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REVIEW

Effects of pregabalin on sleep in generalized anxiety disorder

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Abstract

Sleep disturbance is a cardinal symptom in both DSM-IV and ICD-10 criteria for generalized anxiety disorder (GAD). This review summarizes the results of clinical trials and pooled analyses that provide data on pregabalin's effect on sleep disturbance in patients diagnosed with GAD. The hypothesized mechanism of action of pregabalin is distinctly different from other anxiolytics. Pregabalin binds to a membrane $\alpha 2\delta$ subunit protein to inhibit release in excited central nervous system neurons of neurotransmitters implicated in pathological anxiety. Treatment with pregabalin has been found to be associated with significant improvement in GAD-related sleep disturbance across seven placebo-controlled clinical trials. Treatment with pregabalin is associated with improvement in all forms of insomnia and improvement in sleep has been found to be correlated with reduction in functional impairment and improvement in quality of life on subjective global measures. Results of a mediational analysis suggest that 53% of the effect of pregabalin on sleep disturbance was due to a direct effect and 47% was due to an indirect effect, mediated through prior reduction in anxiety symptom severity. In patients with GAD, improvement in sleep has been found to be associated with a reduction in daytime sleepiness. However, dose-related sedation is reported, typically in the first 2 wk of treatment, in approximately 10–30% of patients, depending on the dose used and the speed of titration. Insomnia is a common component of the clinical presentation of GAD and pregabalin appears to be an efficacious treatment for this often chronic and disabling symptom.

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Key words: Anxiety, insomnia, pregabalin, sleep disturbance.

Introduction

Generalized anxiety disorder (GAD) is a common disorder with a lifetime prevalence in the community estimated to range from 2.8 to 5.7% (Alonso & Lepine, 2007; Kessler *et al.* 2005). Insomnia occurs even more frequently in the general population, with prevalence rates in the range of 5–15%, even when the diagnosis is restricted to severe complaints of disturbance in sleep onset or sleep maintenance that persist for >2 wk and are associated with significant impairment in functioning (Ohayon, 2002). Insomnia that presents as a symptomatic complaint, yet does not meet full diagnostic criteria, has been estimated to occur in approximately 25–30% of adults in the general population and has been associated with significant levels of occupational impairment (Kessler *et al.* 2011; Ohayon, 2002).

GAD and insomnia frequently co-occur. This is partly attributable to the fact that sleep disturbance is a cardinal diagnostic criterion for GAD in both the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition and the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (Slade & Andrews, 2001). In fact, the symptom of insomnia has been reported to be the most frequent primary complaint among patients presenting with GAD in the primary care practice setting, with an incidence of 32.5% (Wittchen *et al.* 2002). Full diagnostic co-morbidity between insomnia and GAD is also very common.

Insomnia and major depressive disorder (MDD) have a high level of co-morbidity; the presence of insomnia is associated with a significantly higher likelihood of having a GAD diagnosis when compared to patients who do not report insomnia (Breslau *et al.* 1996; Johnson *et al.* 2006; Taylor *et al.* 2005). The results of several longitudinal studies indicate that insomnia, either as a symptom or a diagnosis, typically precedes the onset of MDD, frequently by >1 yr, with onset of insomnia associated with a 4-fold increased risk of developing a subsequent episode of MDD (Breslau *et al.* 1996; Chang *et al.* 1997; Eaton *et al.* 1995; Johnson *et al.* 2006; Weissman *et al.* 1997).

In contrast, the onset of an anxiety disorder (most notably, GAD) has been reported to precede the onset of

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insomnia in the majority of cases (Johnson *et al.* 2006; Ohayon & Roth, 2003). The occurrence of an anxiety disorder has also been reported to be associated with a 3- to 5-fold higher risk of developing subsequent insomnia (Breslau *et al.* 1996; Chang *et al.* 1997; Eaton *et al.* 1995; Johnson *et al.* 2006; Paffenbarger *et al.* 1994; Weissman *et al.* 1997).

The development of insomnia is associated with a significant impairment in functioning and quality of life (Breslau *et al.* 1996; Hamilton *et al.* 2007; LeBlanc *et al.* 2007). Therefore, it is an important target for any effective treatment of GAD. Among patients entering treatment studies, in whom GAD is typically a chronic illness with a median duration >5 yr, moderate-to-severe levels of insomnia have developed in $>75\%$ of patients (Montgomery *et al.* 2009).

Sleep disturbance in GAD

Individuals diagnosed with GAD report a range of subjective sleep complaints, including difficulty with sleep onset (in approximately 50%) and difficulty with sleep maintenance (in approximately 65%; Belanger *et al.* 2004).

The few available studies of patients evaluated in sleep laboratories have found GAD to be characterized by significant reduction in sleep efficiency and total sleep time with delayed sleep onset and increased awakenings (including early morning awakening; Arriaga & Paiva, 1990; Fuller *et al.* 1997; Papadimitriou *et al.* 1988; Saletu-Zyhlarz *et al.* 1997). Furthermore, polysomnography indicates that some individuals with GAD have significant reduction in slow-wave (stage 3/4) sleep (Monti & Monti, 2000) and rapid eye movement (REM) sleep abnormalities (e.g. reduced REM percentage and increased REM latency; Reynolds *et al.* 1983).

The goal of this review is to summarize the effect of pregabalin on sleep disturbance in patients diagnosed with GAD.

