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ORIGINAL RESEARCH

Modeling the longitudinal latent effect of pregabalin on self-reported changes in sleep disturbances in outpatients with generalized anxiety disorder managed in routine clinical practice

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Background: Anxiety disorders are among the most common psychiatric illnesses, with generalized anxiety disorder (GAD) being one of the most common. Sleep disturbances are highly prevalent in GAD patients. While treatment with pregabalin has been found to be associated with significant improvement in GAD-related sleep disturbance across many controlled clinical trials, mediational analysis has suggested that a substantial portion of this effect could be the result of a direct effect of pregabalin. Thus, the objective of this study was to model the longitudinal latent effect of pregabalin or usual care (UC) therapies on changes in sleep in outpatients with GAD under routine clinical practice.

Methods: Male and female GAD outpatients, aged 18 years or above, from a 6-month prospective noninterventional trial were analyzed. Direct and indirect effects of either pregabalin or UC changes in anxiety symptoms (assessed with Hamilton Anxiety Scale) and sleep disturbances (assessed with Medical Outcomes Study-Sleep Scale [MOS-S]) were estimated by a conditional latent curve model applying structural equation modeling.

Results: A total of 1,546 pregabalin-naïve patients were analyzed, 984 receiving pregabalin and 562 UC. Both symptoms of anxiety and sleep disturbances were significantly improved in both groups, with higher mean (95% confidence interval) score reductions in subjects receiving pregabalin: −15.9 (−15.2; −16.6) vs −14.5 (−13.5; −15.5), P=0.027, in Hamilton Anxiety Scale; and −29.7 (−28.1; −31.3) vs −24.0 (−21.6; −26.4), $P<0.001$, in MOS-S. The conditional latent curve model showed that the pregabalin effect on sleep disturbances was significant (γ=−3.99, $P<0.001$), after discounting the effect on reduction in anxiety symptoms. A mediation model showed that 70% of the direct effect of pregabalin on sleep remained after discounting the mediated effect of anxiety improvement.

Conclusion: A substantial proportion of the incremental improvements in anxiety-related sleep disturbances with pregabalin vs UC were explained by its direct effect, not mediated by improvements in anxiety symptoms.

Keywords: latent curve analysis, pregabalin, usual care, generalized anxiety disorders, sleep disturbances

Introduction

Anxiety disorders are among the most common psychiatric illnesses, with generalized anxiety disorder (GAD) being one of the most common in primary care.[1–3] Lifetime prevalence of GAD has been estimated to be 2%–3% in Europe and near 6% in the United States.[1,4,5] GAD is a chronic disorder characterized mainly by pathological worry, which presents with a variety of somatic and psychological symptoms.[6] It has

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been found that GAD has a great impact on health-related quality of life, and especially on sleep. It has also been found to have an impact on patient functionality, causing substantial disability.[1]

The pharmacological management of GAD is centered mainly on anxiolytic drugs (ie, benzodiazepines), either in monotherapy or in combination.[7] However, benzodiazepines have limited efficacy in relieving comorbid depressive symptoms and have undesirable effects, and the general guidance is that benzodiazepines should be restricted to short-term use.[8–11] Despite this, usual care (UC) practice including these drugs is still widespread.[8–11] As they are recommended, effective treatments that may be used on a long-term basis include selective-serotonin reuptake inhibitors (SSRIs) and selective serotonin-norepinephrine reuptake inhibitors (SNRIs), and many patients with GAD are receiving such medicines on a daily basis, either as monotherapy or as an add-on treatment.[11–14] Pregabalin has also shown to be effective in the reduction of the psychic and somatic symptoms of GAD,[15–17] and has therefore been recommended, along with other anxiolytic drugs (ie, SSRI, SNRI, etc.), as a first-choice treatment in this disorder.[11] In addition, pregabalin has shown a beneficial effect on sleep and sleep architecture that differs from that of benzodiazepines in healthy volunteers; this effect is characterized by the enhancement of slow-wave sleep (SWS).[18,19] Polysomnography revealed fewer awakenings, more time spent in SWS, and less time spent in stage 1 sleep, suggesting that pregabalin consolidates fragmented sleep and increases depth of sleep in some health conditions (fibromyalgia, neuropathic pain, partial epilepsy, etc.).[19] Nevertheless, polysomnography studies have not been carried out yet in patients with GAD. Therefore, the exact relationship between SWS and GAD symptom recovery is still unknown. Pregabalin has also been shown to improve sleep disturbances in patients with epilepsy and subjects with a variety of chronic pain conditions including fibromyalgia.[20,21] In a recent observational benzodiazepine-withdrawal study with pregabalin,[22] patients who still exhibited significant anxiety symptoms at the end of the study showed a significant improvement in their self-reported sleep quality as assessed with the Medical Outcomes Study-Sleep Scale [MOS-S]).[23] As was also recently reported by Bollu et al[24] this would suggest that the effect of pregabalin on these patients' sleep quality was partly independent of its anxiety-symptom amelioration effect. The moderate correlation between the improvement in sleep quality and the improvement in illness severity could be interpreted in the same way.[25] However, it is important to highlight that results from clinical trials could differ from results from daily clinical practice.[26] In clinical trials, patients are selected according to restrictive criteria that usually exclude patients receiving several treatments, which is not necessarily the case for the many GAD patients treated in real clinical practice.[17]

While treatment with pregabalin has been found to be associated with significant improvement in GAD-related sleep disturbance across seven placebo-controlled clinical trials,[27] mediational analysis has suggested that a substantial portion of this effect could be the result of a direct effect of pregabalin.[24] A recent review of the effect of pregabalin on sleep disturbance indicates that this drug has a direct effect on sleep that is different from its analgesic, anxiolytic, and anticonvulsant effects,[28] and that polysomnographic data reveal that pregabalin primarily affects sleep maintenance.[19] To our knowledge, no one to date has explored whether such a direct effect of pregabalin on sleep disturbances, not mediated through prior reduction in anxiety symptom severity, remains when compared with UC treatments in routine clinical practice. Thus, the aim of this study was to carry out a mediation path analysis to test the effect of pregabalin on the reduction in self-reported anxiety-related sleep problems due to the improvement of GAD symptoms when added to the management of community-treated patients with GAD. A stand-alone estimation of mediation for adding pregabalin effects was carried out, in addition to a comparison against UC anxiolytic therapies.

Methods

Study design

A post-hoc analysis was carried out on the existing data from outpatients with GAD diagnosed according to the DSM-IV-TR definition gathered from a 6-month, multicenter, prospective noninterventional trial (the ADAN [Amplification of Definition of Anxiety] study).[29] In brief, the ADAN study was designed to determine the effect of abridging the DSM-IV criteria for GAD, and the study protocol was approved by the local ethics committee of the Hospital Clínico de San Carlos in Madrid. It was conducted according to the Declaration of Helsinki for medical research in the human being. The study was carried out between October 2007 and January 2009 in outpatient mental health clinics all over Spain. Due to the noninterventional design of the study, only three visits (baseline, 3, and 6 months) were planned.

