Original article

Pregabalin for the discontinuation of long-term benzodiazepines use: An assessment of its effectiveness in daily clinical practice

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ARTICLE INFO

Article history:
Received 7 June 2010
Received in revised form 15 December 2010
Accepted 17 December 2010
Available online 21 February 2011

Keywords:
Pregabalin
Benzodiazepine dependence
Benzodiazepine withdrawal
Benzodiazepine discontinuation

ABSTRACT

Purpose: To evaluate the effectiveness and tolerability of pregabalin in the management of the discontinuation of benzodiazepines in long-term users.

Subjects and methods: We performed a 12-week, prospective, uncontrolled, non-interventional, and observational study in patients aged 18 years old or above, who met DSM-IV-TR criteria for benzodiazepine dependence without other major psychiatry disorder. Evaluations included the Benzodiazepine Withdrawal Symptom Questionnaire, the Hamilton Anxiety Rating Scale, the Clinical Global Impression Scale, and the Sheehan Disability Scale. A urine drug screen for benzodiazepines was performed at baseline and every 4 weeks thereafter. The primary effectiveness variable was success rate, defined as achievement of benzodiazepine-free status at week 12 according to the urine drug screen.

Results and discussion: The mean dose at week 12 was 315 (±166) mg/day. The success rate of the benzodiazepine taper in the primary efficacy population (n = 282) was 52% (95% confidence interval [CI], 46–58). Success rates for women and men were 58% (95% CI, 49–67) and 46% (95% CI, 38–55), respectively. The success rates did not differ according to either the benzodiazepine of abuse or the presence of other substance use disorders. Significant and clinically relevant improvements were observed in withdrawal and anxiety symptoms, as well as in patients’ functioning. At week 12, tolerability was rated as good or excellent by 90% and 83% of the clinicians and patients, respectively.

Conclusion: Our results suggest that pregabalin is an efficacious and well-tolerated adjunctive treatment for benzodiazepine withdrawal.

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1. Introduction

Benzodiazepines are frequently used among the general population of the United States and Europe [22,25] although they have demonstrated their efficacy in the short-term treatment of anxiety and sleep disorders, there has been a concern over the years that they were being overprescribed and abused [30]. According to the results from the 2006 National Survey on Drug Use and Health, 2.8% of the U.S. population, i.e., 7.0 million people used psychotherapeutic drugs for nonmedical purposes; of them, 1.8 million used tranquilizers and 385,000 used sedatives [11]. There are also concerns about benzodiazepines long-term efficacy and safety, including the risk of dependence and withdrawal reactions when discontinued [2,30]. It has been estimated that 30 to 40% of long-term users of benzodiazepines experience difficulties in withdrawing [2]. The management of benzodiazepine discontinuation includes gradual dosage tapering and psychological support when needed [3]. It has been proposed that a stepped care approach should be followed for discontinuing long-term benzodiazepine use, because minimal interventions (e.g. an advisory letter) and systematic discontinuation programs guided by a physician or psychologist without the augmentation of psychotherapy or pharmacotherapy are efficacious [37]. In addition, several adjunctive pharmacological agents have been used to facilitate the tapering of benzodiazepines, including anxiolytics such as buspirone, antidepressants such as trazodone, dothiepin or imipramine, and anticonvulsants such as valproate or carbamazepine [10]. The results of a recent systematic review have pointed out that only carbamazepine might be a

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doi:10.1016/j.eurpsy.2010.12.004
useful adjunctive medication for benzodiazepine withdrawal [10]. However, although carbamazepine significantly improved the rate of benzodiazepine-free patients, the reduction of withdrawal severity was modest [10]. The adverse effects and drug interactions of carbamazepine may further limit its usefulness for the routine treatment of benzodiazepine withdrawal or other substance-related disorders [10,27].