Pregabalin pharmacology

Despite its name, pregabalin has no clinically relevant binding to any γ-aminobutyric acid (GABA) type A or type B receptors or transporters (Li *et al.* 2011). Instead, pregabalin exhibits high affinity binding to the $\alpha 2\delta$ type 1 protein of a neuronal voltage-gated calcium channel. Pregabalin binding reduces the intracellular availability of calcium that is required for membrane fusion and release of neurotransmitter into the synaptic cleft, thus resulting in significant inhibition of the release of neurotransmitters implicated in pathological anxiety, such as glutamate and monoamine neurotransmitters (Coderre *et al.* 2005; Cunningham *et al.* 2004; Dooley *et al.* 2000*a*, *b*; Li *et al.* 2011; Maneuf *et al.* 2001; Maneuf & McKnight, 2001).

Pregabalin's mechanism of action (MOA; reducing neuronal excitability) stands in contrast to the MOA of benzodiazepines, which act by enhancing inhibitory activity in the GABAergic receptor complex, the most widely distributed fast inhibitory neurotransmitter in the central nervous system (Kent *et al.* 2002). The MOA of pregabalin also differs from the MOA of the selective serotonin reuptake inhibitor (SSRI) and serotonin–norepinephrine reuptake inhibitor (SNRI) antidepressants that have demonstrated anxiolytic activity and that appear to act via monoaminergic circuits that are hypothesized to underlie various anxiety-related symptoms and behaviours (Andrade, 2011; Martin *et al.* 2010).

The MOA of pregabalin is associated with broad-spectrum efficacy across a range of clinical disorders, in which the final common pathway appears to be central sensitization (as in neuropathic pain and possibly fibromyalgia; Freeman *et al.* 2008; Owen, 2007) or neuronal excitability (as in epilepsy and GAD; Hamandi & Sander, 2006; Kasper *et al.* 2009) or some forms of insomnia associated with hyperarousal (Drake *et al.* 2003).

The different MOAs among the three major classes of anxiolytics (pregabalin, benzodiazepines and SSRI/SNRI anxiolytics) are also associated with differences in the effect on sleep and sleep architecture, as well as the risk of daytime sedation as an adverse effect.

Effect of pregabalin on sleep architecture: data from a healthy volunteer population

Hindmarch *et al.* (2005*a*) conducted a randomized, double-blind, placebo-controlled evaluation of the effect of pregabalin and alprazolam *vs.* placebo on sleep. Before reviewing these data, it is important to note that the study was conducted in a normal control population and it is uncertain whether the results generalize to patients diagnosed with GAD. Compared to placebo, pregabalin significantly increased restorative stage 3/4 sleep, both as a proportion of the total sleep period and the duration of stage 4 sleep. In contrast, alprazolam significantly reduced slow-wave sleep when compared to placebo, which is consistent with findings from previous studies (Barbanoj *et al.* 2005). Even though the study subjects were normal volunteers with no sleep complaints, treatment with pregabalin and alprazolam both resulted in significant increases in total sleep time and improvement in sleep efficiency. These results in normal volunteers are consistent with preclinical results in rodents, which have showed that pregabalin enhances slow-wave and non-REM sleep (Kubota *et al.* 2001). In studies of clinical populations such as those with neuropathic pain, epilepsy, fibromyalgia and GAD (as summarized in the following section), treatment with pregabalin has also been found to significantly increase total sleep time and sleep efficiency (de Haas *et al.* 2007; Roth *et al.* 2010; Russell *et al.* 2009; Sabatowski *et al.* 2004; van Seventer *et al.* 2006).

