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CLINICAL TRIAL

The adverse event profile of pregabalin across different disorders: a meta-analysis

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Abstract
Purpose In a recent meta-analysis of 38 double-blind randomized controlled trials (RCTs) comparing pregabalin (PGB) to placebo, we found 20 adverse events (AEs) to be significantly associated with PGB treatment. In the present study, we evaluated whether the incidence of these 20 AEs differs across distinct disorders in which PGB was investigated.
Methods Among the 38 previously identified RCTs of PGB, we selected only those including a PGB 600 mg/day arm and subsequently classified them into four distinct groups according to the disorder in which PGB was investigated: (1) drug-resistant partial epilepsy, (2) psychiatric disorders, (3) fibromyalgia, and (4) neuropathic pain. We used risk differences (RDs) to quantify the placebo-corrected proportion of subjects discontinuing PGB due to intolerable AEs and to determine the placebo-corrected incidence of each of the 20 PGB AEs across the four disorders.
Results Twenty-two RCTs were included in this study. Neither the proportion of subjects discontinuing PGB due to intolerable AEs nor the incidence of PGB AEs (with the exception of ataxia) differed significantly across the four disorders. Ataxia was more common in drug-resistant partial epilepsy compared to fibromyalgia. When limiting analyses to subjects on placebo, most vestibulo-cerebellar AEs (ataxia, diplopia, and blurred vision) were found to be more common in drug-resistant partial epilepsy compared to all other disorders. Diplopia and blurred vision were more common in epilepsy than in neuropathic pain; and ataxia had a higher incidence in epilepsy than in anxiety disorder and fibromyalgia. Among other CNS AEs, somnolence was more common in epilepsy compared to neuropathic pain and in anxiety disorders alone compared to neuropathic pain and fibromyalgia. Asthenia was also more common in epilepsy than in neuropathic pain and fibromyalgia.
Conclusions Although drug-resistant partial epilepsy is associated with a higher probability of developing vestibulo-cerebellar AEs, the risk for PGB toxicity does not differ across distinct disorders.

Keywords Epilepsy · Antiepileptic drugs · Pregabalin · Adverse effects · Nocebo effect · Meta-analysis

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Introduction

Antiepileptic drugs (AEDs) are frequently investigated across a wide range of conditions, including epilepsy, neuropathic pain, psychiatric disorders, and migraine. Despite their widespread use, a comprehensive understanding of their tolerability profile is still lacking. Meta-analyses of randomized controlled trials (RCTs) of AEDs [1–15] have attempted to bridge this knowledge gap, but their assessment of AED toxicity has been hampered by sample size limitations due to exclusion of studies performed outside of a selected disorder (particularly epilepsy).

We recently addressed these methodological limitations in a systematic review and meta-analysis of all available RCTs for the second-generation AED pregabalin (PGB) [16]. This AED was suitable for this type of analysis because it had been investigated in a large variety of conditions and had been shown to have a favorable pharmacokinetic/pharmacodynamic profile. Thirty-eight double-blind, placebo-controlled RCTs

evaluating the therapeutic effects of PGB across different neurologic and psychiatric conditions were included in our analysis, and 20 treatment-emergent adverse events (AEs) were found to be significantly associated with PGB.

Questions arise, however, as to whether differences exist in the tolerability profile of PGB across distinct disorders. In addition to neurobiological diversities, presence or absence of concomitant treatment in a given disorder may impact on the reporting of AEs. In fact, while PGB has been mainly investigated in monotherapy trials in neuropathic pain, fibromyalgia, and anxiety conditions, its effectiveness in drug-resistant partial epilepsy has been explored exclusively in add-on studies. Defining and quantifying these differences in AE reporting across distinct disorders is an essential component of the process to validate analyses in which all data from studies performed in different disorders are pooled for the assessment of the tolerability profile of a given AED.

Using our previously identified sample of double-blind placebo-controlled RCTs of PGB, we compared the incidence and clinical relevance of adverse PGB effects across four different disorders, namely drug-resistant partial epilepsy, neuropathic pain, fibromyalgia, and anxiety conditions. This analysis was complemented by the assessment of AE reporting across the four disorders limited to subjects randomized to placebo.

