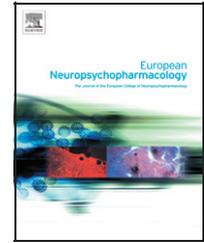




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Efficacy of pregabalin in depressive symptoms associated with generalized anxiety disorder: A pooled analysis of 6 studies

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Abstract

Epidemiological evidence supports comorbidity of generalized anxiety disorder (GAD) and major depressive disorder (MDD) or dysthymia, and its association with significant disability. As pregabalin, a new $\alpha_2\text{-}\delta$ anxiolytic treatment for GAD, unlike most other licensed treatments for GAD has not undergone investigation in patients with MDD, we examined its efficacy in depressive symptoms associated with GAD, through a post-hoc analysis of the existing clinical trial database. The results provide consistent evidence that in patients with GAD pregabalin reduced associated symptoms of depression. This was seen in the 150 mg/day, 300–450 mg/day and 600 mg/day dosing groups. Even in subjects with more prominent depressive symptoms, pregabalin remained effective for both sub-syndromal depression and GAD symptoms, with pregabalin 300–450 mg/day demonstrating the most beneficial response. In conclusion, pregabalin, an alternative treatment option for GAD with a novel mechanism of action, also demonstrated efficacy in treating depressive symptoms typically encountered in GAD patients.

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1. Introduction

Recent epidemiological data provide evidence on the comorbidity of generalized anxiety disorder (GAD) and major depressive disorder (MDD) or dysthymia. In the US

National Comorbidity Survey Replication–NCSR (Kessler et al., 2005), the 12-month prevalence of GAD assessed in a nationally representative face-to-face household survey in 9282 respondents using a fully structured diagnostic interview was 3.1%, with 77.5% of GAD cases of a moderate or serious severity. This study also found statistically significant correlations between GAD and Major Depressive Disorder (0.62, $p < 0.05$) or dysthymia (0.55, $p < 0.05$). The European Study of the Epidemiology of Mental Disorders (Alonso et al., 2004) examined 12-month comorbidity patterns of mood and anxiety disorders in

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21,425 completed computer-assisted diagnostic interviews. Among subjects with GAD, 69.4% also fulfilled the diagnostic criteria for at least one other disorder during the previous 12-months, with females having significantly higher comorbidity (75.7%, 95% CI 66.9, 84.6) than males (51.6%, 95% CI 32.4, 70.8). GAD had strong associations with MDD (OR 33.7, 95% CI 23.2, 49.1) and dysthymia (OR 17.6, 95% CI 10.4, 29.7), and these associations were again particularly pronounced in women. Prevalence rates of GAD in primary care samples were found to vary between 2.8% and 8.5% (Roy-Byrne and Wagner, 2004; Kroenke et al., 2007; Ansseau et al., 2005), and of comorbid GAD plus MDD were 4.1% (Ansseau et al., 2005). A recent epidemiological study of the prevalence of GAD among primary care patients in Denmark, Finland, Norway, and Sweden found that the age-standardized rates ranged from 4.1–6.0% for males and from 3.7–7.1% for females (Munk-Jørgensen et al., 2006).

The presence of comorbid MDD in GAD subjects is associated with significant disability (Hunt et al., 2002; Wittchen, 2004). The disability associated with GAD comorbid with MDD was greater than that when GAD was comorbid with other disorders (Hunt et al., 2004). In addition, comorbidity with MDD significantly lowered the likelihood of recovery from GAD while increasing the likelihood of its

recurrence (Bruce et al., 2001). The presence of comorbid mood disorder in subjects with GAD was associated with a more chronic course of illness, a poorer outcome and a higher incidence of relapse and suicide (Fawcett, 1990; Clayton et al., 1991). GAD with comorbid mood symptoms may also be associated with a lower response to pharmacological treatment (Silverstone and Salinas, 2001). In addition, both minor depressive disorder and sub-syndromal depressive symptomatology were found to be highly prevalent in subjects with GAD and associated with significant functional impairment (Rappaport and Judd, 1998; Rappaport et al., 2002).