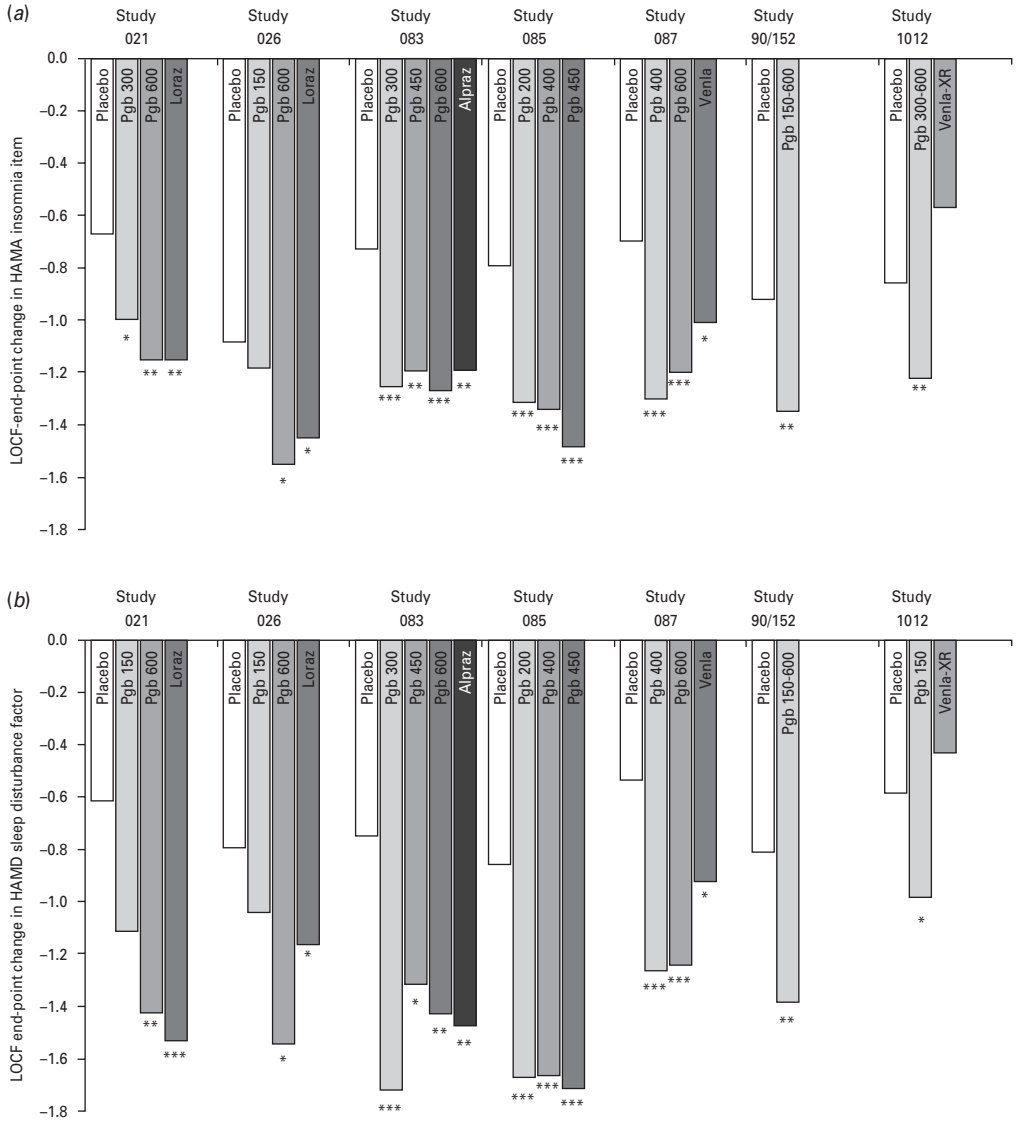

Fig. 1. Change in insomnia for individual short-term, placebo-controlled trials of pregabalin in generalized anxiety disorder [last observation carried forward (LOCF) end-point analysis]. (*a*) Hamilton Anxiety Rating Scale (HAMA) insomnia item change score; (*b*) Hamilton Rating Scale for Depression (HAMD) sleep disturbance factor change score. Pgb, Pregabalin; Loraz, lorazepam; Alpraz, alprazolam; Venla, venlafaxine. * $p<0.05$ *vs.* placebo; ** $p<0.01$ *vs.* placebo; *** $p<0.001$ *vs.* placebo.

Efficacy in treating insomnia in patients with GAD: results from individual studies

The efficacy of pregabalin in treating symptoms of insomnia in patients with GAD has been established on the basis of results from seven previously reported randomized, double-blind, placebo-controlled, short-term trials (RCTs; Feltner *et al.* 2003; Kasper *et al.* 2009; Montgomery *et al.* 2006, 2008; Pande *et al.* 2003; Pohl *et al.* 2005; Rickels *et al.* 2005).

Across all seven individual RCTs, consistent improvement in insomnia on pregabalin treatment was demonstrated on the Hamilton Anxiety Rating Scale (HAMA) insomnia item (Fig. 1*a*), which rates the overall severity of sleep disturbance on a 5-point scale, ranging from 0 (not present) to 4 (very severe). Consistent improvement on pregabalin treatment was also demonstrated for each individual RCT on the three-item sleep disturbance factor of the Hamilton Depression Rating Scale (HAMD; Fig. 1*b*). The HAMD sleep disturbance factor rates early insomnia (difficulty falling asleep), middle insomnia (difficulty staying asleep or restless/disturbed sleep) and late insomnia (waking up too early) on a 3-point severity scale.

Two of the seven GAD trials concurrently evaluated the anxiolytic efficacy of pregabalin and venlafaxine, both the immediate-release formulation (Montgomery *et al.* 2006) and the extended-release formulation, venlafaxine-XR (Kasper *et al.* 2009). When compared to placebo, improvement on the HAMD sleep disturbance

