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Increasing the dosage of pregabalin in patients with focal epilepsy decreases the frequency of seizures and ameliorates symptoms of anxiety, depression and insomnia

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Abstract. – OBJECTIVE: The effectiveness of the treatment depends on the adequate dosage of medications. In clinical practice, drugs are often used at doses that are too low, which results in suboptimal levels of clinical improvement. The aim of the study was to evaluate the effects of increasing the dose of previously taken pregabalin in a group of patients with focal epilepsy and generalized anxiety disorder (GAD).

PATIENTS AND METHODS: This open study involved 993 patients (46 ± 14 years old) suffering from epilepsy with focal seizures and concomitant GAD treated with pregabalin add-on therapy. The severity of anxiety was assessed with GAD-7 Scale. The number of epileptic seizures was monitored before and after the increase of the pregabalin dose.

RESULTS: On the initial visit, the mean daily dose of pregabalin was 159 ± 82 mg. During the study period (nine months) the mean dose was increased to 327 ± 163 mg. After nine months, based on the intention-to-treat analysis, 27.1% (N = 253) of the subjects experienced seizure resolution, and 57.8% (N = 539) reduction in seizure frequency by at least 50%. At the beginning of the study, despite pregabalin administration, 60.7% of patients were above the diagnostic threshold for GAD diagnosis. The add-on therapy resulted in the improvement of the depressive and anxiety symptoms, and insomnia, greater in those that experienced seizure resolution or reduction in their frequency.

CONCLUSIONS: (1) Patients with focal epilepsy with concomitant anxiety disorder experience reduction in seizure frequency, improvement of anxiety, depressive symptoms and insomnia using PGB as an add-on therapy. (2) Our data suggest that pregabalin as an add-on treatment is a reasonable choice for patients with focal epilepsy who have concomitant symptoms of an anxiety disorder.

Key Words:
Epilepsy, Anxiety, Pregabalin, Depression, Insomnia.

Introduction

Epilepsy is the most common neuropsychiatric condition that affects approximately one percent of the world population. According to the estimates of the World Health Organization (WHO) 50 million people suffer from epilepsy worldwide[1]. In Poland there are over 643,000 people with epilepsy, based on the data of the Ministry of Health in 2016[2]. Epilepsy is a heterogeneous clinical disease characterized by recurrent unprovoked abnormal electrical discharges in the brain typically manifest by sudden alterations of motor, sensory and cognitive functions. Epilepsy is classified as focal or of the generalized type, with focal epilepsy being more common than generalized epilepsy in both children and adults[3].

The current management of patients with partial epileptic seizures is considered to be suboptimal, despite the availability of many anti-epileptic drugs (AEDs). Among patients with partial epileptic sei-

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zures more than 30% are classified as treatment refractory to mono or combination therapies necessitating the need additional add-on AED treatments[4]. The classification of patients into treatment refractory partial epileptic seizures as opposed to only pseudo-refractory seizures pose significant clinical issues in determining AED management and has been documented in numerous publications. According to Kutlu et al[5], the list of the main causes of pseudo-refractory epilepsy includes incorrect diagnosis, misclassification leading to inappropriate treatment, poor compliance and the use of inadequate low doses of AEDs.

The treatment of epilepsy is not limited to achieving a seizure free status but also includes addressing and managing common psychiatric comorbidities that adversely impact on the quality of life. Mood and anxiety disorders are the most frequent psychiatric disorders associated with epilepsy. Interictal anxiety symptoms are reported in two-thirds of patients with epilepsy and usually are an under recognized and untreated aspect of the disease[6].

Pregabalin (PGB) is an approved AED for add-on therapy for refractory partial seizures. It is one of the newer AED's that has efficacy against anxiety and represents a novel treatment strategy for generalized anxiety disorder (GAD). PGB binds to the alpha-2-delta subunit protein of voltage gated calcium channels and has anxiolytic and anti-epileptic effects *via* the reduction of neurotransmitter release including glutamate, norepinephrine and substance P[7-9].

Taking into account the effectiveness of PGB in the treatment of both epilepsy and anxiety disorders a case can be made for pharmacotherapy with this medication where both disorders are present provided an appropriate dose beneficial to both disorders can be determined.

The initial assumption of the study was that for patients treated with PBG for epilepsy, in addition to seizure control, it is also important to evaluate for the adequacy of control of anxiety symptoms as PGB can also address anxiety disorder. Patients with drug resistant partial seizures and comorbid generalized anxiety disorder are a group that would normally have PGB doses adjusted upwards as a matter of clinical course in an attempt to reduce refractoriness. The increase in PGB dosing could also result in a reduction of anxiety related symptoms present at the baseline when PGB is increased.

The aim of the study was to evaluate the impact of PGB dose adjustment on the severity of symptoms of generalized anxiety disorder previously diagnosed in refractory focal epilepsy patients undergoing an increase in dosage for improvement of seizure frequency control with a secondary end-point, the evaluation of associated changes in depression and insomnia secondary.