Study population

In the ADAN study, trained psychiatrists with at least 5 years' experience in mental illness diagnosis were asked to

select consecutive, newly-diagnosed GAD patients according to DSM-IV criteria (Mini International Neuropsychiatric Interview was applied) and the so-called abridged criteria.[29] Male and female patients aged 18 or above who had provided their written informed consent to participate in the study and who showed a poor/insufficient response to previous anxiolytic therapy were considered eligible. Poor/insufficient response to previous anxiolytic therapy was defined, in this post-hoc analysis, according to Rickels et al[30] as persistent anxiety symptoms or showing a suboptimal response after a course of a standard-dose regimen with any drug indicated for GAD, alone or in combination, for at least 6 months prior to the baseline study visit. Persistent symptoms or suboptimal response was considered when patients claiming to suffer from anxiety symptoms scored >16 points on the Hamilton Anxiety Scale (HAM-A) and ≥3 on the Clinic Global Impression – Severity Scale (CGI-S) at baseline visit. Patients unable to understand patient-reported-outcomes questionnaires written in Spanish for any reason, including receiving drug-based therapies or severe illnesses that in the judgment of the participating physicians might interfere with the patient's ability to fill in the questionnaires, were excluded from participating in the study.

The post-hoc analysis included here was based on the study population mentioned earlier that included outpatients with GAD, as per the DSM-IV definition only, who were classified into one of the following treatment groups: pregabalin group – patients changing from any treatment at baseline (SSRI/SNRI or other anxiolytic drugs) and starting on or including pregabalin in their therapy for the following 6 months of follow-up; or UC treatment group – patients changing their prior anxiolytic treatment or adding a new anxiolytic other than pregabalin. More detailed information on the treatments followed by patients can be found in the Results section and in Table 1. No patients included in the analysis could have been exposed to pregabalin previously. Only patients changing to pregabalin or modifying their prior anxiolytic treatment were considered. Those continuing on any of the mentioned treatments without any modification in their therapy or those previously exposed to pregabalin were excluded from the analyses. Patients increasing the dose of the prior anxiolytic without adding a new drug were also excluded.

Patient-reported outcomes measured during the study

At baseline, sociodemographic data, current therapy including symptomatic treatments and information on psychiatric and medical illnesses were all recorded. At 3- and 6-month visits, psychiatrists collected data relating to patients' follow-up and current treatments. Functional outcome measures were completed at all three visits and included the following instruments: the HAM-A,[31,32] the CGI-S,[33] and the MOS-S.[23] The HAM-A is a 14-item, interviewer-administered scale formulated as a semistructured interview to assess the subject's level of anxiety. Items are scored from 0 (not present) to 3 (severe). The total score ranges from 0 to 42 points and can be categorized into four severity groups: normal (0–9); mild (10–15); moderate (16–24); or severe (25–42). The MOS-S questionnaire is a patient-reported measure consisting of 12 items that assess the key constructs of sleep. It is self-administered, and patients are asked to recall sleep-related activities over the past four weeks. Instrument scoring results in six scales or domains: sleep disturbance (4 items); snoring (1 item); awakening with shortness of breath or headache (1 item); quantity of sleep (1 item); optimal sleep (1 item); sleep adequacy (2 items); and daytime somnolence (3 items). In addition, two summary index measures that assess sleep problems can also be constructed with 6 or 9 items, respectively, to provide composite scores. Both index measures are highly correlated. The sleep problems index in this article always refers to the 9-item composite measurement only. Quantity of sleep is scored as the average number of hours slept per night. The other scales and composite measurements are scored on a transformed 0–100 metric, where higher scores indicate more of the concept being assessed.

Statistical analysis

For statistical analysis, only patients that fulfilled all inclusion criteria and none of the exclusion criteria listed above were included. Descriptive statistics were extracted for the continuous variables in the study, including the assessment of central tendency and dispersion statistics with their 95% confidence intervals when possible. After describing the output variables considered in the study, a repeated measures analysis of variance (ANOVA) was carried out to interpret changes in the patient-reported outcome (PRO) measures over time and to assess any differences between treatment groups. In a separate analysis, each of the PRO instruments (HAM-A and MOS-S) was used as the dependent variable, treatment group as a between-groups factor, and time as a within-groups factor. Main effects and interaction terms were assessed. Bonferroni adjustment was applied for post-hoc comparisons when necessary.

Table 1 Sociodemographic variables: overall and by treatment group

Variables	Overall	Usual care	Pregabalin
Total patients (N)	1,546	562 (36.4%)	984 (63.6%)
Sex (%)			
Female	68	66	69
Civil status (%)			
Single	24	25	23
Married	56	58	57
Cohabitation	6	5	6
Widow	5	3	5
Divorced/separated	10	9	10
Educational level (%)			
Illiterate	0.4	0.4	0.4
Functional illiterate	3.8	4.3	2.5
Primary	34.5	33.2	34.6
Secondary	21.1	19.1	21.6
Graduate	19.9	20.7	20.8
Postgraduate	19.5	21.9	19.0
Occupation (%)			
Student	1.9	3.0	1.3
Employed	52.5	55.2	54.1
Long-term disabled	7.3	3.9	7.3
Unemployed	7.6	7.1	7.0
Retired	6.1	6.4	4.8
Homemaker	22.6	22.5	23.4
Other	2.1	1.8	2.0
Age (mean, SD) years	45.48 (12.95)	44.35 (13.48)	45.72 (12.52)
BMI (mean, SD) kg/m^2	25.38 (4.17)	25.35 (4.45)	25.37 (4.00)
Anxiolytic treatment at baseline (%)[a]			
SSRI/SNRI + benzodiazepine	46.7	42.7	49.0
Benzodiazepine	24.7	30.8	21.2
SSRI/SNRI	6.4	5.9	6.7
SSRI/SNRI + benzodiazepine + antiepileptic	5.8	3.7	6.9
SSRI/SNRI + benzodiazepine + opioid	1.9	2.0	1.8
SSRI/SNRI + antiepileptic	1.0	0.5	1.3
Benzodiazepine + antiepileptic	1.0	1.4	0.7
SSRI/SNRI + benzodiazepine + antiepileptic + opioid	0.5	0.5	0.4
SSRI/SNRI + opioid	0.3	0.4	0.3
Opioid	0.2	0.4	0.1
Antiepileptic	0.1	0.2	0
Other possible therapy patterns	11.5	11.6	11.5

Notes: [a]Most frequent treatment profiles. Antiepileptic drugs may include gabapentin, topiramate, carbamazepine, or lamotrigine. Other possible therapy patterns may include any of the following alone or in combination with SSRI/SNRI drugs, benzodiazepines, or antiepileptic: buspirone, trazodone, IMAOs, tricyclic antidepressants, etc.
Abbreviations: BMI, body mass index; IMOA, mono-amino-oxidase inhibitor; SD, standard deviation; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

Latent curve model methodology was used to estimate, after adjusting for anxiety reduction, whether differences between pregabalin and UC exist in the evolution of sleep problems over time. In our work, the latent curve model containing time-variant covariates (anxiety levels) and a time-invariant covariate (treatment group) was considered the most adequate procedure to test the hypothesis of this work. Nevertheless, other more frequent and simple models, like repeated measures ANOVA, mediation model, and a time-invariant conditional latent curve model, were also estimated in order to make it easier to interpret results by comparison.