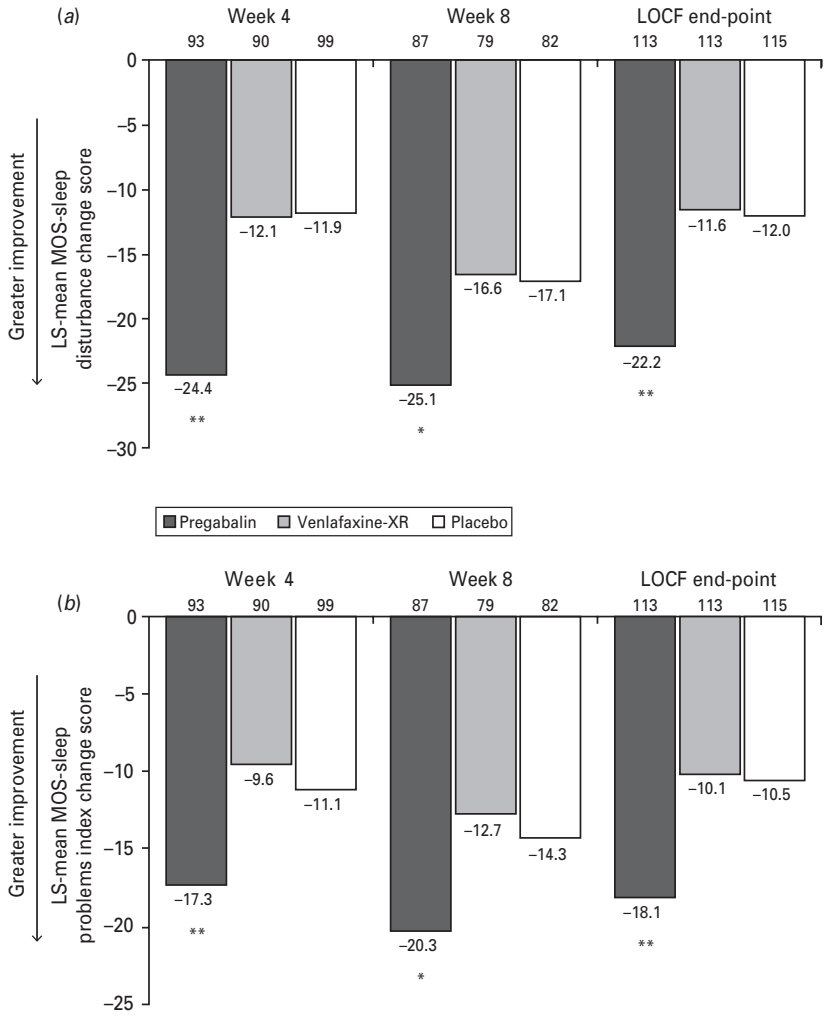

Fig. 2. Least squares (LS) mean change from baseline in Medical Outcomes Study (MOS)-sleep factors. (*a*) MOS-sleep disturbance factor; (*b*) MOS-sleep problems index. * $p<0.05$ *vs.* placebo; ** $p<0.001$ *vs.* placebo.

factor at the 6-wk end-point in the first study (Montgomery *et al.* 2006) was significantly greater than placebo (−0.53) for fixed doses of 400 mg/d pregabalin (−1.26; $p<0.001$) and for 600 mg/d pregabalin (−1.24; $p<0.001$). The magnitude of improvement in the HAMD sleep disturbance factor was lower for the immediate-release formulation of venlafaxine when compared to placebo (−0.92; $p<0.05$; Montgomery *et al.* 2006).

Similar findings were obtained in an 8-wk, flexible-dose study that evaluated treatment with 300–600 mg/d pregabalin and 75–225 mg/d venlafaxine-XR (Kasper *et al.* 2009). Compared to placebo (−0.58), treatment with pregabalin was associated with significant end-point improvement on the HAMD sleep disturbance factor (−0.98; $p<0.05$), whereas end-point improvement was not observed *vs.* placebo for treatment with venlafaxine-XR (−0.43; not significant; Kasper *et al.* 2009). In this same study, the effect of both drugs on insomnia was also assessed using a validated sleep outcome measure, the 12-item Medical Outcomes Study (MOS) Sleep Scale, which includes both a MOS-sleep disturbance factor and a MOS-sleep problems index (Hays *et al.* 2005). As can be seen in Fig. 2*a*, *b*, treatment with pregabalin was associated with significant improvement in both MOS-sleep factors at week 4, week 8 and at last observation carried forward (LOCF) end-point, whereas significant improvement was not observed *vs.* placebo in patients treated with venlafaxine-XR.

Effect of pregabalin on HAMD insomnia factor scores

Symptomatic anxiety has been most frequently associated with high levels of arousal that interfere with the ability to fall asleep (early insomnia; Drake *et al.* 2003). However, patients who meet criteria for GAD often present with insomnia that interferes with both sleep initiation and sleep maintenance. Pooled data from four treatment studies (Montgomery *et al.* 2009) found that GAD patients most commonly reported 'severe' levels of early insomnia (28.7%), but 24.0% reported 'severe' difficulty staying asleep and 13.7% reported 'severe' early morning awakening, a symptom typically associated

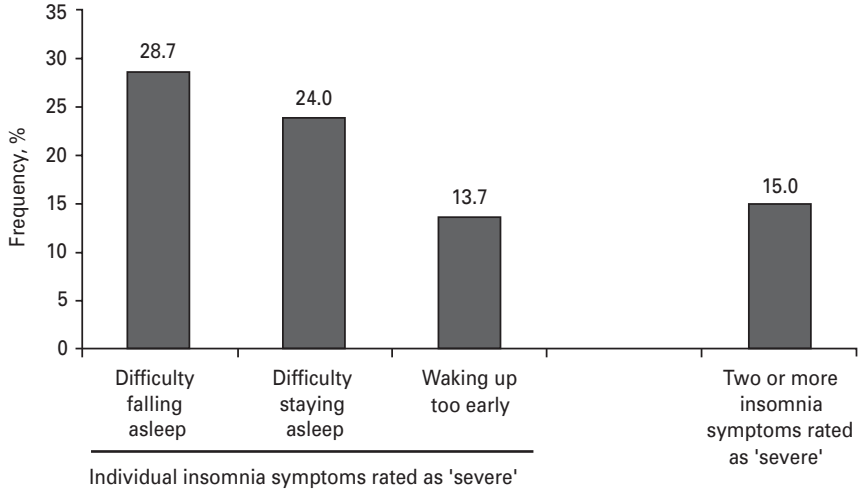

Fig. 3. Frequency of insomnia complaints rated as 'severe' by patients with generalized anxiety disorder: pooled results from four randomized clinical trials.