Patients and Methods

Study Design and Participants

This open obsevational study engaged neurologists principally involved in managing epilepsy.

The neurologists were asked to select patients with partial epilepsy with comorbid generalized anxiety disorder. The patients selected represented typical clinical cases. The diagnosis of partial epilepsy and comorbidities was based on clinical data judgment, EEG and neuroimaging.

Neurologists participating in the study had no restrictions placed on them impeding or interfering with standards of care and normal judgment in determining best practices in the interest of the patient in compliance with generally applicable laws and principals of professional ethics.

Inclusion criteria comprised: adults of both sexes (women of childbearing age using contraception) with focal epilepsy (simple and complex partial seizures, with or without secondary generalization meeting the 1981 classification criteria of International League of Epilepsy) with a minimum of 4 seizures in the previous 8 weeks prior to entering the study requiring add-on therapy for refractory seizures and with coexisting anxiety disorder and already on PGB with clinical indications for PGB dosage change, the ability to fill out a diary regarding epileptic seizures, compliance with follow-up examinations, and consent to participate in the study.

Exclusion criteria included the lack of ability to obtain a survey response from the patient, psychogenic pseudo-epileptic seizures and contraindications for the use of PGB in accordance with the summary of product characteristics. As the survey did not meet the criterion of a medical experiment, the approval of the Bioethical Committee was not required. The survey was conducted anonymously and blinded as to the patient's personal data by the study organizer.

Assessments

Symptoms of generalized anxiety disorder were evaluated with the GAD-7 scale (General Anxiety Disoder-7). Depression symptoms were

evaluated with a self-administered Beck Depression Inventory while sleep disturbances were evaluated with the Athens Insomnia scale (AIS).

The change in seizure frequency was assessed with examinations performed every three months for a total of four examinations during the study period of 9 months.

Neurologists participating in the study adjusted the doses of PGB at each visit starting from the first visit on the basis of their clinical judgment of the status of seizure frequency and performed an assessment regarding the presence and severity of symptoms of GAD. Personalized dosage reflected daily clinical practice.

On the first visit socio-demographic and clinical data, as well as results from EEG and neuroimaging, were collected. Socio-demographic data included the patient's age, education and place of residence (city/village). Clinical data included the patient's body weight, duration of epilepsy, type of seizures, number of seizures in the 8 weeks prior to entering the study, occurrence of other comorbidities and medical diagnoses. Data on pharmacotherapy: drugs used for epilepsy as well as drugs used for comorbidities (with particular emphasis on mood stabilizers and other psychoactive drugs), with their dosage.

GAD-7 and AIS were administered at all four visits while BDI were administered only at the first and last visit. PGB dosage was recorded on each visit. Starting from visit 2 the number of seizures during the last 6 weeks based on the patient's diary was recorded as well as changes in treatment of other associated disorders. Results of the latest EEG were obtained at visit four.

Data Analysis

The severity of symptoms of generalized anxiety disorder were scored using the GAD-7 scale with a threshold of > 10 points. Insomnia was assessed based on the AIS with a threshold of > 11 points. Depressive symptoms evaluated with BDI were divided into three categories from 12 to 36 – mild; from 27 – 49, moderate; from 63 – severe.

Statistical Analysis

Statistical analysis was performed using STATISTICA 11.0 PL software. Statistical significance was set at a p-value below 0.05. All tests were two-tailed. Imputations were not done using missing data. Nominal and ordinal data were expressed as percentages. Interval data were expressed as mean value ± standard deviation. Comparisons between the two groups were done with t-student test for independent groups or ANOVA in case of interval data. Nominal and ordinal data were compared with chi 2 test. Relative risks were calculated with univariable logistic regression. Correlation coefficients were calculated according to Pearson.

Results

Study Group Characteristics

The study includes data received from 87 neurologists and their 1,177 patients (mean age 48 ± 15 years) treated for simple/complex partial and secondarily generalized seizures and having comorbid generalized anxiety disorder. The final analysis included 933 (84% of the total group, 482 women and 451 men) patients who met the inclusion criteria, with a minimum of 4 seizures in the prior 8 weeks before entering the study requiring add-on therapy and concomitant anxiety disorder with clinical indications for PGB treatment. There were 472 patients with simple/complex partial seizures and 461 with secondary generalized seizures. Demographic and clinical data are presented in Table I.

Depressive symptoms and insomnia were observed in 80.0% and 55.8% of patients respectively. Depressive symptoms (83.7% *vs.* 76.8%; $p < 0.01$) and sleep disturbances (60.8% *vs.* 51.6%; $p < 0.01$) were more common in patients with a history of epilepsy longer than 5 years. Insomnia was more frequent among older patients, however, the difference was not significant.

Depressive symptoms were found in 78.6% of patients with simple/complex partial seizures and 81.3% of secondary generalized seizures ($p = 0.08$). The frequency of insomnia in these subgroups was similar (56.2% *vs.* 55.5%; $p = 0.29$).