Current clinical management of GAD usually involves pharmacotherapy, psychotherapeutic interventions, or their combination (Hidalgo and Davidson, 2001). Historically, benzodiazepines have been the preferred pharmacologic intervention for GAD, however their use is associated with drowsiness/sedation, potential for abuse and dependence and lack of efficacy in depressive symptoms associated with GAD (Montgomery, 2006). Current treatment guidelines for GAD emphasize the role of selective serotonin reuptake inhibitors (SSRIs), selective serotonin-norepinephrine reuptake inhibitors (SSNRIs), tricyclic antidepressants (TCAs), and the 5-HT_{1A} agonist buspirone, rather than benzodiazepine anxiolytics (Bandelow et al., 2002; Baldwin et al., 2005). It is thought that the ideal treatment for GAD would

Table 1 Overview of studies included in the pooled data analysis

Study	Subjects and dosage	Concomitant medication	17-HAMD score at baseline
			Mean (SD)
Feltner et al. 2003 4 WK DB+1 WK taper after the study end	Pgb 150 mg, n=69	Zolpidem 5 mg PRN for insomnia, but not more than 2 nights per week	Pgb 150 mg, 14.2 (3.9)
	Pgb 600 mg, n=70		Pgb 600 mg 13.6 (3.6)
	Lzp 6 mg, n=68		Lzp 6 mg 13.9 (3.9)
	Pbo, n=69		Pbo 13.3 (3.5)
Pande et al. 2003 4 WK DB+1 WK taper after the study end	Pgb 150 mg, n=70	Same as in Feltner et al. 2003	Pgb 150 mg, 12.8 (4.1)
	Pgb 600 mg, n=66		Pgb 600 mg, 13.8 (4.8)
	Lzp 6 mg, n=68		Lzp 6 mg, 14.0 (4.6)
	Pbo, n=67		Pbo, 13.0 (4.8)
Rickels et al. 2005 3 WK DB target dose+2 WK DB taper and follow up	Pgb 300 mg, n=91	Same as in Feltner et al. 2003	Pgb 300 mg, 13.0 (4.5)
	Pbg 450 mg, n=90		Pbg 450 mg, 13.0 (4.6)
	Pgb 600 mg, n=89		Pgb 600 mg, 13.0 (4.6)
	Alp 6 mg, n=93		Alp 6 mg, 13.0 (4.4)
Pohl et al. 2005 5 WK double-blind target dose+1 WK double-blind taper	Pgb 200 mg, n=78	Same as in Feltner et al. 2003	Pgb 200 mg, 14.0 (3.6)
	Pbg 400 mg, n=89		Pbg 400 mg, 14.0 (4.0)
	Pgb 450 mg, n=88		Pgb 450 mg, 14.0 (4.4)
	Pbo, n=86		Pbo, 14.0 (4.4)
Data on file, Pfizer, Inc. 4 WK DB+1 WK taper after the study end	Pgb 150 mg, n=71	Same as in Feltner et al. 2003	Pgb 150 mg, 15.9 (4.1)
	Pgb 600 mg, n=71		Pgb 600 mg, 15.6 (4.5)
	Lzp 6 mg, n=70		Lzp 6 mg, 15.5 (4.6)
	Pbo, n=70		Pbo, 15.9 (4.5)
Montgomery et al. 2006 5 WK DB target dose+1 WK DB taper	Pbg 400 mg, n=98	Same as in Feltner et al. 2003	Pbg 400 mg, 12.2 (3.6)
	Pgb 600 mg, n=111		Pgb 600 mg, 12.2 (4.0)
	Venl 75 mg, n=114		Venl 75 mg, 12.0 (3.4)
	Pbo, n=103		Pbo, 12.8 (4.9)

WK=week EP=endpoint Pbo=placebo Alp=alprazolam BL=baseline Pgb=pregabalin Lzp=lorazepam Venl=venlafaxine GAD=generalized anxiety disorder 17-HAMD=17 item Hamilton Rating Scale for Depression HAMA=Hamilton Anxiety Rating Scale CGI-I=Clinical Global Impressions–improvement scale.

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