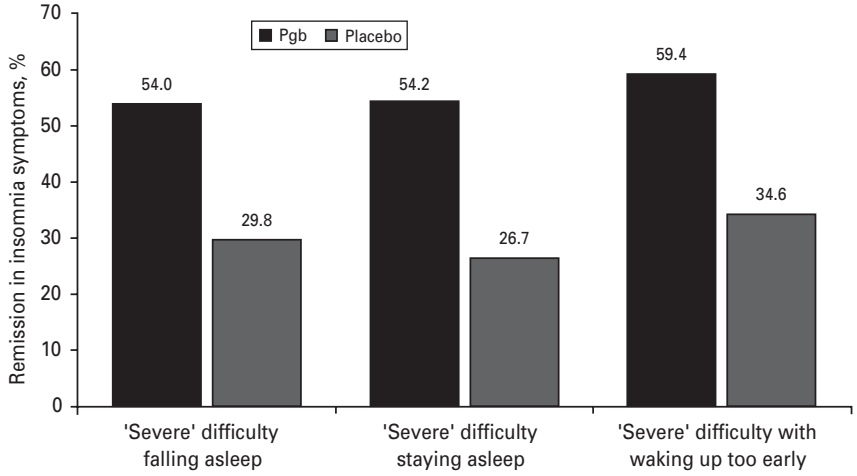

Fig. 4. Remission rates for severe insomnia (baseline Hamilton Rating Scale for Depression insomnia factor score >3) during 4–6 wk double-blind treatment with pregabalin (Pgb) or placebo ($n=1354$).

with MDD (Fig. 3). Even in this subgroup of patients with 'severe' insomnia, 4–6 wk treatment with pregabalin was associated with full symptomatic remission of early, middle and late insomnia in $>50\%$ of patients (Fig. 4).

GAD presenting with high levels of insomnia

A pooled analysis of six double-blind, placebo-controlled clinical trials provides the largest dataset to examine the efficacy of pregabalin and benzodiazepines in treating patients with GAD presenting with moderate-to-severe levels of insomnia (Montgomery *et al.* 2009). A high (moderate-to-severe) level of insomnia was operationally defined as a score of $\geqslant 4$ (of a maximum of 6) on the three-item HAMD sleep disturbance factor. Of a combined sample of 1854 patients, 1002 (54.0%) met criteria for moderate-to-severe insomnia. Treatment with pregabalin in the dosage range of 300–600 mg/d was associated with significant improvement in insomnia in this moderate-to-severe subgroup (Fig. 5). Onset of significant improvement in insomnia occurred by week 1 in both the pregabalin and the benzodiazepine treatment groups. End-point improvement in insomnia was similar after 4–6 wk treatment with both pregabalin and benzodiazepines.

Insomnia and quality of life/functioning

In the study by Kasper *et al.* (2009) summarized previously, the MOS-sleep problems index identified 64.5% of patients with GAD as meeting criteria for insomnia (using the validated criteria score of $\geqslant 45$; Hays *et al.* 2005). The HAMA total score (with the insomnia item not included) was similar at baseline in the insomnia *vs.* non-insomnia subgroups (25.7 *vs.* 25.0). Despite similar levels of anxiety severity, the presence of insomnia was associated with significantly greater impairment in quality of life, as measured by the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) total score (45.3 *vs.* 53.6; $p<0.0001$; Mychaskiw *et al.* 2009). Similarly, the

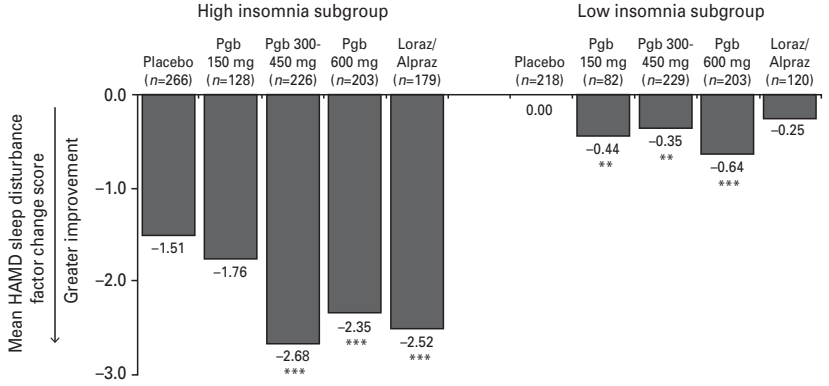

Fig. 5. Efficacy of short-term treatment with pregabalin (Pgb) and benzodiazepines in improving sleep disturbance in patients with generalized anxiety disorder presenting with moderate-to-severe insomnia (high subgroup) or mild-to-no insomnia (low subgroup). Loraz/Alpraz, lorazepam and alprazolam. Hamilton Rating Scale for Depression (HAMD) sleep disturbance factor is the sum of items 4 (early), 5 (middle) and 6 (late) insomnia. *p* value *vs.* placebo is based on analysis of covariance. ** $p<0.01$; *** $p<0.001$. Figure reproduced with permission (Montgomery *et al.* 2009).

mean scores at baseline on the Sheehan Disability Scale were significantly higher (greater impairment) in the insomnia *vs.* non-insomnia subgroup (17.5 *vs.* 14.3; $p<0.0001$; Mychaskiw *et al.* 2009). A Spearman correlational analysis found that end-point improvement on the MOS-sleep problems index was associated with significant improvement in the Sheehan Disability Scale ($r=0.46$; $p<0.0001$) and in the Q-LES-Q scale ($r=-0.48$; $p<0.0001$; an inverse correlation since a higher Q-LES-Q score is associated with improved quality of life).