Antiepileptic Treatment

In the group of patients with simple/complex partial seizures 67.2% and 67.3% respectively received one antiepileptic drug and PGB at visit 1 and 4. Two antiepileptic drugs and PGB were received by 27.1% of those patients at visit 1, and 26.2% at visit 4. Carbamazepine and valproic acid were used respectively in 44.1% and 44.6% of cases at both visits (Table II).

In the group of patients with secondary generalized seizures 52.5% and 50.9% respectively received one antiepileptic drug and PGB at visit 1 and 4. Two antiepileptic drugs and PGB were giv-

Table I. Characteristics' of the study group [N=933].

Sex:	
Men [N; %]	451; 48.3
Women [N; %]	482; 51.7
Age [years]	46 ± 14
Age > 65 years [N; %]	92; 9.9
Body mass [kg]	74 ± 13
Educational level:	
Primary [N; %]	82; 8.8
Vocational [N; %]	249; 26.7
Secondary [N; %]	361; 38.7
Higher [N; %]	241; 25.8
Diagnosis:	
Epilepsy with simple / complex partial seizures [N, %]	472; 50.6
Epilepsy with secondary generalized seizures [N, %]	461; 49.4
Duration of illness:	
≤ 5 years [N; %]	564; 54.0
> 5 years [N; %]	429; 46.0
The number of seizures episodes during last 6 weeks [N]	8 ± 5
< 4 [N; %]	0
4-5 [N; %]	341; 36.5
6-7 [N; %]	227; 24.3
8-10 [N; %]	231; 24.8
> 10 [N; %]	134; 14.4
Range	4-81
Type of epilepsy based on MRI / CT imaging:	
Symptomatic [N; %]	334; 35.8
Unknown cause [N; %]	505; 54.1
Missing data [N; %]	94; 10.1
Electroencephalography assessment:	
Normal EEG [N; %]	201; 21.5
Generalized epileptiform discharges [N; %]	496; 53.2
Focal changes [N; %]	417; 44.7
Single epileptic focus [N; %]	362; 86.8
Multiple epileptic foci [N; %]	55; 13.2
Generalized Anxiety Disorder 7-item (GAD-7) scale [pts]	11.0 ± 4.1
Beck inventory [pts]	20.3 ± 10.1
0-11pts [N; %]	187; 20.0
12-26 pts [N; %]	498; 53.4
27-49 pts [N; %]	244; 26.2
50-63 pts [N; %]	4; 0.4
Athens insomnia scale [pts]	11.6 ± 5.5
≤ 10 pts (Normal) [%]	412; 44.2
≥ 11 pts (Insomnia) [%]	521; 55.8

en to 42.5% of those patients at visit 1, and 41.4% at visit 4. Carbamazepine and valproic acid were respectively used in 60.3% and 58.4% of cases at both visits (Table II).

Pregabalin Add-on Therapy

At the first visit, 916 patients (98.2%) were being treated with PGB (mean dose 159 ± 82 mg/day), similar doses were used in patients with simple/complex partial seizures and secondarily generalized seizures (Table II). The most commonly used daily dose was 150 mg/day. Only a few patients were on doses > 300 mg/day (N = 13; 1.4%) and in addition, 12 patients (1.3%) used gabapentin.

PGB was mostly used as a second add-on AED (67.2% patients with simple complex /partial seizures and 52.5% with secondary generalized seizures) and less frequently as a third add-on AED (27.1% of patients with simple/ complex partial seizures and 42.5% secondary generalized seizures). PGB was most frequently added on to valproic acid and levetiracetam therapy.

During 234 ± 38 days of follow-up, contact with 25 patients (2.7%) was lost. In addition, 11 patients (1.2%) discontinued treatment with PGB due to intolerance (N = 4), transient inability to

Table II. Antiepileptic therapy and its effectiveness.

