3 to 7 days, and up to a maximum of 600 mg/day after a further 7 day period.⁶² Similar dosing regimens are recommended in a recently published pharmacological treatment algorithm for GAD.⁶³ This recommendation is consistent with doses and tapering methods used in controlled trials. In controlled trials, tapering down after the treatment period has most often been done over 1 week, although shorter durations have been used,³⁵ and slower tapers of up to 2 weeks have been used for doses of 600 mg/day.³⁶

Significant risk of relapse makes relapse prevention an essential component of successful treatment for the anxiety disorders, including GAD.^{9,64} Evidence for the ability of pregabalin to assist with prevention

of relapse in successfully treated GAD is currently restricted to a single study conducted over 24 weeks. Although this study provided some initial evidence for the ability of pregabalin to assist in maintaining treatment gains, reduce the probability of relapse, and delay relapse in those who did experience a return of symptoms, these results require replication and should be viewed as preliminary.³⁷

It is worth noting that some authors do not view pregabalin as a suitable first-line treatment for GAD. The small number of efficacy studies, along with the lack of demonstrated efficacy in treating commonly comorbid disorders such as major depression, have led some to suggest that pregabalin may be best reserved as a second-line treatment, or for certain specific presentations (see below).⁶³

Special populations and situations

Despite some understandable caution regarding the use of pregabalin as a front-line treatment for GAD, there may be some situations in which the drug may possess some specific advantages over other, more established treatments such as the antidepressants and benzodiazepines. One situation where pregabalin may be considered as an alternative to the use of SSRI or SNRI antidepressants is where side effects of these agents have proven intolerable to the patient. For example, sexual dysfunction is a common adverse effect of SSRI use.^{65,66} In such cases where sexual dysfunction may lead to non-adherence, an alternative such as pregabalin may have merit. Two cases have also been reported in the literature where adjunctive use of pregabalin reversed sexual dysfunction associated with citalopram treatment of GAD.⁶⁷

Comorbid medical illness may also prevent or restrict the use of antidepressants in treatment of some cases, particularly when such illness impacts on the activity of liver enzymes responsible for antidepressant metabolism. The non-CYP450 dependent nature of pregabalin’s pharmacokinetics means that the drug may be safer and more tolerable than antidepressants where liver enzymes are abnormal. Caution should be taken when prescribing pregabalin to individuals with renal impairment, as the rate of excretion of the drug is slowed, and may therefore require reduced dosages.²⁸

Pregabalin may be preferable to the use of benzodiazepines in individuals with current or previous



substance use disorders. While benzodiazepines have significant abuse/dependence potential, the risk of such problems with pregabalin appears to be significantly less. For individuals with substance use problems, pregabalin may offer a medication that is effective for GAD, without exposing the patient to the risk of dependence or abuse that may occur with benzodiazepines in this population. It should be noted, however, that although pregabalin appears to have significantly lower abuse potential than benzodiazepine anxiolytics, previous studies have identified euphoria as an adverse event in up to one sixth of patients.^{33,37} Furthermore, as mentioned above, abuse and addiction have been documented in patients in Sweden, accounting for approximately 8% of abuse/addiction adverse events in this country.⁵⁸

Pregabalin may also offer advantages where an individual with GAD is concurrently prescribed other pharmacological agents. Pregabalin's lack of effect on CYP450 enzymes means that it is unlikely to interfere with the metabolism of other medications. Additionally, other medications that induce or inhibit these enzymes are also unlikely to interfere with the pharmacokinetics of pregabalin. Concurrent prescription of benzodiazepines or opiates are unlikely to be affected by pregabalin.

Pregabalin may also be advantageous when other comorbid conditions are present which have also been shown to respond to pregabalin treatment. There is some evidence that pregabalin is effective in treatment of migraine,⁶⁸ fibromyalgia,⁶⁹ post-herpetic neuralgia,⁷⁰ and as an adjunct in the treatment of seizure disorders such as partial epilepsy.⁷¹ For individuals with any of these conditions comorbid with GAD, pregabalin offers a single pharmacotherapeutic intervention which may exert a therapeutic effect in more than one area.

Conclusions

Generalized anxiety disorder is a chronic psychiatric disorder that leads to marked impairment and reduced quality of life. Previous pharmacological interventions for GAD have utilised drugs such as antidepressants and benzodiazepines. Pregabalin is a novel GABA analogue that as demonstrated short-term, rapid reduction in GAD symptoms. There is preliminary evidence for efficacy in treatment of GAD in older adults, and longer term efficacy of the drug over 24 weeks in preventing relapse.