Effect of pregabalin on sleep in GAD: results of a mediational analysis

The study by Kasper *et al.* (2009) also provided an opportunity to address the mechanistic question as to whether improvement in sleep observed in patients with GAD treated with pregabalin was a direct effect on the GAD symptom of insomnia or an indirect consequence of first reducing other anxiety symptoms, which then enhanced a patient's ability to initiate and maintain sleep. A mediational analysis was performed in which a series of multivariate regression models are simultaneously fit to the average of the HAMA total score and MOS-sleep disturbance subscale (Kline, 2005; MacKinnon, 2008). The direct and indirect effects on sleep disturbance are then estimated as the percentage of total effect that was explained by each path.

The results of this mediational analysis (Bollu *et al.* 2010) found that 53% of the effect of pregabalin on sleep disturbance was due to a direct effect on the GAD symptom of insomnia and 47% was due to an indirect effect, mediated through prior reduction in anxiety symptom severity (Fig. 6). The results of a mediational analysis of pain-related sleep interference in patients diagnosed with fibromyalgia (Russell *et al.* 2009) found similar improvement in sleep, which was attributable both to a direct effect of pregabalin in reducing insomnia and to an indirect effect resulting from improvement in pain that was interfering with sleep. Pregabalin has been found to improve sleep across a wide range of disorders, including neuropathic pain, epilepsy and fibromyalgia (de Haas *et al.* 2007; Roth *et al.* 2010; Russell *et al.* 2009; Sabatowski *et al.* 2004; van Seventer *et al.* 2006). The degree of sleep improvement may not be solely correlated with reduction in pain or improvement in epilepsy. These findings are consistent with the hypothesis that pregabalin could have a primary effect of improving sleep that is independent of its anxiolytic or anti-nociceptive effect. However, it is important to remember that GAD is the only psychiatric indication for which pregabalin is currently approved in the EU.

GAD and insomnia in the elderly: effect of pregabalin

One population that is especially at risk for insomnia is the elderly patient with GAD. The base rate of insomnia complaints in the non-anxious elderly is notably higher than it is in young adults, with a prevalence of 30–50% (Foley *et al.* 1999; Ohayon, 2002). The efficacy of pregabalin in treating GAD in the elderly was evaluated in a double-blind, placebo-controlled trial (Montgomery *et al.* 2008). Elderly patients were treated with flexible daily doses of pregabalin in the range of 150–600 mg, with a mean daily dose of 270 mg. Initial dose titration in this elderly sample was slower than in previous adult studies, with pregabalin treatment initiated at 50 mg/d, followed by an increase to 100 mg/d on day 3 and 150 mg/d on day 5.

At baseline, 65.7% of patients met criteria for moderate-to-severe insomnia (HAMD sleep disturbance score $\geqslant 3$ of a maximum score of 6); with 57.9% reporting severe early insomnia, 40.4% severe middle insomnia and 26.4% severe early morning awakening. Treatment with pregabalin significantly reduced the HAMA total score compared to placebo and significantly improved

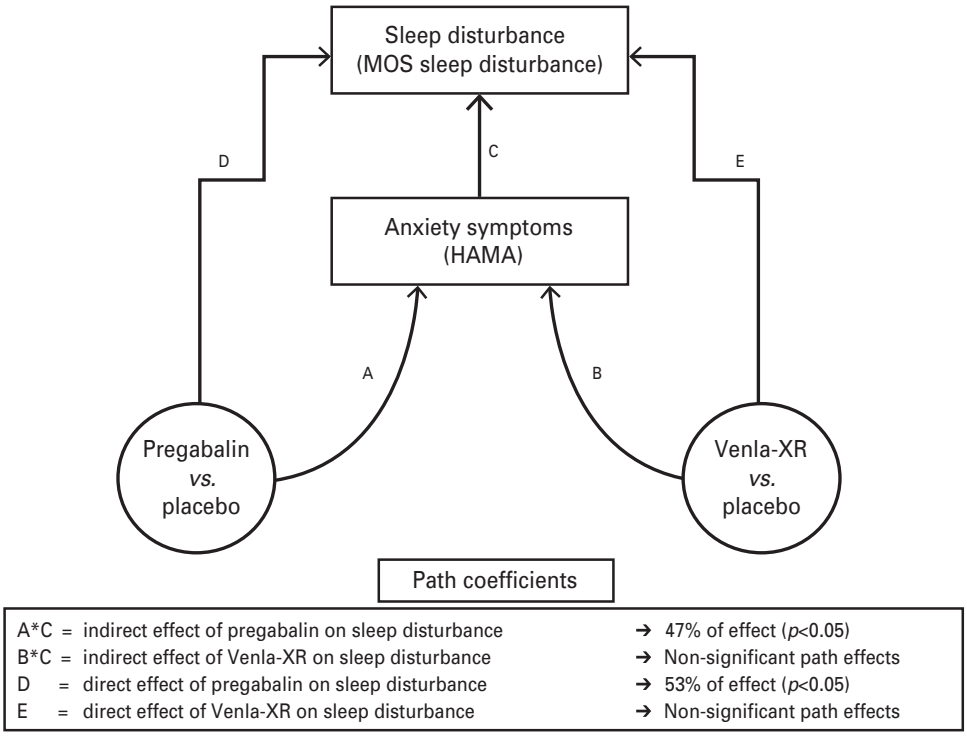

Fig. 6. Direct and indirect effects of pregabalin in improving sleep: results of a mediational analysis. HAMA, Hamilton Anxiety Rating Scale; MOS, Medical Outcomes Study; Venla-XR, venlafaxine-XR.

insomnia symptoms in the moderate-to-severe subgroup, with 64.2% achieving insomnia responder status on a LOCF end-point analysis (*vs.* 44.1% on placebo; $p < 0.05$). Furthermore, complete remission of insomnia symptoms was achieved by 43.3% of patients with severe early insomnia, 40.4% of patients with severe middle insomnia and 42.2% of patients with severe late insomnia.