A mediation path-analysis model was estimated using a structural equation model.[34,35] In the proposed model, the treatment administered to patients was considered a dummy exogenous variable $\{x_i: i=1, 2, \ldots, N\}$, taking values $x_i=1$ for pregabalin treatment and $x_i=0$ otherwise. Figure 1 shows the estimated model assessing the effect of pregabalin on MOS-S scores when HAM-A scores mediate. The model estimating the mediated effect of pregabalin on sleep quality benefits when considering anxiety changes needs to include one exogenous variable (receiving pregabalin or not) and two endogenous variables: the change from baseline to month 6 in sleep quality (y_{1i}), which is the dependent variable, and the change from baseline to month 6 in anxiety levels (y_{2i}), which is the mediator variable. Treatment has a direct effect on sleep quality (γ_{11}) and on anxiety levels (γ_{21}), and also a

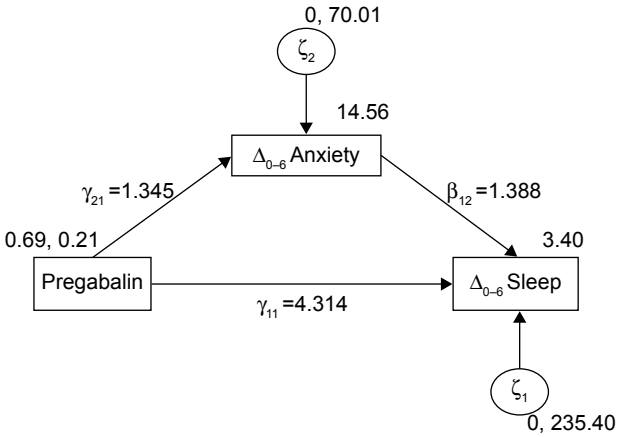

Figure 1 Raw maximum likelihood estimates for the mediation model for sleep disturbances.

Notes: Boxes represent observed variables, and circles unobserved error variables. Lines represent regression effects, and the values above them, raw estimated regression weights. Values above exogenous variables represent means and variances, values above endogenous variables represent means. Mediated effect: $\gamma_{21} \times \beta_{21}$ =1.345×1.388=1.867. Δ_{0-6} Anxiety = change in anxiety level from baseline to month 6. Δ_{0-6} Sleep = change in sleep problems from baseline to month 6. Pregabalin: treatment dummy variable (0= usual care, 1= pregabalin).

mediated effect on sleep quality through anxiety levels ($\gamma_{21} \times \beta_{12}$). Anxiety level has a direct effect on sleep quality (β_{21}). The total effect of treatment on sleep quality is the simple sum of the direct effect plus the indirect effect. The mediation model can be represented by the following set of equations:

$$y_{1i} = \gamma_{11} x_{1i} + \beta_{12} y_{2i} + \zeta_{1i} \quad (1)$$

for sleep changes, and

$$y_{2i} = \gamma_{21} x_{1i} + \zeta_{2i} \quad (2)$$

for anxiety changes. The proposed set of equations can be represented as in Figure 1, replacing variable symbols with conceptual labels describing the content of variables. If complete mediation exists, the indirect mediated effect represented by the product $\gamma_{21} \times \beta_{12}$ should be significant, and the direct effect γ_{11} should equal zero. If partial mediation exists, the mediated effect should still be significant, but the direct effect γ_{11} should not disappear. Raw effects should be considered (and not the standardized values). In order to test the significance of the interaction of terms, the Sobel test was applied.[36,37] The test statistic can be defined as:

$$z = \gamma_{21}\beta_{12}/(\beta_{12}^2\hat{\sigma}_{\gamma}^2 + \gamma_{21}^2\hat{\sigma}_{\beta}^2). \quad (3)$$

Since the exogenous variable was not measured on a continuous scale, a bootstrap estimation was also used to estimate parameters and standard errors using 1,000 samples.

A latent curve model[33] was also estimated using structural equation modeling. Given that individual variability (individual trajectory of PROs over time) will always be present and may affect the estimation of the mean trajectory, a multivariate approach is preferred, as suggested, in order to obtain better estimates of slope standard errors. Moreover, once a random effects model had been defined, it was also possible to estimate the effect of covariates on the parameters of the model. A null model comparison was estimated first, consisting of an unrestricted latent linear trend for the changes in sleep symptoms over time (baseline, months 3 and 6) with individual random effects on the slope and on the intercept. This model was estimated for UC and pregabalin treatment groups separately in order to compare parameter estimates with those known from the corresponding ANOVAs. Secondly, a competing model was estimated establishing pregabalin treatment as exogenous predictor (1= pregabalin, 0= usual care) of the random slope and intercept. Thirdly, a more elaborated model was tested, including anxiety symptoms measured at each time point as exogenous variables affecting sleep problems acting as covariates. The multilevel model for the latent trajectory was based on two different equations. At the individual level, the trajectory equation for each patient over time was expressed as a linear, time-dependent trend:

$$y_{it} = \alpha_i + \lambda_t \beta_i + \varepsilon_{it}, \quad (4)$$

representing that each patient $i=\{1, \ldots, N\}$ followed an individual trajectory over time y_{it} with a random intercept α_i and a random slope β_i, for case i. The pattern of the trajectory is determined by the λ_t constants, which were selected for the appropriate pattern. The set of values λ_1=0, λ_2=0.5, and λ_3=1 were selected to represent a linear pattern for the three repeated measurements in order to scale the estimate of the slope as the change from baseline to month 6 (instead of the change by time unit). It should be noted that λ_1=0, which is similar to not drawing the corresponding effect arrow in Figure 2. Intercept and slope at the individual level can be expressed as deviations from the mean intercept and the mean slope, and described using two equations (in the unconditional model), one for the random intercept:

$$\alpha_i = \mu_{\alpha} + \zeta_{\alpha i} \quad (5)$$

and another for the random slope:

$$\beta_i = \mu_{\beta} + \zeta_{\beta i}, \quad (6)$$

where μ_{α} and μ_{β} represent the mean intercept and the mean slope, respectively, across all cases, while $\zeta_{\alpha i}$ and $\zeta_{\beta i}$ represent