Pregabalin is an alpha2-delta ligand that has shown analgesic, anxiolytic, and anticonvulsive properties [34]. In patients with generalized anxiety disorder (GAD), pregabalin appears to show an anxiolytic effect similar to that of alprazolam, lorazepam or venlafaxine [24]. Pregabalin has also shown efficacy in treating depressive symptoms in GAD patients [33] and exhibits sleep improving properties [14]. Ancodatal reports suggest that gabapentin, a parent compound of pregabalin, may be useful in opiate withdrawal [17] and benzodiazepine withdrawal [8]. In a randomized, double-blind comparison with lorazepam, high doses of gabapentin have shown to ameliorate the symptoms of alcohol withdrawal [21]. In a recent randomized, double-blind study, pregabalin was as efficacious as naltrexone in the treatment of alcohol dependence [18]. In an open-label study of 15 long-term benzodiazepine users, pregabalin (225–900 mg/day), used as adjunctive medication for the discontinuation of benzodiazepines, obtained a significant reduction of anxiety symptoms, and all patients were able to successfully discontinue their benzodi-

We ran a study to evaluate the short-term course and outcome of the benzodiazepine detoxification process in the real practice setting in Spain. The objective of the analysis we are presenting herein was to evaluate the effectiveness and tolerability of pregabalin in the management of the withdrawal of benzodiazepines in long-term users.

2. Subjects and methods

2.1. Subjects

Patients were included in this study if they were at least 18 years old, met DSM-IV-TR for benzodiazepine dependence regardless of if they met criteria for any other substance use disorder and have been included in a benzodiazepine detoxification process on an outpatient basis. Patients were excluded if, according to the investigator judgment, they were unable to understand or fulfill the questionnaires/scales, showed evidence of major psychiatric conditions such as schizophrenia, bipolar disorder or recurrent major depression or were pregnant. For this analysis we selected those patients who received pregabalin as treatment of their benzodiazepine dependence and who had a urine drug analysis available at the study entry.

2.2. Design

This was an analysis of a prospective, uncontrolled, and observational study, carried out in Spain, from January 2007 to October 2007, by 161 investigators of Specialized Drug Dependence Attention Centers and Mental Health Centers with specific programs of substances detox.

All patients who met the selection criteria were included in the study and were followed for 12 weeks. Pharmacological treatments as well as any other healthcare interventions were established individually according to the clinical judgment of each investigator.

The study was approved by the Ethics Committee of the Hospital General Universitario Gregorio Marañón (Madrid, Spain). The study was carried out in accordance with the principles contained in the Declaration of Helsinki. All patients or their legal representatives gave informed consent before taking part in this study.

2.3. Assessments

Following the schedule established on the benzodiazepine detoxification program, patients were evaluated at baseline, weeks 1, 2, and 4, and every 4 weeks thereafter. The baseline evaluation included the recording of age and sex, medical and psychiatric history, concomitant medication use and a urine drug screen. Urine drug screen for benzodiazepines was performed using a rapid benzodiazepine test strip. Discontinuation symptoms were assessed at each of the follow-up visits using the Benzodiazepine Withdrawal Symptom Questionnaire [35], which has been evaluated at the primary care setting showing good psychometric properties [7]. In addition, upon the study entry and at each of the study follow-up visits, we administered the Hamilton Anxiety Rating Scale [13,16] and the Clinical Global Impression Scale (clinician and patients versions) [12]. Patients also completed the Sheehan Disability Scale [5,32] at baseline and at the end of the study.

Tolerability was evaluated with an ad-hoc four-point Likert Scale ranging from 1 (excellent) to 4 (poor).

2.4. Statistical analysis

Demographic and baseline clinical characteristics were described using the mean and standard deviation for continuous measures (e.g., age, BWSQ score) and the frequency and percentage for categorical variables (e.g., sex, concomitant medications).