	Visit I	Visit II	Visit III	Visit IV	Statistical significance
Epilepsy with simple/complex partial seizures					
Pharmacotherapy	**[N = 472]**	**[N = 462]**	**[N = 461]**	**[N = 455]**	
1 drug + PGB [N; %]	317; 67.2	327; 70.8	321; 69.6	306; 67.3	0.98
2 drugs + PGB [N; %]	128; 27.1	118; 25.5	116; 25.2	119; 26.2	
3 or more drugs + PGB [N; %]	3; 0.6	2; 0.4	3; 0.7	2; 0.4	
Not specified [N; %]	24; 5.1	15; 3.2	21; 4.6	28; 6.2	0.22
Carbamazepine or valproic acid [N; %]	208; 44.1	205; 44.4	201; 43.6	203; 44.6	0.99
PGB dose [mg]	152 ± 83	235 ± 108	293 ± 138	303 ± 154	< 0.001
PGB dose > 300 mg/day [N; %]	7; 1.5	35; 7.6	92; 20.0	104; 22.9	< 0.001
Body mass [kg]	73.1 ± 13.6	72.7 ± 13.6	72.9 ± 13.5	73.3 ± 13.4	0.92
Number of seizure episodes since the last visit [N]	8.0 ± 5.7	5.4 ± 3.7	4.1 ± 3.4	3.2 ± 2.8	< 0.001
Seizure freedom [N; %]	0	36; 7.8	74; 16.1	106; 23.3	< 0.001
At least 50% decrease of seizure episodes [N; %]	0	220; 47.6	305; 66.2	295; 64.8	< 0.001
Epilepsy with secondary generalized seizures					
Pharmacotherapy	**[N = 461]**	**[N = 458]**	**[N = 456]**	**[N = 442]**	
1 drug + PGB [N; %]	242; 52.5	247; 53.9	236; 51.8	225; 50.9	1.00
2 drugs + PGB [N; %]	196; 42.5	193; 42.1	187; 41.0	183; 41.4	
3 or more drugs + PGB [N; %]	11; 2.4	9; 2.0	8; 1.8	8; 1.8	
Not specified [N; %]	12; 2.6	9; 2.0	25; 5.5	26; 5.9	0.003
Carbamazepine or valproic acid [N; %]	278; 60.3	278; 60.7	267; 58.6	258; 58.4	0.85
PGB dose [mg]	162 ± 84	268 ± 121	338 ± 162	353 ± 167	< 0.001
PGB dose > 300 mg/day [N; %]	6; 1.3	62; 13.5	133; 29.2	145; 32.8	< 0.001
Body mass [kg]	75.0 ± 13.2	75.0 ± 13.2	75.3 ± 13.4	75.4 ± 13.5	0.96
Number of seizure episodes since the last visit [N]	7.3 ± 5.0	4.6 ± 3.4	3.6 ± 3.1	3.3 ± 4.6	< 0.001
Seizure freedom [N; %]	0	28; 6.1	83; 18.2	147; 33.3	< 0.001
At least 50% decrease of seizure [N; %]	0	259; 56.6	313; 68.6	244; 55.2	< 0.001

obtain drug at pharmacy (N = 6) or disappointment due to lack of effect (N = 1).

Within the period of observation the dose of PGB was increased to a medium dose of 327 ± 163 mg/day by visit four.

Efficacy of Add-on Therapy

A decrease in the frequency of epileptic seizures was observed in patients with simple/complex seizures and secondary generalized seizures (Table II, Figure 1 and Figure 2). Based on the intention-to-treat analysis, 84.9% (N = 792) of the patients reported improvement, including freedom from seizures [27.1% (N = 253)], or at least a 50% reduction in seizure frequency [57.8% (N = 539)]. At the end of the follow-up period, a seizure free status was more frequently observed among patients with secondary generalized seizures than with simple/complex seizures (33.3% *vs.* 23.3% $p < 0.001$).

The subgroups achieving seizure freedom and at least a 50% reduction in the frequency of seizures had a greater increase in dosage of PGB (221 ± 144 and 199 ± 112 *vs.* 184 ± 89 mg/day, respectively) and were on higher average PGB doses at the end of the study (340 ± 180 and 330

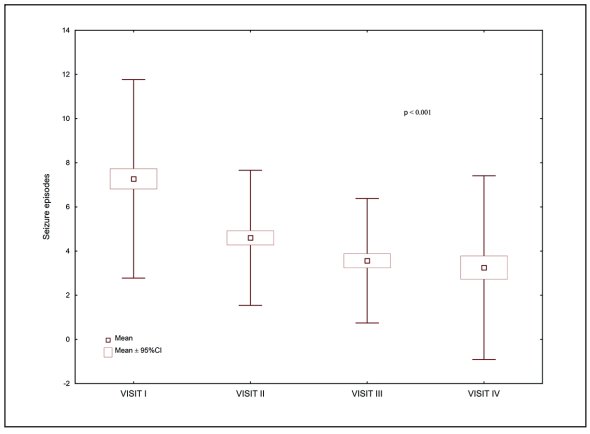

Figure 1. Reduction in simple/complex partial seizures frequency.

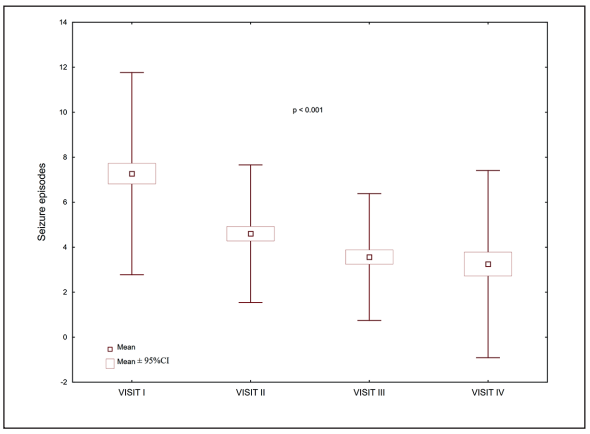

Figure 2. Reduction in secondary generalized seizures frequency.