Methods

Study selection and search methods

Selection criteria and search strategies of PGB studies have been described in detail previously [16]. In summary, only large (≥20 subjects per arm), double-blind, randomized, placebo-controlled trials investigating the efficacy and safety of PBG treatment in adults (age ≥18 years) with different neurological and psychiatric conditions were included. PGB RCTs were identified by searching in MEDLINE, EMBASE, and Cochrane CENTRAL to February 2010. Additional studies were identified from reference lists of retrieved papers and from online clinical databases.

For the purposes of this analysis, we assessed the toxicity profile of PGB at a dose of 600 mg/day. Therefore, RCTs without a PGB arm at 600 mg/day were excluded. In fact, most PGB AEs appear or are more common at higher doses [16]. Moreover, some doses have not been explored in different conditions, hampering inter-disorder comparability. In this respect, PGB at 600 mg/day has been tested in different disorders and enhances the power of our analysis to detect inter-group differences.

RCTs meeting the above criteria were classified into four distinct groups according to the disorder in which PGB was investigated: (1) drug-resistant partial epilepsy, (2) psychiatric disorders (i.e., generalized anxiety disorder and social anxiety disorder), (3) fibromyalgia, and (4) neuropathic pain.

Analysis strategy

We initially compared the placebo-corrected risk of discontinuing PGB due to intolerable AEs across the four distinct disorder groups. For this analysis, we extracted information on the proportion of patients withdrawing from each eligible study because of intolerable AEs. Data were collected separately for the PGB and placebo arms.

We also compared the placebo-corrected risk of individual AEs during PGB treatment across the four disorders. This analysis was limited to the 20 AEs that were previously found to be associated with PGB treatment [16].

Each analysis was complemented by a similar assessment limited to patients taking placebo. In particular, endpoints to be compared across different disorders included (1) the proportion of patients discontinuing placebo due intolerable AEs and (2) the incidence of individual AEs during placebo intake.

Statistical analysis

We estimated risk differences (RDs, 95% CI) to compare across disorders the placebo-corrected risk of discontinuing PGB due to intolerable AEs and the placebo-corrected risk of individual AEs during PGB treatment. Statistical heterogeneity was evaluated using the I^2 test, with an $I^2>70\%$ indicating heterogeneity. A chi-squared test for heterogeneity was also used. Unless significant clinical or statistical heterogeneity was present, all analyses used a fixed-effects model. In cases of $I^2>70\%$, a random-effects model was used [17]. These analyses were performed using RevMan 5.1 [18].

Mean percentages (95% CI) were calculated for inter-group comparisons limited to patients taking placebo, including the proportion of patients discontinuing placebo due to intolerable AEs and the incidence of individual AEs during placebo treatment. The 95% CIs were calculated with equations described by Fleiss [19].

Results

Of the 38 previously identified, double-blind, placebo-controlled RCTs of PGB [16], 22 (58%) randomized subjects to PGB 600 mg/day. These studies included a total of 5,802 subjects, 2,471 of whom were randomized to a 600 mg/day PGB dose and 2,235 to placebo. Four studies were performed in drug-resistant partial epilepsy, 5 in psychiatric disorders (4 in generalized anxiety disorder and 1 in social anxiety disorder), 3

in fibromyalgia, and 10 in neuropathic pain. Mean duration of studies was 13 weeks (range 12–17) for studies performed on epilepsy, 7 weeks (range 4–10) for psychiatric disorders, 12 weeks (range 8–14) for fibromyalgia, and 10 weeks (range 4–14) for neuropathic pain. Characteristics of the included studies are shown in Table 1. For a detailed description of these studies, see Appendix S2 of our previous study [16].