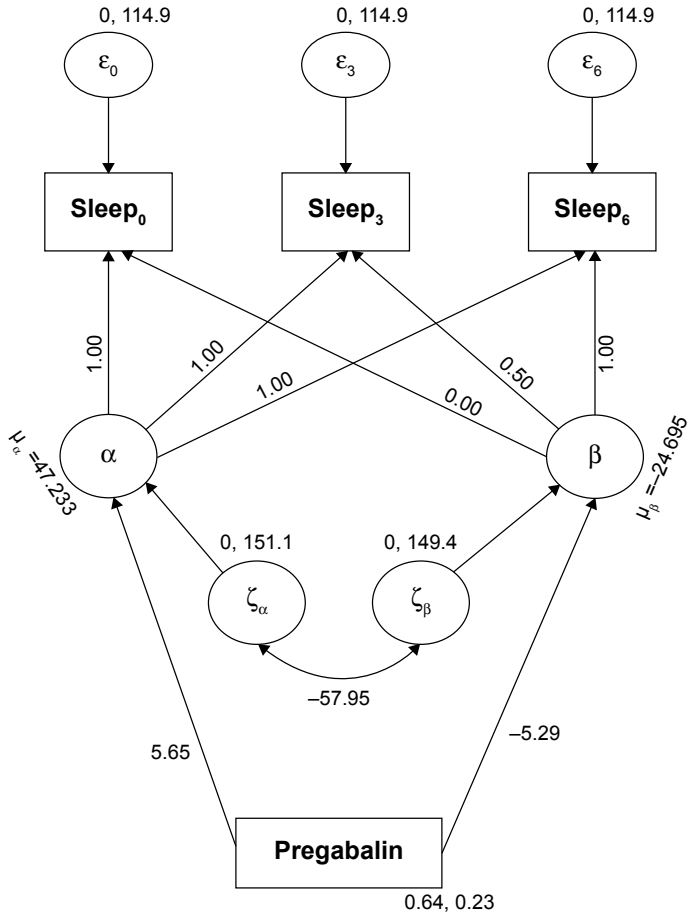

Figure 2 Estimated effect of pregabalin treatment on the random slope and intercept of MOS-S over time.
Notes: Boxes represent observed variables, and circles unobserved error variables. Straight lines represent regression effects, and the values above them, raw estimated regression weights. Curved lines represent covariances and values above their estimate. Values above exogenous variables represent means and variances, and values above endogenous variables represent means. Estimated mean values for the random slope (α) and intercept (β) have been labeled.
Abbreviations: MOS-S, Medical Outcomes Study-Sleep Scale; $Sleep_0$, sleep score at baseline; $Sleep_3$, sleep score at month 3; $Sleep_6$, sleep score at month 6.

the individual disturbance of mean values. Once the model was known to be identified, separate estimates for the mean latent intercept and mean slope values were obtained for each treatment group. Estimates of the latent curve model were compared with those of the repeated measures ANOVAs in order to validate the parameter estimates obtained. After checking parameter concordance, a restricted latent curve model was proposed in which the treatment effect on random slope and intercept could be assessed. This baseline model was used to compare the mediating effect of controlling for anxiety symptoms over the random slope and intercept.

The statistics software packages IBM SPSS Statistics version 20 and IBM AMOS version 20 (IBM Corporation, Armonk, NY, USA) were used to analyze the data sets.

Results

Sample

The ADAN study database included 1,815 patients. Of these, 1,546 subjects had complete information about the treatments received (both at baseline and during follow-up) and fulfilled selection criteria to be included in the analysis. Females made up 68%, mean age was 45.5 years (standard deviation =13.0), and mean body mass index 25.38 kg/m^2 (standard deviation =4.17). Table 1 shows other sociodemographics collected in the study and the most frequent treatment profiles before starting the follow-up period by treatment group. Patients with no information gathered about their treatments, either prior to or during the follow-up period, were excluded from the analyses, and 250 patients (13.8%) who were already being treated with pregabalin were also withdrawn since they were not naïve to the target treatment. A total of 19 patients did not have any information about their treatments and were discarded. None of the treatment patterns (before + during follow-up) were used in more than 10% of cases. The most common pattern was changing from one SSRI/SNRI plus one benzodiazepine to one SSRI/SNRI plus one benzodiazepine plus one antiepileptic (9.7%).

The pharmacological treatment profiles found in the study can be summarized as follows: 14.5% were being treated with SSRI/SNRI medication and remained on SSRI/SNRI treatment during follow-up, but with different drugs, without including pregabalin; 42.3% started the study on SSRI/SNRI medication and included or switched to pregabalin during follow-up; 21.3% were being treated with medication other than SSRI/SNRI or pregabalin and changed to or included pregabalin during follow-up; 11% were on medication other than SSRI/SNRI or pregabalin and changed to SSRI/SNRI during follow-up; 5.8% were on SSRI/SNRI and changed to other medication (not SSRI/SNRI or pregabalin) during follow-up; and 5.1% were on medication other than SSRI/SNRI or pregabalin and remained on other medication (not SSRI/SNRI or pregabalin) during follow-up. In summary, our analysis focuses on those patients changing from any treatment at baseline (SSRI/SNRI or other) and initiating or including pregabalin treatment during the 6 month follow-up; this adds up to 984 patients (63.6%). Other treatment profiles accounted for 562 (36.4%) patients, and these were considered the comparison group. This group was labeled the "usual care" (UC) treatment group. A total of 36 out of 562 patients (6.4%) had received pregabalin before baseline visit in the UC group. Treatment profiles were similar in both groups, except for benzodiazepine-alone treatment, which was found to be less frequently used in the pregabalin group (Table 1, $P<0.05$).

Patient-reported outcomes

Mean anxiety scores, as measured by HAM-A, described a descending trend over time at 3 and 6 months (Table 2). The term representing the interaction of the time pattern with the type of treatment was significant ($F=6.6$, $P=0.002$), and hence the reduction in anxiety over time should be considered different between treatments. The overall difference between treatment groups also reached significance ($F=4.9$, $P=0.027$), representing a smaller score for the anxiety average in the pregabalin group. The MOS-S showed a similar descent pattern at months 3 and 6 (Table 2). The term representing the interaction of the time pattern with the type of treatment was also significant ($F=15.470$, $P<0.001$), and hence the reduction in sleep problems over time should be considered different between treatments. The general changes in sleep problems over time followed a linear pattern ($F=1,955.2$, $P<0.001$), which depicts a continued decrease in sleep problems over time, a decrease that plateaus slightly in the final time period. Furthermore, the overall difference between treatment groups also reached significance ($F=16.3$, $P<0.001$), representing a smaller score for the MOS-Sleep overall average in the pregabalin group. All comparisons between time point measurements were significant within each treatment group ($P<0.001$). While in the pregabalin group the improvement in sleep from baseline to month 6 is –29.7, in the UC group this was smaller, –24.0, representing a significant difference of 5.689 points favoring the pregabalin group ($P<0.001$).