± 158 vs. 278 ± 133 mg/day, respectively). In both subgroups the percentage of patients with a dose greater than 300 mg/day was higher (27.3 and 29.5 *vs.* 20%), however, significantly higher only in the subgroup with at least a 50% reduction in the frequency of seizures ($p < 0.05$) (Table III).

Dosage of higher than 300 mg/day of PGB was associated with a higher frequency of seizure freedom or at least a 50% reduction in seizure frequency: OR = 1.64 (95% CI: 0.95 – 2.84); $p = 0.08$ and OR = 1.79 (1.07 – 2.98); $p = 0.03$. However, there was no relationship between the subgroups stratified according to PGB dose at visit IV in the improvement of seizures (Table IV).

The beneficial effect was more pronounced in patients with seizures of unknown origin, lower frequency of seizures prior to initiation of PGB therapy and with secondary generalized seizures.

Patients with PGB add-on therapy obtained improvement in depressive (observed in 73.1% of patients), anxiety symptoms (observed in 98.3% of patients with GAD at the initial visit), and insomnia (observed in 97.3% patients with insomnia at the initial visit) (Figure 3, 4, 5). The improvement was independent of the type of seizure, except for slightly, although significantly greater benefit in the Beck inventory in the subgroup with simple/complex partial seizures (-13.1 ± 10.3 *vs.* -11.0 ± 8.1 pts; $p < 0.001$).

The level of improvement in depressive and anxiety symptoms and insomnia was greater in patients that obtained freedom from seizures or at least a 50% reduction in seizure frequency (Table III).

The highest PGB doses (> 300 mg/day) were more frequently prescribed for patients with secondarily generalized seizures, generalized epileptiform discharges in the EEG and anxiety symptoms, but less frequently in those with focal changes in the EEG. The subgroup of patients with the highest PGB doses experienced greater improvement on the GAD-7 scale (Table IV). In addition, PGB dose increases across the study period but not at visit IV correlated with the observed improvement in the GAD-7, Beck inventory and AIS [r = -0.146 (-0.211 – -0.080), $p < 0.001$; r = -0.150 (-0.215 – 0.084), $p < 0.001$; r = -0.088 (-0.155 – 0.004), $p < 0.01$; respectively].

Adverse Drug Reactions (ADRs)

ADRs were reported in 6 patients (0.6%), including drowsiness (N = 2), psychomotor retardation (N = 1), abdominal pain (N = 1), nausea (N=1), weight gain (N = 1), no serious ADRs were reported.

Discussion

The main results of this study show that treatment with PGB in patients with drug resistant focal epileptic seizures and coexisting generalized anxiety disorder is ineffective due to inadequate dosing of PGB. In our study, for patients treated for simple/complex partial seizures and secondarily generalized seizures and GAD the mean dosage of PGB before the start of the study was 159 ± 82 mg/day (98% of the study group). After nine months the mean dose was increased to 327 ± 163 mg/day. It is important to stress that our study utilized flexible dosing which allows neurologists to titrate the medication dose to efficacy and tolerability that is more relevant to "real world" practice than clinical trials and thus provide useful insight into the use of PGB in typical clinic situations.

As a result, based on the intention-to-treat analysis, it was found that 27.1% of the subjects in the 234 ± 38 days period experienced seizure freedom and a further 57.8% - a reduction in seizure frequency by at least 50%. We also found a significant reduction in symptoms of anxiety, depression and insomnia. The add-on therapy with PGB was well tolerated and this is reflected in the low percentage of patients discontinuing therapy - only 1.2%, mainly due to ADRs (over half of those discontinuing).

Therapeutic benefits included: decrease in the frequency of epileptic seizures (observed in 84.9% of patients), decrease in anxiety symptoms

Table III. Characteristics of the study group of patients stratified according to the observed therapeutic effects of pregabalin (PGB) add-on therapy at the end of the study.