Treatment discontinuation due to intolerable AEs across different disorders

Discontinuation of PGB

Since analysis of data showed no evidence of heterogeneity (I^2 between 0 and 53%), a fixed-effects model was used. There were no significant differences in the risk of

Table 1 Characteristics of the randomized, double-blind, placebo-controlled trials of pregabalin (PGB) included in our study

Studies (first author, date, disorder subtype)	Patients taking PGB at any dose (*n*)	Patients taking PGB at 600 mg/day (*n*)	Patients taking placebo (*n*)	Treatment regimen	Duration of double-blind phase (weeks)	Duration of titration phase (days)
Drug-resistant partial epilepsy[a]						
Arroyo, 2004 [20]	191	92	97	TID	12	8
Beydoun, 2005 [21]	214	214	98	BID (*n*=103) TID (*n*=111)	12	8
Elger, 2005 [22]	268	137	73	BID	12	0
French, 2003 [23]	353	89	100	BID	12	0
Total (partial epilepsy)	1,026	532	368			
Psychiatric disorders[b]						
Feltner, 2003, GAD [24]	205	66	67	TID	4	6
Montgomery, 2006, GAD [25]	320	110	101	BID	6	6
Pande, 2003, GAD [26]	139	70	69	TID	4	6
Pande, 2004, SAD [27]	89	47	46	TID	10	6
Rickels, 2005, GAD [28]	270	89	91	TID	4	7
Total (psychiatric disorders)	1,023	382	374			
Fibromyalgia[c]						
Arnold, 2008 [29]	561	188	184	BID	14	14
Mease, 2008 [30]	558	190	190	BID	13	7
Protocol A008-1100, 2008 [31]	551	186	184	BID	14	14
Total (fibromyialgia)	1,670	564	558			
Neuropathic pain[d]						
Arezzo, 2008, diabetic neuropathy [32]	82	82	85	BID	13	7
Lesser, 2004, diabetic neuropathy [33]	240	82	97	TID	5	6
Richter, 2005, diabetic neuropathy [34]	161	82	85	BID	6	14
Tolle, 2008, diabetic neuropathy [35]	299	101	96	BID	12	7
Protocol 1008-040, 2007, diabetic neuropathy [36]	86	86	81	TID	9	14
Protocol A008-1071, 2007, diabetic neuropathy [37]	305	152	151	BID	13	7
Freynhagen, 2005, postherpetic neuralgia or diabetic neuropathy [38]	273	132	65	BID	12	7
Protocol A008-1120, 2009, postherpetic neuralgia [39]	273	97	98	BID	13	7
Dworkin, 2003,[e] postherpetic neuralgia [40]	89	89	84	TID	9	8
van Seventer, 2006, postherpetic neuralgia [41]	275	90	93	BID	13	7
Total (neuropathic pain)	2,083	993	935			
Total (all disorders)	5,802	2,471	2,235			

We included all subjects in the analysis

GAD Generalized anxiety disorder, *SAD* social anxiety disorder

[a] In all PGB studies performed in partial epilepsy, patients were taking one to three antiepileptic drugs

[b] Except for Rickels, 2005, all PBG studies in psychiatric disorders did not allow treatment with any psychotropic drug. In Rickels, 2005, use of benzodiazepines was not allowed

[c] Except for A008-1100, 2008, all studies in fibromyialgia did not allow use of any medication for pain. In A008-1100, 2008, whether use of medications for pain was allowed or not was not specified

[d] Except for 1008-040, 2007, A008-1071, 2007, and A008-1120, 2009, all studies in neuropathic pain did not allow use of any medication for pain. In 1008-040, 2007, A008-1071, 2007, and A008-1120, 2009, whether use of medications for pain was allowed or not was not specified

[e] In about one-third of patients, creatinine clearance was between 30 and 60 mL/min. Those subjects were treated with 300 mg/day

discontinuing PGB due to treatment-emergent AEs across the four disorders. The RD (95% CI) for AE-related PGB discontinuation was 0.18 (0.13–0.22) for drug-resistant partial epilepsy, 0.08 (0.03–0.13) for anxiety disorders, 0.17 (0.13–0.22) for fibromyalgia, and 0.13 (0.10–0.16) for neuropathic pain.

Discontinuation of placebo

Similarly to the analysis for PGB, there were no significant differences in the risk of discontinuing placebo due to intolerable AEs across the four disorders. The percentage (95% CI) of patients who discontinued placebo due to AEs was 6% (4.1–8.8%) for drug-resistant partial epilepsy, 9% (6–12%) for anxiety disorders, 11% (8–14%) for fibromyalgia, and 6% (4–8%) for neuropathic pain.