The primary effectiveness variable was the success rate, defined as achievement of a benzodiazepine-free status at week 12 according to the urine drug screen. Since an intention to treat (ITT) analysis was carried -out, if the urine drug analysis was not available at week 12, the patient was categorized as a failure, included dropped out before week 12 for any reason. Other effectiveness variables were the severity of withdrawal symptoms as measured with the total score of the BWSQ, anxiety symptoms according to the HARS total score, and functional impairment with the SDS domains’ scores. The significance of changes versus baseline in the observed scores on the different scales and subscales at the different study time-points was calculated using paired Student’s t test with Bonferroni correction; following this procedure the significance level was set at 0.01 for the HARS and CGI, at 0.0125 for the BWSQ, and at 0.05 for the SDS. Mean changes from baseline on the different scales according to the benzodiazepine of abuse were calculated using an analysis of covariance (ANCOVA) model with treatment as a factor and baseline value as a covariate. In order to also assess the clinical significance of the changes in the different measures, the effect size was obtained by calculating the difference between the mean values of a specific measure before and after treatment, and then dividing that difference by the standard deviation of that measure before treatment [15]. The effect size was interpreted according to the criterion established by Cohen, which considered an effect size of 0.20 as small, 0.50 as moderate and 0.80 as large [15]. Success rates in patients who received pregabalin as monotherapy was compared to that of patients receiving pregabalin in combination with other drugs using the chi-square test. For categorical outcomes, the corresponding 95% confidence intervals were also calculated. With the exception of the analysis of the SDS, all the efficacy analyses were carried out in the primary efficacy population population, defined as all patients included who were prescribed pregabalin and met the selection criteria. In these effectiveness analyses, again with the exception of the SDS, missing data were imputed using the last observation carried forward (LOCF). The analysis of the SDS scores was performed
using an observed cases approach. All patients included in the study were also included in the analyses of tolerability.

All statistical analyses were performed using SAS version 8.2 (SAS Institute, Cary, NC, USA). All analyses were two-tailed and considered significant if \( P < 0.05 \).

3. Results

3.1. Study Participants

Out of a total of 480 patients recruited into the study, 323 had urine drug analysis available at baseline, and 282 patients met the criteria to be in this analysis. These 282 patients constituted the primary effectiveness population. Seventy-one patients (25.2%) withdrew from the study. The reasons for withdrawal were lost to follow-up (n = 22, 7.8%), patient’s request (n = 15, 5.3%), relapse (n = 7, 2.5%), poor tolerability (n = 6, 2.1%), other reasons (n = 12, 4.3%), and unknown reasons (n = 9, 3.2%).

The mean patient age was 41 years, with men comprising 55% of the population and with a slight majority of patients (53%) receiving a benzodiazepine because of a physician’s prescription (Table 1). The most frequent benzodiazepine of abuse was alprazolam (n = 177, 62.8%), the mean duration of the benzodiazepine dependence was 2 years, and the average number of previous detoxification attempts was 0.7 (Table 1). A substantial proportion of patients were taking two or more benzodiazepines upon the study entry (n = 71, 25%). Ninety-seven (34%) patients had a current psychiatric diagnosis other than a substance use disorder: 13% had an anxiety disorder, 10% had a personality disorder, 8% had a depressive disorder and 5% had other disorders. Substance-related disorders other than nicotine- and caffeine-related disorders were also common (n = 133, 47%); polysubstance disorder (n = 50, 18%; this group was composed of those patients who were using at least two groups of substances but excluding caffeine and nicotine); alcohol-related disorders (n = 32, 11%); opiod-related disorders (n = 19, 7%); cannabis-related disorder (n = 14, 5%); cocaine-related disorders (n = 13, 5%); sedative-, hypnotic-, or anxiolytic-related disorder (not including benzodiazepines; n = 3, 1%); and other substance-related disorder (n = 4, 1%). Nicotine- and caffeine-related disorders were present in 47% and 15% of the patients, respectively.

3.2. Pregabalin treatment and other management issues

The mean (±SD) initial dose of pregabalin was 127 (±79) mg/day, ranging from 25 mg/day to 450 mg/day. The mean doses at weeks 1, 2 and 4 were 184 (±102) mg/day, 235 (±108) mg/day, and 288 (±136), respectively. The mean dose at week 12 was 315 (±166) mg/day, with a dose range of 25 to 600 mg/day. Treatment was initiated with pregabalin monotherapy in 175 (62.1%) patients, while the remaining 107 (37.9%) patients received pregabalin in combination with other drugs; the most common drugs in the combination group were diazepam (n = 29), clonazepam (n = 17), mirtazapine (n = 13), alprazolam (n = 10) and lorazepam (n = 10). In addition to pharmacological treatment, ninety patients (32%) received psychotherapy.