Mediational analysis of the effect of treatment on sleep disturbances

Figure 1 shows model estimates when the mediator variable representing the change in anxiety level from baseline to month 6 (Δ_{0-6} Anxiety $= y_2$) mediates the effect of introducing pregabalin on reduction in sleep problems (Δ_{0-6} Sleep $= y_1$). Values above squared variables represent mean changes, values close to circled unobserved error variables represent centered means (0) followed by error variances, and values above arrows represent estimated regression weights. The first value above the pregabalin variable

Table 2 Mean values (95% confidence interval) [effect size] at baseline by type of patient-reported outcome for each treatment group, differences between treatment at each time measurement, and mean differences from baseline to follow-up visit

	Baseline	Change at month 3[a]	Change at month 6[a]	*F*-value significance (*df*1, *df*2)		
				T	t	*T* × t
HAM-A				0.027	<0.001	0.002
UC	25.1 (24.4; 25.8)	–10.1 (–11.0; –9.2) [1.5]*	–14.5 (–15.5; –13.5) [2.0]*	(1, 1,299)	(2, 2,458)	(2, 2,458)
PGB	26.4 (26.0; 26.9)	–10.2 (–10.8; –9.7) [1.4]*	–15.9 (–16.6; –15.2) [2.3]*			
Difference	1.4 (0.5; 2.2) [0.5]**	0.1 (–0.7; 0.9) [0.03]	1.5 (0.5; 2.4) [0.5]**			
MOS-S composite score				<0.001	<0.001	<0.001
UC	46.2 (46.5; 49.8)	–16.5 (–18.6; –14.3) [1.0]*	–24.0 (–26.4; –21.6) [1.4]*	(1, 1,183)	(2, 2,366)	(2, 2,366)
PGB	54.6 (53.5; 55.7)	–20.4 (–21.9; –18.9) [1.3]*	–29.7 (–31.3; –28.1) [1.9]*			
Difference	6.5 (4.5; 8.4) [1.5]**	4.0 (1.9; 6.0) [0.9]**	5.7 (3.4; 8.0) [1.3]**			

Notes: [a]Change in differences computed as follow-up minus baseline; *$P<0.001$ vs baseline visit; **$P<0.001$ PGB vs UC.
Abbreviations: HAM-A, Hamilton Anxiety Scale; MOS-S, Medical Outcomes Study-Sleep Scale; PGB, pregabalin; *T*, treatment; *t*, time; *T* × *t*, interaction treatment × time; UC, usual care.

(0.69) represents the proportion of cases in the pregabalin group (pregabalin =1), and the second value, the estimated variance for this proportion (0.21=0.69× [1–0.69]). Values above squares representing dependent observed variables denote variances. Table 3 contains parameter estimates for the regression weights, their standard errors, and observed significance level for maximum likelihood estimates, along with bootstrap standard error estimates (SE), standard error estimates for the standard errors (SE-SE), mean parameter estimates (Mean), and bias for the parameter estimates (Bias) and for the standard errors (SE-Bias). All regression estimates were significantly different from 0, and hence we were able to assume that a partial mediation effect was present. Bootstrap estimates did not differ from those obtained by maximum likelihood. Bootstrap standard error estimates were slightly smaller, regression weight estimates slightly bigger, and significance levels unaltered. The direct effect of introducing pregabalin treatment on sleep changes was reduced from γ_{11} =6.18 in the model estimating the stand-alone direct effect (not shown here) to γ'_{11} =4.314 in the mediated model (reducing it to 69.7% of its initial value). Pregabalin direct effect on anxiety changes conveyed a reduction of γ_{21} =1.345 points more than UC, and the direct effect of anxiety reduction on sleep improvement was β_{12} =1.388 greater for the pregabalin group. Both direct effects result in a combined indirect effect of $\gamma_{21} \times \beta_{12}$ =1.345×1.388=1.867. The sum of the direct effect (γ'_{11} =4.314) plus the indirect mediated effect ($\gamma_{21} \times \beta_{12}$ =1.867) adds up to the total effect of 4.314+1.867=6.181, which matches the direct not-mediated effect of pregabalin treatment on MOS-S changes. The Sobel test produced a value of z=2.555 for the mediated effect ($\gamma_{21} \times \beta_{12}$ =1.867), which is significant (P=0.0053).

Latent curve analysis on sleep disturbances

Maximum likelihood estimates obtained with the unrestricted latent curve model for the mean slope were very close to those obtained by repeated measures ANOVA, although new estimates for the standard errors were smaller; hence, estimates of confidence intervals were also narrower. For the UC group, the ANOVA estimate for the slope was dif. (0–6) =–23.981 (SE =1.007), while the latent curve estimate was μ_β =–24.695 (SE =0.605). For the pregabalin group, the ANOVA estimate for the slope was dif. (0–6) =–29.670 (SE =0.676), while the latent curve estimate was μ_α =–29.993 (SE =0.642). The difference in slopes when comparing estimates for the pregabalin group and the UC group was $\Delta\mu_\beta$ =–5.298 points steeper for the pregabalin group.

The alternative estimate of the difference between treatment groups obtained with the restricted model including the effect of treatment (pregabalin) on the random slope and intercept was similar (Figure 2). In this model, μ_β =–24.695 (SE =0.885) represents the latent mean slope for the UC group, and μ_α =47.233 (SE =0.675) the latent mean intercept for this treatment group. The estimated increase in the random slope due to the inclusion of pregabalin treatment was γ_β =–5.292 (SE =1.109, P<0.001), and the estimated change in the random intercept γ_α =5.652 (SE =0.846, P<0.001), both being significant. Again, our estimates conveyed a steeper slope for the linear reduction of sleep problems over time in the pregabalin group.

Lastly, we obtained the estimated change in slope (and intercept) after discounting the effect of anxiety changes over time using the restricted model with covariates (Figure 3). The mean slope for the MOS-S trajectory for the UC group after adjusting for anxiety reduction was μ_β =–7.598 (SE =1.233, P<0.001), while the mean intercept for this group was μ_α =15.970 (SE =1.102, P<0.001). The estimated change in the random slope of MOS-S change over time due to pregabalin treatment, as compared with UC, was γ_β =–3.990 (SE =0.863, P<0.001), and the estimated impact on the random intercept was γ_α =3.973 (SE =0.794, P<0.001), both of which were significant. The effect of anxiety values on MOS-S values was always significant and ranged from 1.297 (SE =0.032) at month 3 to 1.529 (SE =0.039) at month 6.