	Seizure freedom [N = 253]	At least 50% decrease of seizure episodes [N = 539]	Below 50% decrease of seizure episodes [N = 105]	Statistical significance *p*
Women [N; %]	139; 54.9	272; 50.5	55; 52.4	0.50
Age [lat]	46 ± 13	45 ± 14	48 ± 14	0.09
Body mass [kg]	74.3 ± 13.2	74.2 ± 13.8	74.9 ± 12.1	0.90
Diagnosis:				
Epilepsy with simple / complex partial seizures [%]	106; 41.9	295; 54.7	54; 51.4	0.003
Epilepsy with secondary generalized seizures [%]	147; 58.1	244; 45.3	51; 48.6	
Duration of illness:				
≤ 5 years [N; %]	146; 57.7	283; 52.5	48; 45.7	0.10
> 5 years [N; %]	107; 42.3	256; 47.5	57; 54.3	
Number of seizure episodes during the last 6 weeks before visit I [N]	6 ± 5.4	8 ± 5.4	7 ± 4.4	0.001
< 8 seizure episodes [N; %]	206; 81.4	276; 51.2	71; 67.6	< 0.001
Type of epilepsy based on MRI / CT scan and EEG:	[N=217]	[N=508]	[N=94]	
Symptomatic [N; %]	83; 38.2	192; 37.8	51; 54.3	0.01
Unknown cause [N; %]	134; 61.8	316; 62.2	43; 45.7	
Generalized epileptiform activity [N; %]	94; 43.3	317; 62.4	48; 51.1	< 0.001
Antiepileptic pharmacotherapy at visit I				
1 drug (excluding PBG) [N; %]	151; 59.7	327; 60.7	55; 52.4	0.28
2 drugs (excluding PGB) [N; %]	95; 37.5	174; 32.3	46; 43.8	0.05
3 or more drugs (excluding PGB) [N; %]	1; 0.4	10; 1.9	2; 1.9	0.25
Not specified [N; %]	6; 2.4	28; 5.2	2; 1.9	0.08
Carbamazepine or valproic acid [N; %]	138; 54.5	268; 49.7	55; 52.4	0.44
PGB dose before visit I	162 ± 80	162 ± 85	143 ± 80	0.09
Dose > 300 mg/day [N; %]	2; 0.8	10; 1.9	0	0.43
PGB dose at visit IV	340 ± 180	330 ± 158	276 ± 133	0.002
Dose > 300 mg/day [N; %]	69; 27.3	159; 29.5	21; 20.0	0.14
Increase in PGB dose from visit I [N; %]	194; 76.7	451; 83.7	79; 75.2	0.02
Dose increase from the visit I [mg]	221 ± 144	199 ± 112	184 ± 89	0.04
Focal changes [N; %]	85; 39.2	248; 48.8	49; 52.1	0.002
Scales on visit I:				
GAD-7 [pts]	10.2 ± 4.0	11.4 ± 4.1	10.5 ± 4.1	< 0.001
GAD-7 ≥ 10 pts [N; %]	138; 54.5	366; 67.9	60; 57.1	0.001
Athens insomnia scale [pts]	10.8 ± 5.4	12.0 ± 5.5	12.0 ± 5.5	0.01
Score ≥ 11 pts [N; %]	123; 48.8	321; 59.6	58; 55.7	0.02
Beck inventory [pts]	19.7 ± 9.4	21.0 ± 10.2	17.7 ± 11.1	0.01
Score > 26 pts [N; %]	70; 27.7	149; 27.6	15; 14.3	0.01
Changes in scales on visit IV				
GAD-7 [pts]	-7.0 ± 4.0	-7.5 ± 4.0	-5.5 ± 4.3	< 0.001
Athens insomnia scale [pts]	-7.5 ± 5.1	-8.4 ± 5.3	-6.7 ± 6.0	< 0.01
Beck inventory [pts]	-12.3 ± 7.7	-12.8 ± 9.8	-7.8 ± 9.3	< 0.001

(observed in 98.3% of patients with GAD at the initial visit), insomnia (observed in 97.3% patients with insomnia at the initial visit) and depressive symptoms (observed in 73.1% of patients).

The treatment of anxiety and depressive symptoms in patients with epilepsy is a challenge because of a substantial lack of recommendations focusing on the treatment of this group[10]. The use of antiepileptic drugs, including mood-stabilizing drugs (valproic acid, carbamazepine, lamotrigine), gabapentinoids (gabapentin, PGB) is recommended, as well as SSRIs or SNRIs[11]. These agents, however, have a delayed onset of action and are associated with a small risk of seizure exacerbation. Of particular clinical importance is the fact that anxiety exerts a profoundly negative effect on the quality of life of patients with epilepsy[12,13].

Therefore, it is conceivable that AED's with anti-anxiety properties may be particularly beneficial for patients with epilepsy.

Table IV. Efficacy of the add-on pregabalin (PGB) therapy in relation to the drug dose at the end of the study.