Occurrences of treatment-emergent AEs across different disorders

AEs in patients taking PGB

In most cases, analysis of data showed no evidence of heterogeneity (I^2 between 0 and 70%) and a fixed-effects model was used. For AEs displaying an $I^2>70\%$ (incoordination and somnolence in psychiatric disorders; dizziness, somnolence and edema in neuropathic pain), a random-effects model was used instead.

Figure 1 shows RDs (95% CI) for each of the 20 AEs [16] across the four distinct disorders. Of these 20 AEs, 8 (40%) were reported in all four disorders (dizziness, incoordination, ataxia, blurred vision, somnolence, thinking abnormal, asthenia, dry mouth), 3 (15%) in three disorders (vertigo, amblyopia and constipation), 7 (35%) in two (balance disorder, diplopia, confusional state, euphoria, fatigue, tremor, peripheral edema), and 2 (10%) in one (disturbance in attention, edema).

There were no significant differences in the risk of developing any of these AEs across the four disorders, except for ataxia, which was more common in drug-resistant partial epilepsy compared to fibromyalgia. In the case of two AEs (edema and disturbance in attention), no between-group comparisons could be made due to their occurrence in one disorder only. See also Appendix 1.

AEs in patients taking placebo

As shown in Fig. 2, several AEs involving the central nervous system (CNS) were reported more frequently in drug-resistant partial epilepsy compared to other disorders. This was the case for three of the nine (33%) vestibulo-cerebellar AEs: diplopia and blurred vision, which were more common in epilepsy than in neuropathic pain; and ataxia, which had a higher incidence in epilepsy than in anxiety disorder and fibromyalgia.

Among other CNS AEs, somnolence was more common in epilepsy compared to neuropathic pain, and in anxiety disorders alone compared to neuropathic pain and fibromyalgia. Asthenia was also more common in epilepsy than in neuropathic pain and fibromyalgia.

Significant differences across the four disorders were found in the incidence of two gastrointestinal/metabolic AEs. Peripheral edema was seen more frequently in neuropathic pain compared to fibromyalgia. Dry mouth had a higher incidence in anxiety disorders than in neuropathic pain and fibromyalgia. See also Appendix 2.

Discussion

In this study, we found that the risk for PGB toxicity does not differ across four biologically distinct disorders, i.e., drug-resistant partial epilepsy, anxiety disorders, fibromyalgia, and neuropathic pain. The only exception was ataxia, which was reported more frequently in drug-resistant partial epilepsy compared to fibromyalgia. However, balance disorder, which is often considered an equivalent symptom [42], was not reported by patients with epilepsy, thereby counterbalancing any inter-group differences found in the assessment of ataxia. This explanation is also reinforced by the two other manifestations of vestibulo-cerebellar dysfunction, vertigo and incoordination, the occurrences of which did not differ significantly across the four disorders.

Our findings were obtained by using a rigorous methodology, which controlled for the intrinsic variability in the propensity to experience AEs across neurobiologically distinct disorders. In fact, by computing RD estimates (the proportion of patients experiencing a given AE with the active compound minus the proportion of patients experiencing the same AE while taking placebo), we accounted for the effect of placebo, which varied considerably across different disorders. Therefore, our data provide an accurate measure of PGB's potential for toxicity in a given disorder. This information is directly relevant to improved clinical decision-making, including a more informative patient counseling regarding PGB toxicity.

There were some differences in the mean duration of clinical studies. Since we have analysed treatment-emergent AEs, we think that such differences in the length of double-blind phase should not have influenced the pattern of tolerability of PGB. However, we cannot exclude that some minor differences in the frequency of observation of some AEs could be due to different lengths of observation in the clinical studies.

These results also have direct implications for an improved understanding of an AED's toxicity profile. In