Discussion

Mediational analysis is an approach to the study of the interaction of several effect variables with a target outcome. It has been applied to the study of the influence of symptoms

Table 3 Maximum likelihood estimates and bootstrap standard errors in mediation analysis for sleep disturbances

Parameter	Estimate	Maximum likelihood			Bootstrap				
		95% CI	SE	*P*	SE	SE-SE	Mean	Bias	SE-Bias
γ_{11}	4.314	2.25–6.03	0.964	<0.001	0.932	0.022	4.291	–0.023	0.031
γ_{21}	1.345	0.32–2.37	0.524	0.010	0.537	0.012	1.343	–0.002	0.017
β_{12}	1.388	1.28–1.49	0.053	<0.001	0.050	0.001	1.390	0.002	0.002

Abbreviations: Bias, bias for the parameter estimates; CI, confidence interval; SE, standard error; SE-Bias, bias for the standard errors; SE-SE, standard error estimates for the standard errors.

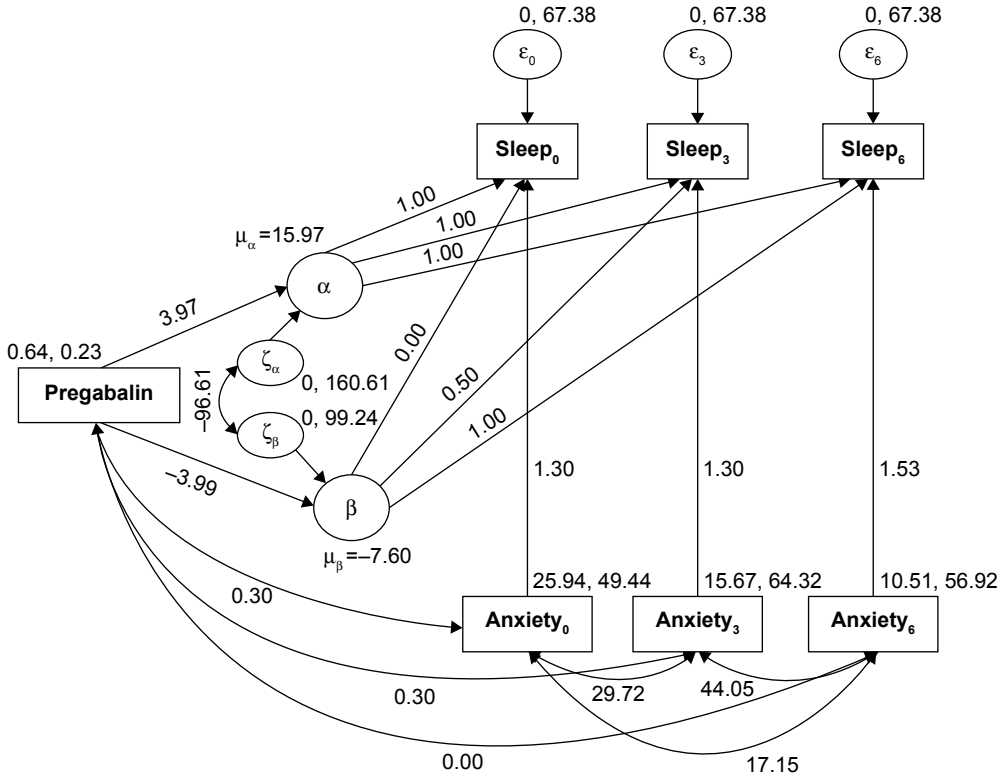

Figure 3 Estimated effect of pregabalin treatment on slope and intercept of MOS-S over time, with the presence of anxiety measures as covariates.
Notes: Boxes represent observed variables, and circles unobserved error variables. Straight lines represent regression effects, and the values above them, raw estimated regression weights. Curved lines represent covariances, and values above their estimate. Values above exogenous variables represent means and variances, and values above endogenous variables represent means. Estimated mean values for the random slope (α) and intercept (β) have been labeled.
Abbreviations: $Anxiety_0$, anxiety score at baseline; $Anxiety_3$, anxiety score at month 3; $Anxiety_6$, anxiety score at month 6; MOS-S, Medical Outcomes Study-Sleep Scale; $Sleep_0$, sleep score at baseline; $Sleep_3$, sleep score at month 3; $Sleep_6$, sleep score at month 6.

in perceived health in several disorders such as depression, anxiety, and pain,[19–21,24] but there is a lack of this type of data assessing the effect on sleep disturbances in real-world conditions of care. The results of this study show that adding pregabalin to the UC for GAD improves sleep disturbances compared with when this drug is not added and the UC is changed or modified with other existing anxiolytics, this being the result of an effect that may be indicative of a dual mechanism: a direct treatment effect and an indirect effect via its anxiolytic action. The direct effect of pregabalin on improving sleep is an important finding, given that sleep disturbances are core complaints in patients suffering from GAD and because of the potential detrimental impact on sleep of many of the pharmacological agents that are currently available.[8,10,12]

Both UC and pregabalin treatment approaches led to a reduction in sleep problems over time. Pregabalin treatment attains a greater reduction in sleep problems after 6 months of treatment, a differential reduction that is attenuated after 6 months. While the reduction in sleep problems for the UC group was –24.0 points, the reduction when adding pregabalin was –29.7 points, indicating a benefit of 5.7 points (23.8% more) for the pregabalin group. A similar pattern was obtained when assessing treatment benefits on anxiety; both treatment strategies led to a significant reduction in anxiety symptoms at month 3 and at month 6, but benefits were greater in the pregabalin group – an extra score reduction of 1.5 points (10.3% more) on the HAM-A scale.

When both treatment effects were combined in a mediation analysis, the direct effect of pregabalin (as compared with UC) on sleep improvement (γ'_{11} =6.18) was significantly attenuated to γ'_{11} =4.31 when the reduction in anxiety symptoms was taken into account. The size of the direct effect of pregabalin on sleep problems was attenuated when anxiety-mediated effect was discounted, but a significant 69.7% of the direct effect on sleep benefits remained, while the mediated effect of anxiety on sleep problems accounted for only 30.3% of the reduction in sleep problems. Bootstrap estimates of the mediation-model effects were not noticeably biased, and standard errors were similar to maximum likelihood estimates, leaving unaltered significance levels.

It was also possible to show that a latent curve model would arrive at similar estimates on the reduction of sleep problems over time during the follow-up. While the 6-month follow-up reduction in sleep problems for the UC group attained a mean value of –24.7, the observed reduction in the pregabalin group was larger, with a mean value of –29.9. The estimated difference in slopes between treatment groups was –5.3 points steeper for the pregabalin group. Latent curve estimates should be considered more accurate than those obtained by repeated measures ANOVA, with smaller standard errors (they are more efficient), and there is no need to adopt a listwise strategy for handling missing values, taking into account all available information for the three measures in time.