Safety and tolerability

Overall, treatment with pregabalin is well tolerated; many of the most frequent adverse events (e.g. somnolence, dizziness) are mild-to-moderate in intensity and are limited to the first 2–3 wk treatment (Montgomery, 2006; Montgomery *et al.* 2008). The efficacy of pregabalin in improving insomnia in patients diagnosed with GAD must be weighed against the potential for causing daytime sedation. There are two sources of information that provide data on the incidence of somnolence during treatment with pregabalin. The first dataset consists of phase II/III clinical trials of pregabalin in GAD. The incidence of somnolence in pooled data from these studies is summarized in Fig. 7*a* (Montgomery *et al.* 2009). As can be seen, there is a modest dose-related increase in somnolence across the dosing range of 150–600 mg/d. In patients with GAD presenting with moderate-to-severe levels of insomnia, treatment with pregabalin, even at the 600 mg/d dose, is associated with a lower incidence of insomnia than treatment with benzodiazepines (31.5% *vs.* 54.2%; Montgomery *et al.* 2009). It is important to note that all of these phase II/III studies were designed as fixed-dose clinical trials with rapid titration (within 7 d) to the assigned dose. In these fixed-dose studies, the median time to onset of somnolence was 1–3 d (depending on the speed of titration) and the median time to resolution of somnolence was 10–24 d, with longer persistence of somnolence occurring at higher doses.

The second dataset, which is more generalizable to actual clinical practice, consists of two flexible-dose studies that permitted titration, based on clinical response, to the optimal dose of pregabalin. In the first study (Kasper *et al.* 2009), the incidence of somnolence was notably lower (9.1%) than in the rapid titration fixed-dose studies (Fig. 7*b*). In the second study, conducted in the elderly (Montgomery *et al.* 2010), the incidence of somnolence was similar in both pregabalin- and placebo-treated patients (10.6% *vs.* 9.4%; Fig. 7*b*).

In addition to evaluating somnolence as a patient-reported adverse event, the flexible-dose study used the MOS-sleep scale to measure the effect of pregabalin treatment on the daytime sleepiness factor. As can be seen in Fig. 8, treatment with pregabalin resulted in improvement on the MOS daytime sleepiness factor that was non-significantly greater than the improvement observed on placebo (Donevan *et al.* 2010). A Spearman analysis found that end-point improvement on pregabalin in the MOS daytime sleepiness factor score was correlated at a trend-significant level with improvement

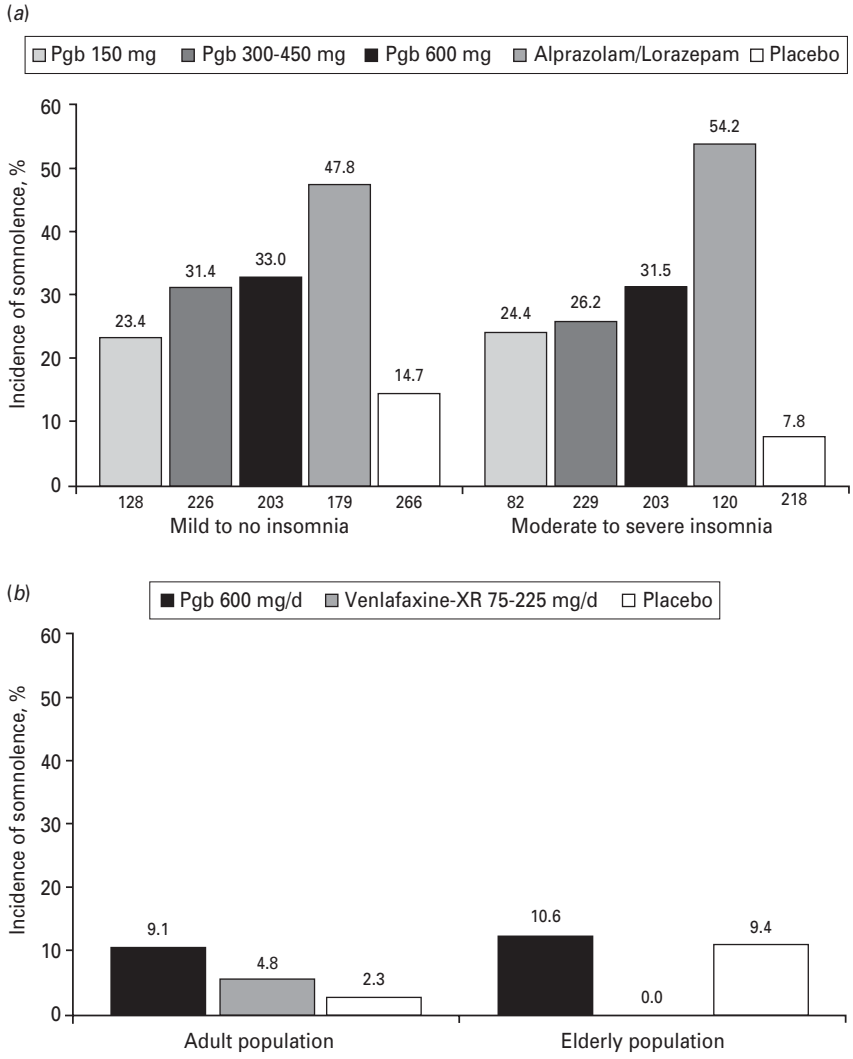

Fig. 7. Incidence of somnolence: pooled data from short-term treatment studies. (*a*) Fixed-dose studies with forced titration; (*b*) flexible-dose studies. Pgb, Pregabalin.