3.3. Effectiveness outcomes

The success rate of the benzodiazepine taper in the primary efficacy population (n = 282) was 52% (95% CI, 46–58). In those patients who completed the 12-week follow-up (n = 211) the success rate was 70% (95% CI, 63–76). Success rates for women and men were 58% (95% CI, 49–67) and 46% (95% CI, 38–55), respectively (P = 0.0516, power 28% for an \( \alpha \) set at 0.0125). The success rate in patients who received pregabalin as monotherapy was 49% (95% CI, 41.0–56) compared to 58% (95% CI, 48.0–67) in those receiving pregabalin in combination with other drugs (P = 0.1263, power 13%). A bivariate analysis shows that the proportion of patients who were benzodiazepine-free at the end of the study did not differ according to the benzodiazepine of abuse (Fig. 1). Similarly, the success rate did not vary according the presence of other substance use disorders: alcohol-related disorders 53% (95% CI, 35–71); cocaine-related disorders 46% (95% CI, 19–75); cannabis-related disorder 50% (95% CI, 23–77); opiod-related disorders 58% (95% CI, 34–80); and polysubstance disorder 54% (95% CI, 39–68). In addition the success rate for patients who received other treatments (n = 41) was 42% (95% CI 26–58).

Withdrawal symptoms were evaluated at each study time-point with the BWSQ and the HARS. The mean BWSQ score decreased progressively and significantly from a mean score (±SD) of 11 (±7.5) at week 1 to a score of 4.4 (±5.5) at week 12 (Fig. 2). Except in patients with abuse of chlorazepate who showed a 37% reduction at week 12 in the mean score of the BWSQ, we found similar reductions in the BWSQ score regardless of the benzodiazepine of abuse (data not shown). Pregabalin-treated patients showed a pronounced and significant amelioration of the anxiety symptoms throughout the study (Fig. 3). The mean change from baseline at the endpoint in the HARS total score was 17, which represents a 68% decrease from the baseline score (24.7 ± 10.2). At baseline, 236/281 patients (84%, 95% CI, 80–88%) had moderate to severe anxiety symptoms, while at the endpoint 137/272 (50%; 95% CI, 44–56%) patients showed a remission of anxiety symptoms and 94/272 (35%; 95% CI, 29–40%) exhibited mild anxiety symptoms. The improvement

Table 1

<table>
<thead>
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<th>Characteristic/variable</th>
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<tr>
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<td>40.7 (9.8)</td>
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<td>Sex, n (%)</td>
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<tr>
<td>Men</td>
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<tr>
<td>Women</td>
<td>122</td>
<td>44.7</td>
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<tr>
<td>Benzodiazepine prescription pattern, n (%)</td>
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<td>Physician’s prescription</td>
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<td>Self-prescription</td>
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<td>Both</td>
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<td>7.8</td>
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<tr>
<td>Duration of benzodiazepine dependence, years, mean (SD)</td>
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<tr>
<td>Number of prior withdrawal attempts, mean (SD)</td>
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<td>0.7 (1.2)</td>
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<td>Benzodiazepine* of abuse, n (%)</td>
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<td>Alprazolam</td>
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<td>Other benzodiazepines</td>
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<td>Two or more benzodiazepines</td>
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<td>HARS, mean (SD)</td>
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<tr>
<td>Somatic</td>
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<tr>
<td>Psychic</td>
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<tr>
<td>SDS, mean (SD)</td>
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<td>4.6 (1.3)</td>
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<tr>
<td>Patient</td>
<td>273</td>
<td>4.6 (1.3)</td>
</tr>
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</table>

HARS: Hamilton Rating Scale; n: number of patients that could be evaluated; SD: standard deviation; SDS: Sheehan Disability Scale. * Including zolpidem and zopiclone.
in symptoms of anxiety was clinically relevant as early as week 1, showing an effect size of 0.58 at week 1 and 1.67 at week 12. The improvement of the somatic and psychic factors of the HARS at week 12 was also pronounced, that is, a decrease of 70% (an effect size of 1.29) and 66% (an effect size of 1.83) for the somatic and psychic factors, respectively, from the baseline scores (Fig. 3). This effect over the anxiety symptoms did not differ according to the benzodiazepine of abuse (Fig. 4).