The drug does not undergo extensive hepatic metabolism, allowing for prescription in conjunction with other medications. Pregabalin may also be used in individuals with health conditions which alter liver functioning.

Pregabalin use is associated with adverse events such as dizziness and drowsiness in approximately one third of individuals. These are usually reported as mild-to-moderate, and transient. Early evidence suggests that the drug does not have the same abuse/dependence potential as benzodiazepines, and discontinuance effects are less than those observed for lorazepam. Despite this, up to one 40% of individuals taking pregabalin for GAD at higher doses discontinued treatment.

Despite the cautious optimism over the role of pregabalin in the treatment of GAD, there are several limitations in the current literature that need to be resolved before the utility of the drug can be more firmly established. First, all eight of the previous trials for pregabalin were designed as efficacy studies, in which potential confounding variables such as comorbid diagnoses were excluded. While efficacy studies are carefully designed to maximise internal validity through strict exclusion criteria, this has the potential to limit the generalizability of the findings to routine clinical practice. As such, effectiveness studies in which pregabalin is used under conditions typical of routine clinical inpatient and outpatient practice are needed to determine whether the results of efficacy trials are applicable outside carefully controlled trials. Less than half of the efficacy studies allow prescribers to vary the dose according to observed treatment response and adverse effects. Again, further studies in which dosage adjustments were permitted, may more closely resemble the typical prescribing interactions encountered by individuals with GAD and their prescribing medical practitioners.

Long term improvement in GAD symptoms as a result of pregabalin has only been investigated in a single study.³⁷ This research examined the use of pregabalin only up to 24 weeks. As GAD is known to be a chronic condition², in which there is a significant risk of relapse,⁶⁴ additional longer term studies are required, including research which extends beyond 24 weeks. Currently, the optimal duration of administration remains unknown, as is whether pregabalin can be ceased after a period



of time without risking relapse. Further research is required in these areas.

Although previous research has established the rapid onset of anxiolytic effect of pregabalin, there is some initial evidence that this may not immediately lead to expected improvements in quality of life for the individual with GAD.³⁶ It is yet to be demonstrated whether improvements in quality of life occur with pregabalin treatment of GAD, or whether these lag behind reductions in anxiety symptoms. Effectiveness studies in which assessment of GAD symptoms are accompanied by subjective evaluations in quality of life are required so that the impact of pregabalin can be more fully assessed.

Despite the efficacy studies demonstrating the positive effect of pregabalin on GAD symptoms, only one study has contrasted the efficacy of the drug against the economic costs and benefits in a cost-effectiveness evaluation. Cost-effectiveness of pregabalin in the treatment of GAD is particularly important given that there are a range of other treatments which have demonstrated efficacy in reducing symptoms, and which are also available as generic drugs, and therefore may be cheaper than a newer agent like pregabalin. Additional cost-effectiveness studies are required, across different nations, to establish the health economics of pregabalin use in GAD.

A final area for future research is to examine individual outcomes using a less arbitrary criteria for treatment response. All of the controlled trials of pregabalin in the treatment of GAD have utilised a criterion of a 50% reduction in HAM-A scores from baseline. This criteria is an arbitrary one which does not take into account either the psychometric reliability of the HAM-A, or the relative distributions of the normal and GAD populations on this measure. More sophisticated statistical methods are now available which use less arbitrary criteria to establish the reliability and clinical significance of the change in symptoms for each individual.^{72,73} Future research could use these in addition to the 50% reduction criteria to provide a less arbitrary measure of individual response in pregabalin treatment.

Conclusion

Pregabalin is a novel agent with demonstrated efficacy in the treatment of GAD. The drug is safe, with adverse effects that are generally uncommon and

minor. The pharmacokinetics of the drug allow for it to be used when other drugs are also prescribed, or other illnesses are comorbid. Despite the initial success of pregabalin in the treatment of GAD in the first efficacy studies, however, there are still a number of findings which require replication. The small available literature regarding pregabalin treatment of GAD also has several limitations which may be addressed in future research.

Disclosures

This manuscript has been read and approved by the author. This paper is unique and not under consideration by any other publication and has not been published elsewhere. The author and peer reviewers report no conflicts of interest. The author confirms that they have permission to reproduce any copyrighted material.

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