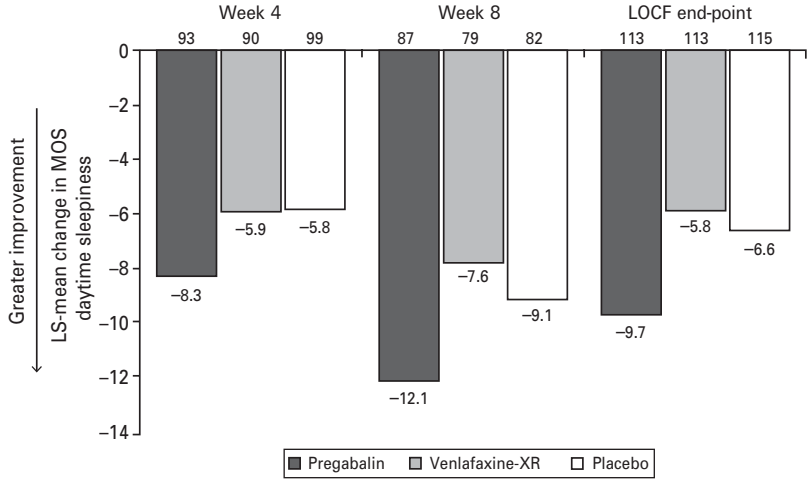

Fig. 8. Least squares (LS) mean change from baseline in Medical Outcomes Study (MOS) daytime sleepiness factor. Data not significant.

in the HAMD sleep disturbance factor score ($r=0.18$; $p=0.065$). This suggests that improvement in daytime sleepiness/fatigue may be a secondary benefit of treatment with pregabalin that is separate from the occurrence of somnolence as an early-onset adverse event.

In addition to daytime somnolence, treatment of anxiety with benzodiazepines is associated with significant impairment in both cognitive and psychomotor function (Lister *et al.* 1988). Furthermore, the attentional and psychomotor effects of benzodiazepines has been linked to a 1.5- to 2-fold increased risk of being in an automobile accident (Barbone *et al.* 1998; Hemmelgarn *et al.* 1997) and a >5-fold increased risk of being in a serious accident requiring hospitalization (Neutel, 1995). The effect of pregabalin and alprazolam on cognitive, psychomotor and driving performance has been evaluated in a cohort of non-anxious subjects using a battery of psychometric tests (Hindmarch *et al.* 2005*b*). Treatment with alprazolam was associated with significant impairment compared to placebo in all attentional, cognitive and reaction time tests, which included brake reaction time in an on-the-road vehicle. In contrast, treatment with pregabalin was associated with improvement relative to placebo in brake reaction time and notably less impairment compared to alprazolam in daytime sedation and other measures of attention and cognitive functioning (Hindmarch *et al.* 2005*b*). Impairments were observed on pregabalin in some tests (e.g. critical flicker fusion, tracking accuracy in a compensatory tracking task), but the impairments were modest, transient and significantly lower than the effects observed on alprazolam.

The results of this study suggest that pregabalin may have a more favourable cognitive and psychomotor safety profile compared to alprazolam. However, the magnitude of the cognitive and psychomotor effects can only be fully evaluated in a clinical population of patients diagnosed with GAD. The only available data we are aware of come from a RCT of pregabalin for the treatment of GAD in elderly patients (Montgomery *et al.* 2008). Because the elderly are particularly sensitive to adverse cognitive effects of benzodiazepines, the study included standardized cognitive assessments (e.g. Digit Symbol Substitution Test, set test). Treatment with pregabalin was not associated with cognitive impairment when compared to placebo on any of the cognitive test battery (Baldinetti *et al.* 2010).

A final safety concern regarding treatment with various classes of anxiolytics is the potential for abuse, dependence and symptoms of withdrawal when discontinuing long-term therapy. Compared to benzodiazepines, pregabalin appears to have a lower risk of abuse and dependence (Feltner *et al.* 2008; Montgomery & Kasper, 2010). However, occasional cases of abuse have been reported and therefore caution should be exercised in prescribing pregabalin to patients with a history of substance abuse or alcoholism.

Conclusions

Insomnia is one of the most frequent and disabling symptoms of GAD. As such, it is an important target for any effective therapy. Pregabalin belongs to a relatively new class of anxiolytics whose MOA, reducing neuronal excitability, stands in contrast to the anxiolytic mechanism of benzodiazepines, which target inhibitory activity in the benzodiazepine-GABAergic receptor complex. As this review has shown, treatment with pregabalin is associated with improvement in early, middle and late forms of insomnia, with improvement in sleep among patients with GAD resulting in reduction in functional impairment and improvement in quality of life. Overall, treatment with pregabalin is well tolerated and many of the most common adverse events are mild to moderate in intensity and limited to the first 2–3 wk treatment. Although sedation may occur as an adverse event in some patients, the incidence is lower compared to benzodiazepines. Pregabalin is a valuable treatment option for patients with GAD who present with insomnia.

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Statement of Interest

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