In the global measure of improvement, the CGI, patients also showed a significant improvement of the disease severity as early as the first week, which was clinically relevant by the first week according to the clinician’s assessment, and by week 2 according to the patient’s judgment (data not shown). At the study endpoint, the disease severity had improved to a great and similar extent both as evaluated by the clinician (from a score of 4.5 ± 1.0 at baseline to a score of 2.3 ± 1.3 at the study endpoint; \( P < 0.0001 \); effect size: 2.20) and by the patient (from a score of 4.6 ± 1.3 at baseline to a score of 2.5 ± 1.4 at study endpoint; \( P < 0.0001 \); effect size: 1.69). Finally, patients also experienced a significant and clinically relevant improvement in their functioning as shown by the changes from baseline to endpoint in the SDS global and domain scores, with a decrease greater than 3 points across each specific domain (Fig. 5).

### 3.4. Tolerability

At week 1, tolerability was evaluated as good or excellent in 80% and 64% of the clinicians and patients, respectively, while at week 12 the corresponding rates were 90% and 83%.

### 4. Discussion

To our knowledge, this is the first systematic evaluation of pregabalin for the management of patients discontinuing long-term benzodiazepine use. In our study, treatment with pregabalin in benzodiazepine-dependent patients was associated with an important rate of successful benzodiazepine taper. Pregabalin produced a significant and clinically relevant reduction in the symptoms of anxiety as measured by the Hamilton Anxiety Rating Scale and a significant and important reduction (i.e., 60% reduction from weeks 1 to 12) in withdrawal symptoms as evaluated by the Benzodiazepine Withdrawal Symptoms Questionnaire. The success rate of the taper in our analysis, 52%, was similar to that reported with carbamazepine in a placebo-controlled trial 12 weeks after the taper [31]. Although the authors of this latter study reported a 74% success rate, this rate did not account for the early drop-outs in the carbamazepine-treated patients [31]; a more
A conservative approach of including all randomized patients yields a success rate of 52%. The success rate of taper in our analysis was lower than those reported with valproate and trazodone [29] or imipramine [28], but again, these trials did not account for early dropouts in calculating the success rate. In any case, taper success rates are difficult to compare across studies and, especially, with that of our analysis because the population included in our analysis differs from that included in clinical trials. Importantly, all three previously mentioned randomized clinical trials did not include patients with a current diagnosis of alcohol or substance use.

Fig. 3. Changes over time in anxiety symptoms (primary efficacy population–LOCF analysis). HARS: Hamilton Anxiety Rating Scale; LOFT: last observation carried forward. *P < 0.0001 vs. baseline.

Fig. 4. Mean changes from baseline at endpoint in the anxiety scores according to the benzodiazepine of abuse (primary efficacy population–LOCF analysis). Vertical bars represent 95% confidence interval. BDZ: benzodiazepine; LOCF: last observation carried forward; LSM: least mean square.

Fig. 5. Mean changes from baseline at endpoint in disability scores (primary efficacy population–LOCF analysis). Vertical bars represent 95% confidence interval of the mean. LOCF: last observation carried forward; SDS: Sheehan Disability Scale. Figures under the bars correspond to the effect sizes.
disorders [28, 29, 31], while in our analysis, a substantial proportion (47%) of patients had a concurrent diagnosis of a substance use disorder (excluding caffeine or nicotine use disorders). Benzodiazepine-dependent patients exhibiting another substance use disorder are more difficult to treat, and the results of the benzodiazepine discontinuation treatment are poorer than in patients with uncomplicated dependence [36]. In addition, the benzodiazepine co-dependence may complicate other drug withdrawal symptoms, as it has been reported with opiate withdrawal [9]. Due to the lack of randomization, this analysis had not the objective of comparing the outcomes of pregabalin-treated patients with those who received other treatments; however, for informative purposes, we also provide the success rate for these latter patients (n = 41; 42%, 95% CI 26–58).