Once it was shown that multilevel latent curve estimates were similar to those obtained by traditional ANOVA methods, the effect on sleep problems of adding pregabalin to UC treatment was studied when controlling for anxiety reduction during follow-up. The mean slope for the MOS-S trajectory for the UC group after adjusting for anxiety reduction was –7.60, while the estimated change for the pregabalin group was –3.99 points steeper. The estimated impact on the random intercept due to the inclusion of pregabalin treatment was 3.97 points, which means that pregabalin patients had a more severe condition (on average) at baseline. The estimated model showed that UC produces an effect on the reduction of sleep problems close to the estimated threshold for clinically significant differences of 7.6,[38] after adjusting for anxiety reduction, and including pregabalin leads to a significantly steeper reduction in sleep problems, an increase of close to 53% in the change over the 6-month follow-up (again after controlling for the effect of reduction in anxiety symptoms). In a similar mediation model on the effect of pregabalin on reduction in sleep problems, controlling for anxiety reduction, compared with placebo, Wittchen et al[39] reported a 65.9% direct effect of pregabalin on improvement in insomnia as compared with a 34.1% indirect effect via improvement in anxiety. In our study, the mediation model estimates for the pregabalin effect on sleep improvement accounted for a 69.8% direct effect and a 30.2% indirect effect through anxiety improvement, when compared with UC.

The results of this study show that pregabalin improves sleep, as the result of both a direct treatment effect and an indirect effect via its anxiolytic action that could be indicative of a dual mechanism. As mentioned, the direct effect of pregabalin on improving sleep is an important finding, given that sleep disturbances are core complaints in patients suffering from GAD[5,6] and because of the potential detrimental impact on sleep of many currently available drugs.[8–11] Several sleep instrumental studies have identified negative effects of SSRI/SNRIs, and while benzodiazepines may have sleep benefits, their long-term use is not recommended due to dependence potential.[10,11] Although SSRI/SNRIs have shown significant efficacy in reducing depression and anxiety symptoms, clinical outcomes are likely to be suboptimal for many patients with sleep disturbances.[40] Clinical management of patients should focus on the comprehensive treatment of all anxiety-related symptoms. These findings are consistent with the hypothesis that pregabalin could have a primary effect of improving sleep that is independent of its anxiolytic or antinociceptive effect. In our mediation model, we hypothesized that part of the total effect of pregabalin on sleep disturbance is the direct result of treatment itself, not mediated through anxiety symptoms. Readers should interpret the direct effect of treatment as that due to any factor or factors not studied as a mediator in the model. However, it is important to remember that GAD is the only psychiatric indication for which pregabalin is currently approved in the European Union.

Some limitations should be considered in this work. Firstly, this study was a post-hoc analysis based on an observational design; hence, variables have not been manipulated by the researchers, and random allocation of patients to treatments has not been ensured, as would be done in clinical trials. Also, a sample size calculation was not carried out in order to run this analysis. On the other hand, this analysis was able to show what occurs in the real world of anxiety patients when treated with pregabalin or UC therapies. Another limitation is that the study used a patient-self-reported instrument for sleep disturbances instead of the most sophisticated examination of sleep disorders based on polysomnography evaluation or other types of instrumental tools. However, PRO tools such as the MOS-S are easy to administer and are probably the only viable method to use in real-life conditions of care, giving clinicians an opportunity to explore the health status, in terms of sleep quality, of their patients.

In conclusion, despite the limitations described, this analysis shows, for the first time, that pregabalin treatment was associated with a direct health benefit to sleep problems, in addition to those benefits deriving from the reduction in anxiety symptoms, when compared with the UC pharmacological treatment of patients with a GAD in real-world conditions of care. Thus, we can conclude that the effect of pregabalin treatment on sleep improvement compared with UC was mediated by a reduction in anxiety symptom levels and, also, a direct effect of pregabalin treatment on sleep improvement was experienced.

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Author contributions

All authors had complete access to the data, participated in the analysis and/or interpretation of results, and drafted and approved the content of the manuscript. EA, JLC, JMO, and JR participated in the design and idea for the original study and in the interpretation of data and drafting of the manuscript. MAR performed the statistical analysis, participated in data interpretation, and drafted the first version of the manuscript. All authors were responsible for literature review and extraction of references.

Disclosure

Javier Rejas and Maria Pérez are employees of Pfizer, S.L.U. Miguel Ruiz is an employee of Universidad Autónoma de Madrid and was a paid contractor for Pfizer Inc. in connection with the writing of this manuscript and statistical analysis. The authors report no conflicts of interest in this work.