	PGB dose at visit IV			Statistical significance *p*
	≤ 150 mg [N = 177]	>150 & ≤ 300 mg [N = 435]	> 300 mg [N = 249]	
Women [N; %]	102; 57.6	228; 52.4	114; 45.8	0.05
Age [lat]	44.4 ± 14.6	45.7 ± 13.6	46.9 ± 13.5	0.18
Body mass [kg]	71.5 ± 13.8	73.7 ± 13.1	76.3 ± 13.0	0.001
Diagnosis:				
Epilepsy with simple / complex partial seizures [%]	108; 61.0	231; 53.1	104; 41.8	< 0.001
Epilepsy with secondary generalized seizures [%]	69; 39.0	204; 46.9	145; 58.2	
Duration of illness:				
≤ 5 years [N; %]	89; 50.3	232; 53.3	137; 55.0	0.63
> 5 years [N; %]	88; 49.7	203; 46.7	112; 45.0	
Type of epilepsy based on MR /CT scan and EEG n:				
Symptomatic [N; %]	57; 32.2	154; 35.4	101; 40.6	0.22
Unknown cause [N; %]	98; 55.4	250; 57.5	127; 51.0	
Generalized epileptiform activity [N; %]	83; 46.6	243; 55.8	154; 61.7	0.004
Focal changes [N; %]	94; 53.4	192; 44.2	95; 38.3	0.04
Seizure freedom [N; %]	47; 26.6	123; 28.3	69; 27.7	0.91
At least 50% decrease of seizure episodes [N; %]	98; 55.4	260; 59.8	159; 63.9	0.21
Scales on visit I:				
GAD-7 [pts]	10.4 ± 3.8	10.8 ± 4.3	12.0 ± 3.9	< 0.001
GAD-7 ≥ 10 pts [N; %]	102; 57.6	248; 57.0	197; 79.1	0.04
Athens insomnia scale [pts]	11.7 ± 5.4	11.8 ± 5.7	11.9 ± 5.0	0.95
Score ≥ 11 pts [N; %]	101; 57.1	247; 56.8	144; 57.8	0.25
Beck inventory [pts]	18.5 ± 8.8	20.5 ± 10.9	21.7 ± 9.5	0.006
Score > 26 pts [N; %]	35; 19.8	117; 26.9	75; 30.1	0.003
Changes in scales on visit IV				
GAD-7 [pts]	-6.8 ± 4.5	-7.0 ± 4.2	-7.7 ± 3.4	0.04
Athens insomnia scale [pts]	-8.0 ± 5.3	-8.2 ± 5.8	-8.0 ± 4.5	0.94
Beck inventory [pts]	-11.7 ± 9.6	-12.1 ± 9.6	-12.7 ± 8.6	0.55

The results of the present study are consistent with the study conducted by Brandt et al[14]. In this study of 41 patients with refractory focal seizures, PGB up to 600 mg/day showed greater benefit in the presence of comorbidities. The response reached 75%, however with a high rate of adverse events as every fifth patient discontinued this therapy. In this context, the use

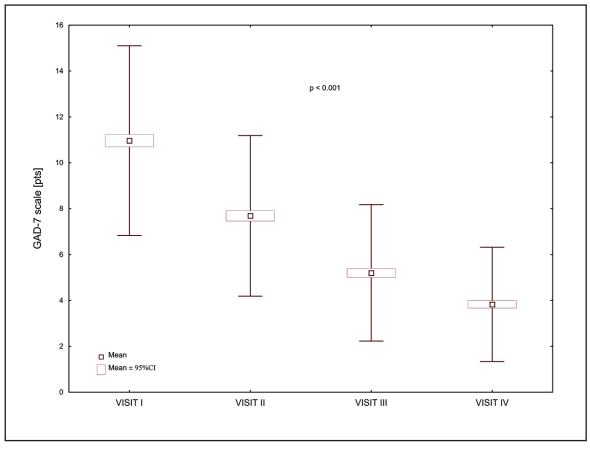

Figure 3. Changes in GAD-7 scale in the whole group of patients with partial seizures with or without generalization.

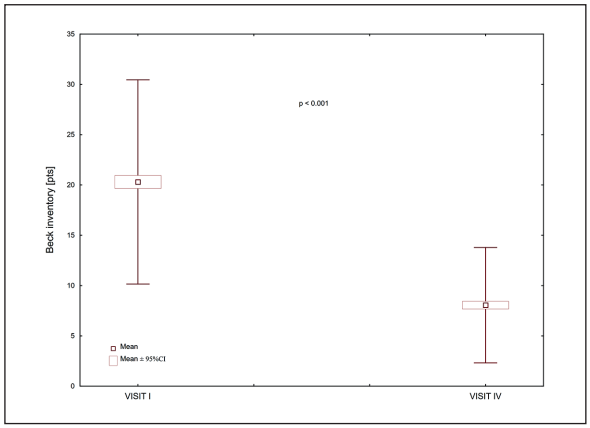

Figure 4. Changes in the Beck inventory in the whole group of patients with partial seizures with or without generalization.

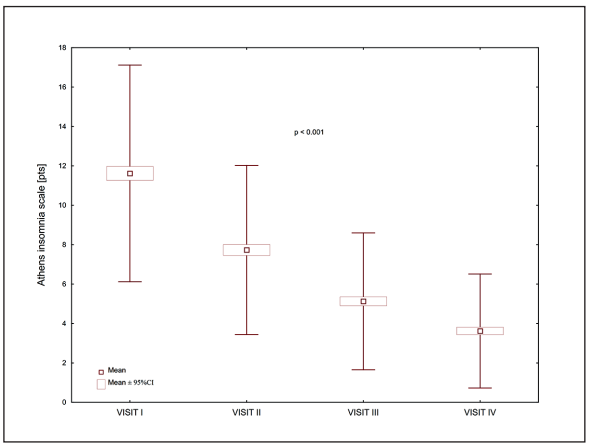

Figure 5. Changes in the Athens insomnia scale in the whole group of patients with partial seizures with or without generalization.

of lower PGB doses in our cohort resulted in a lower frequency of reported ADRs – 0.6 %, and no reports of serious ADRs.