The beneficial effects of pregabalin are more obvious when evaluating its effect over the anxiety symptoms and withdrawal symptoms. The improvement in symptoms of anxiety was remarkable. Thus, by the end of the study only 15% of the patients showed moderate to severe anxiety symptoms compared with 84% of the patients at the baseline. Other anxiolectics evaluated in randomized controlled studies for the treatment of benzodiazepine dependence have demonstrated either no effect [1, 20] or a modest significant effect on anxiety symptoms [28]. In this later study, after 4 weeks, buspirone and imipramine produced a mean decrease from baseline in the HARS anxiety score of 28% and 24%, respectively [29]; although patients exhibited lower baseline levels of anxiety symptoms than in our study, this reduction of the anxiety score contrasts with the 69% decrease observed in our study after 12 weeks, and 50% after 4 weeks. Higher levels of anxiety at the baseline have been associated with a poorer outcome during benzodiazepine withdrawal [1, 28, 31]. Therefore, a robust anxiolytic effect as shown in our study should be a desirable characteristic of a drug intended for the treatment of benzodiazepine dependence. The improvement of anxiety symptoms in our study, especially of the psychic symptoms, was clinically relevant as early as the first week. The rapid onset of the anxiolytic effect of pregabalin may play an important role in the subsequent success of benzodiazepine withdrawal. In a randomized, double-blind study comparing carbamazepine and placebo for the treatment of patients discontinuing long-term benzodiazepine therapy, 15 of the 55 patients included dropped out during a 7 to 14 days period before initiating the benzodiazepine taper; these early drop-outs exhibited high levels of anxiety symptoms at baseline as compared to those who finally initiated the benzodiazepine taper [31]. The apparently pronounced and rapid anxiolytic effect of pregabalin in our study is consistent with that reported in several previous randomized placebo-controlled trials with this drug in patients with GAD [19].

The improvement in anxiety symptoms is consistent with the improvement observed in the severity of withdrawal symptoms. Thus, the BWSQ score decreased progressively and significantly throughout the study, from a score of 11 at week 1 to score of 4.4 at the week 12 (i.e., a 60% reduction). The clinical relevance of the improvement of the anxiety and withdrawal symptoms was supported by the significant and relevant improvement in the functional impairment at work as well as in social and family life as measured by the Sheehan Disability Scale. Pregabalin was well tolerated.

The main limitation of our study is the before and after design that could lead to an overestimation of treatment effects. However, we think that treatment effects regarding anxiety and withdrawal symptoms are consistent and large enough to be considered a mere placebo effect. In addition, as mentioned above, we included a sample of somewhat difficult to treat patients, especially because of the high proportion of patients exhibiting co-dependence with another substance of abuse. Another limitation of our study is the lack of long-term follow-up after completing the withdrawal treatment program. It would have been desirable to test benzodiazepine status several weeks after finalizing the taper in order to confirm the maintenance of the benzodiazepine-free state. In addition, a follow-up visit would have allowed us to assess the potential occurrence of withdrawal symptoms after pregabalin discontinuation. Although the frequency of withdrawal symptoms with pregabalin is considered to be lower than with benzodiazepines and similar to rates reported with the serotonin–noradrenaline reuptake inhibitors [19], an anecdotal case report of withdrawal symptoms after pregabalin discontinuation in a patient withdrawing from alprazolam has been recently reported [4]. In contrast, there has been no evidence of abstinence syndrome following the abrupt discontinuation of pregabalin in healthy volunteers treated with pregabalin for 2 to 4 weeks [6], and overall, the drug is considered to show a low risk of tolerance or dependence [19]. In any case, as recommended by pregabalin's package insert, when discontinuing pregabalin, a gradual tapered off over a minimum of 1 week should be implemented [26].

5. Conclusion

Despite the abovementioned limitations, our results suggest that pregabalin is an efficacious and well-tolerated adjunctive treatment for benzodiazepine withdrawal that improves anxiety and withdrawal symptoms and reduces the degree of disability to a relevant extent. However, these preliminary and promising results should be confirmed in placebo-controlled trials. Long-term maintenance of the pregabalin efficacy, risk of withdrawal symptoms with pregabalin in this population, and what is the most appropriate dosage schedule for these patients are points that should be also evaluated.

Conflicts of interest statement

This study was funded by Pfizer Spain. V. LG. and M. P. are full-time employees of Pfizer, the company sponsoring this study. I. V. is employed by the European Biometric Institute, a clinical research organization contracted by Pfizer to conduct the study. J. B., G. R., A. T., G. C. have no conflict of interest.

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dependence.


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