References

1. Alonso J, Angermeyer MC, Bernert S, et al; ESEMeD/MHEDEA 2000 Investigators, European Study of the Epidemiology of Mental Disorders (ESEMeD) Project. Prevalence of mental disorders in Europe: results from the European Study of the Epidemiology of Mental Disorders (ESEMeD) project. *Acta Psychiatr Scand*. 2004;109(Suppl 420):21–27.
2. Ansseau M, Fischler B, Dierick M, Mignon A, Leyman S. Prevalence and impact of generalized anxiety disorder and major depression in primary care in Belgium and Luxemburg: the GADIS study. *Eur Psychiatry*. 2005;20:229–235.
3. Wetherell JL, Kim DS, Lindamer LA, et al. Anxiety disorders in a public mental health system: clinical characteristics and service use patterns. *J Affect Disord*. 2007;104:179–183.
4. Haro JM, Palacín C, Vilagut G, et al. Prevalencia de los trastornos mentales y factores asociados: resultados del estudio ESEMeD-España. *Med Clin (Bar)*. 2006;126:445–451.
5. Kessler RC, Brandenburg N, Lane M, et al. Rethinking the duration requirement for generalized anxiety disorder: evidence from the National Comorbidity Survey Replication. *Psychol Med*. 2005;35:1073–1082.
6. van Mill JG, Hoogendijk WJ, Vogelzangs N, van Dyck R, Penninx BW. Insomnia and sleep duration in a large cohort of patients with major depressive disorder and anxiety disorders. *J Clin Psychiatry*. 2010;71:239–246.
7. Gould RA, Otto MW, Pollack MH, Yap L. Cognitive behavioral and pharmacological treatment of generalized anxiety disorder: a preliminary meta-analysis. *Behav Ther*. 1997;28:285–305.
8. Martin JLT, Sainz-Pardo M, Furukawa TA, Martín-Sánchez E, Seoane T, Galán C. Benzodiazepines in generalized anxiety disorder: heterogeneity of outcomes based on a systematic review and meta-analysis of clinical trial. *J Psychopharmacol*. 2001;21:774–782.
9. Rickels K, Schweizer E, Csanalosi I, Case WG, Chung H. Long-term treatment of anxiety and risk of withdrawal: prospective study of clorazepate and buspirone. *Arch Gen Psychiatr*. 1988;45:455–450.
10. Baldwin DS, Anderson IM, Nutt DJ, et al. Evidence-based pharmacological treatment of anxiety disorders, post-traumatic stress disorder and obsessive-compulsive disorder: a revision of the 2005 guidelines from the British Association for Psychopharmacology. *J Psychopharmacol*. 2014;28:403–439.
11. Bandelow B, Sher L, Bunevicius R, et al. Guidelines for the pharmacological treatment of anxiety disorders, obsessive – compulsive disorder and posttraumatic stress disorder in primary care. *Int J Psych Clin Prac*. 2012;16:77–84.
12. Keck PE, Strawn JR, McElroy SL. Pharmacologic treatment considerations in co-occurring bipolar and anxiety disorders. *J Clin Psychiatry*. 2006;67:8–15.
13. McElroy SL, Altshuler LL, Suppes T, et al. Axis I psychiatric comorbidity and its relationship to historical illness variables in 288 outpatients with bipolar disorder. *Am J Psychiatry*. 2004;158:420–426.
14. Simon NM, Worthington JJ, Doyle AC, et al. An open-label study of levetiracetam for the treatment of social anxiety disorder. *J Clin Psychiatry*. 2004;65:1219–1222.
15. Feltner DE, Crockatt JG, Dubovsky SJ, et al. A randomized, double-blind, placebo-controlled, fixed-dose, multicenter study of pregabalin in patients with generalized anxiety disorder. *J Clin Psychopharmacol*. 2003;23:240–249.
16. Rickels K, Pollack MH, Feltner DE, et al. Pregabalin for treatment of generalized anxiety disorder: a 4-week, multicenter, double-blind, placebo-controlled trial of pregabalin and alprazolam. *Arch Gen Psychiatry*. 2005;62:1022–1030.
17. Montgomery SA, Tobias K, Zornberg GL, Kasper S, Pande AC. Efficacy and safety of pregabalin in the treatment of generalized anxiety disorder: a 6-week, multicenter, randomized, double-blind, placebo-controlled comparison of pregabalin and venlafaxine. *J Clin Psychiatry*. 2006;67:771–782.
18. Tassone DM, Boyce E, Guyer J, Nuzum D. Pregabalin: a novel gamma-aminobutyric acid analogue in the treatment of neuropathic pain, partial-onset seizures, and anxiety disorders. *Clin Ther*. 2007;29:26–48.
19. Hindmarch I, Dawson J, Stanley N. A double-blind study in healthy volunteers to assess the effects on sleep of pregabalin compared with alprazolam and placebo. *Sleep*. 2005;28:187–193.
20. de Haas S, Otte A, de Weerd A, van Erp G, Cohen A, van Gerven J. Exploratory polysomnographic evaluation of pregabalin on sleep disturbance in patients with epilepsy. *J Clin Sleep Med*. 2005;3:473–478.
21. Roth T, van Seventer R, Murphy TK. The effect of pregabalin on pain-related sleep interference in diabetic peripheral neuropathy or post-herpetic neuralgia: a review of nine clinical trials. *Curr Med Res Opin*. 2010;26:2411–2419.
22. Rubio G, Bobes J, Cervera G, et al. Effects of pregabalin on subjective sleep disturbance symptoms during withdrawal from long-term benzodiazepine use. *Eur Addict Res*. 2011;17:262–270.
23. Hays RD, Stewart AL. Sleep measures. In: Stewart AL, Ware JE, editors. *Measuring Functioning and Well-Being: The Medical Outcomes Study Approach*. Durham, NC: Duke University Press; 1992:235–259.
24. Bollu V, Bushmakin AG, Cappelleri JC, Chen Ch, Feltner D, Wittchen HU. Pregabalin reduces sleep disturbance in patients with generalized anxiety disorder via both direct and indirect mechanisms. *Eur J Psychiatr*. 2010;24:18–27.
25. Montgomery SA, Herman BK, Schweizer E, Mandel FS. The efficacy of pregabalin and benzodiazepines in generalized anxiety disorder presenting with high levels of insomnia. *Int Clin Psychopharmacol*. 2009;24:214–222.
26. Simes RJ. Clinical trials and "real-world" medicine. Trial evidence best informs real-world medicine when it is relevant to the clinical problem. *Med J Aust*. 2002;177:410–411.
27. Holsboer-Trachsler E, Prieto R. Effects of pregabalin on sleep in generalized anxiety disorder. *Int J Neuropsychopharmacol*. 2002;16:925–936.
28. Roth T, Arnold LM, Garcia-Borreguero D, et al. A review of the effects of pregabalin on sleep disturbance across multiple clinical conditions. *Sleep Med Rev*. 2014;18:261–271.
29. Álvarez E, Carrasco JL, Olivares JM, Vilardaga I, López-Gómez V, Pérez M. Broadening of generalized anxiety disorders definition does not affect the response to psychiatric care: findings from the observational ADAN study. *Clin Pract Epidemiol Men Health*. 2012;8:158–168.

30. Rickels K, Shiovitz TM, Ramey TS, Weaver JJ, Knapp LE, Miceli JJ. Adjunctive therapy with pregabalin in generalized anxiety disorder patients with partial response to SSRI or SNRI treatment. *Int Clin Psychopharmacol*. 2012;27:142–150.
31. Hamilton M. Diagnosis and rating of anxiety. *Br J Psychiat*. 1969;3: 76–79.
32. Lobo A, Chamorro L, Luque A, Dal-Ré R, Badia X, Baró E; Grupo de Validación en Español de Escalas Psicométricas (GVEEP). Validation of the Spanish versions of the Montgomery-Asberg depression and Hamilton anxiety rating scales. *Med Clin (Barc)*. 2002;118:493–499.
33. Guy W. Clinical global impressions. In: *ECDEU Assessment Manual for Psycopharmacology*. Rockville, MD: National Institute for Mental Health; 1976:218–222.
34. Baron RM, Keny DA. The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. *J Personal Soc Psychol*. 1986;51:1173–1182.
35. Bollen KA, Curran PJ. *Latent Curve Models. A structural equation perspective*. Hoboken, NJ: John Wiley & Sons; 2006.
36. Sobel ME. Asymptotic confidence intervals for indirect effects in structural equation models. *Sociol Method.* 1982;13:290–312.
37. Soper DS. Sobel Test Calculator for the significance of mediation (Online Software). Available from: http://www.danielsoper.com/statcalc3. Accessed April 2012.
38. Bollu V, Bushmakin AG, Cappelleri JC. Psychometric evaluation of the medical outcomes study sleep scale in patients with generalized anxiety disorder. *Qual Life Res*. 2008;17:A114(abstract 1591).
39. Wittchen HU, Prieto R, Emir B, Donevan S. *Comparative Effects of Pregabalin in Anxiety and Sleep Disturbance: Results of a Path Analysis*. In: 19th European Congress of Psychiaty; March 12–15, 2011; Vienna, Austria.
40. Pollack M, Kinrys G, Krystal A, et al. Eszopiclone coadministered with escitalopram in patients with insomnia and comorbid generalized anxiety disorder. *Arch Gen Psychiatry*. 2008;65:551–562.