The characteristics of patients achieving seizure free status allows for a hypothesis regarding the slightly greater susceptibility to treatment of patients with secondarily generalized seizures of unknown origin. However, these differences were less significant than the relationship between the dose of PGB used and the reduction in seizure frequency. A higher dose of PGB – 300 mg/day – was associated with a 64 % chance of the seizure status becoming seizure free [OR= 1.64 (95% CI: 0.95-2.84) and a 79% chance of reducing the frequency of seizures by at least 50% [OR = 1.79 (1.07-2.98)]. It can therefore be assumed that a further increase in the daily dose of PGB could increase the percentage of patients responding to anti-epileptic treatment. Moreover, it can be pointed out that already lower doses of PGB have a significant anti-anxiety, as well as hypnotic and antidepressant effect.

Our results are also consistent with studies of PGB effectiveness in the treatment of GAD. Olivares et al[15] studied patients with treatment resistant GAD and severe depressive symptoms, the augmentation of PGB dosing resulted in the improvement of anxiety symptoms and as a secondary result in the improvement of depression and insomnia. PGB ameliorated comorbid depressive symptoms, with a reduction in the mean score of the Montgomery-Asberg Rating Scale of 22.3 points (56.6% reduction). The results of this study suggest that PGB as part of a combination regiment with antidepressants, and/or benzodiazepines, might be effective for the treatment of patients with GAD who have shown inadequate response to previously used antidepressants and have severe depressive and insomnia symptoms.

Limitations

Our data do not include the severity of anxiety, depression and insomnia, as well as the frequency of seizures before the start of any treatment after diagnosis of epilepsy. In addition, insomnia was diagnosed and analyzed based on AIS, and not polysomnography. Patient recruitment methods did not allow for an assessment of the initial severity level of GAD symptoms at the time when neurologists initially started PGB therapy, as well as the duration of this therapy and the level of improvement of anxiety symptoms before the start of the current study. In our open study, no drug was used as a comparator to pregabalin. The frequency of ADRs reported may be lower than that reported in clinical trials due to the failure to include patients who discontinued PGB prior to the first visit in this study. In addition, our research is limited by the short observation period and, most importantly, by the lack of a control group. The data regarding the longer term effectiveness of PGB should be investigated in future studies.

Conclusions

Patients with focal epilepsy with concomitant anxiety disorder obtain reduction in seizure frequency, improvement in anxiety, depressive symptoms and insomnia using PGB as an add-on therapy.

Our data suggests that Pregabalin as an add-on treatment is a reasonable choice for patients with focal epilepsy who have concomitant symptoms of anxiety disorder.

Disclosures and Authors' Declaration of Personal Interests

Joanna Jędrzejczak is a full-time employee of the Department of Neurology and Epileptology Centre of the Postgraduate Medical Education in Warsaw. She has served as a speaker, a consultant and an advisory board member for Novartis, Adamed Pharma S.A., Glenmark and provided study was funded by Adamed Pharma S.A. Sławomir Murawiec is a full-time employee of Warsaw Center of

Psychotherapy and Psychiatry in Warsaw. He received research funding from Adamed Pharma S.A., Lundbeck and also served as a speaker, a consultant and an advisory board member for Janssen, Eli Lilly, Sandoz, Angelini, Teva, Gedeon Richter, Polpharma, Aurovitas, Servier, Novartis. Walter Nieves is a Consulting Neurologist at the Neuropsychoanalysis study group of the New York Psychoanalytic Society & Institute. He has nothing to declare. Jerzy Chudek is full-time employee of the Department of Internal Diseases and Oncological Chemotherapy, Faculty of Medical Sciences in Katowice, Medical University of Silesia. He provided studies that were funded by Adamed Pharma S.A., Recordati, Accord Healthcare, Medac Gmbh., Stada. Agnieszka Almgren Rachtan is employee of Europharma Co.Ltd. in Katowice. She assured that participating in the study was funded by Adamed Pharma S.A., Recordati, Accord Healthcare, Medac Gmbh., Stada.

Declaration of Funding Interests

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Compliance with Ethics Guidelines

According to Polish law (Journal of Laws 2001; No 126. Pos.1381), noninterventional studies are not medical experiments and as such do not require either Bioethics Committee approval or informed consent from the patients for their inclusion. To support compliance and Ethics Guidelines on post-authorization studies (Directive 2001/20/EC) that are conducted voluntarily, study information is available in the EU electronic register of post-authorization studies (EU PAS Register) maintained by the European Medicines Agency.

Authors' Contribution

JJ, SM, JC, AAR, WN conceived and designed the study, consulted literature, collected data and wrote and edit the paper. JC did the statistical data analysis. JJ is the last author, i.e., the group leader in this research. All authors read and approved the manuscript.

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