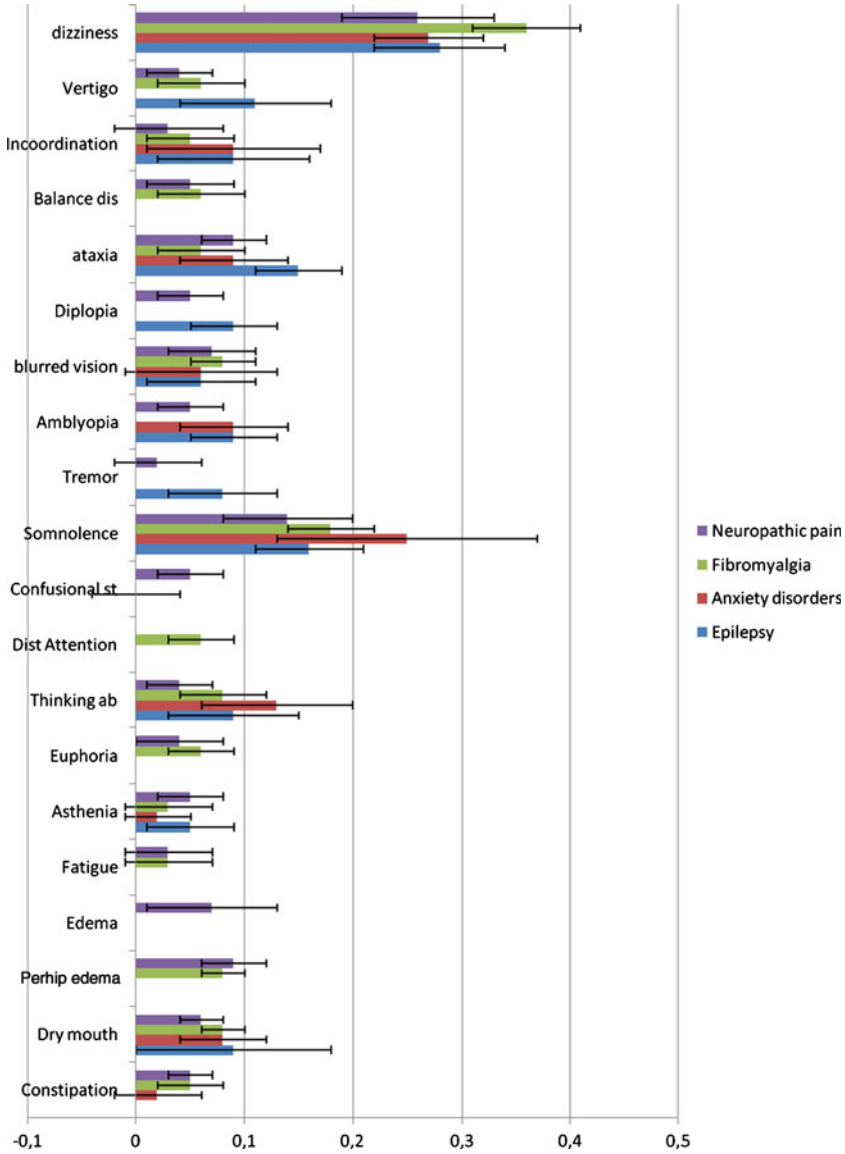

Fig. 1 Comparison of the placebo-corrected incidence of PGB AEs across four distinct disorders. *Bars* present the Risk Difference and *error bars* the 95% CI

particular, they lend further support [16] that the AE profile of a given drug can and therefore should be characterized through the analysis of all available studies, regardless of whether they have been carried out in different diseases. Pooling data from RCTs performed in different conditions may greatly enhance the ability to fully explore the tolerability profile of a certain AED.

Our results indicate that patients with drug-resistant partial epilepsy receiving placebo report a higher incidence of cognition/coordination AEs compared to those with other disorders. Therefore, even though caution is needed because of wide CIs, the analysis of the general trend led us to infer that these patients are more prone to develop this type of symptom. Although these findings are novel, they may not be surprising. Patients with drug-resistant partial epilepsy are typically on concurrent AED treatment, which may also cause cognition/coordination AEs [43, 44]. Underlying etiology and ongoing seizure activity may be contributive factors as well [45]. For instance, somnolence is a common adverse effect that has also been observed in patients with epilepsy not yet treated with AEDs [46]. The incidence of two gastrointestinal/metabolic AEs differed across the four disorders. Peripheral edema was more common in neuropathic pain than in fibromyalgia, while dry mouth was more frequently reported in anxiety disorders than in neuropathic pain and fibromyalgia. These AEs may be manifestations of the underlying disorder [47]. An example is represented by diabetes, in which both edema and neuropathic pain are not infrequent complications [48].

Other explanations for occurrences of AEs during placebo administration may relate to individual expectations of

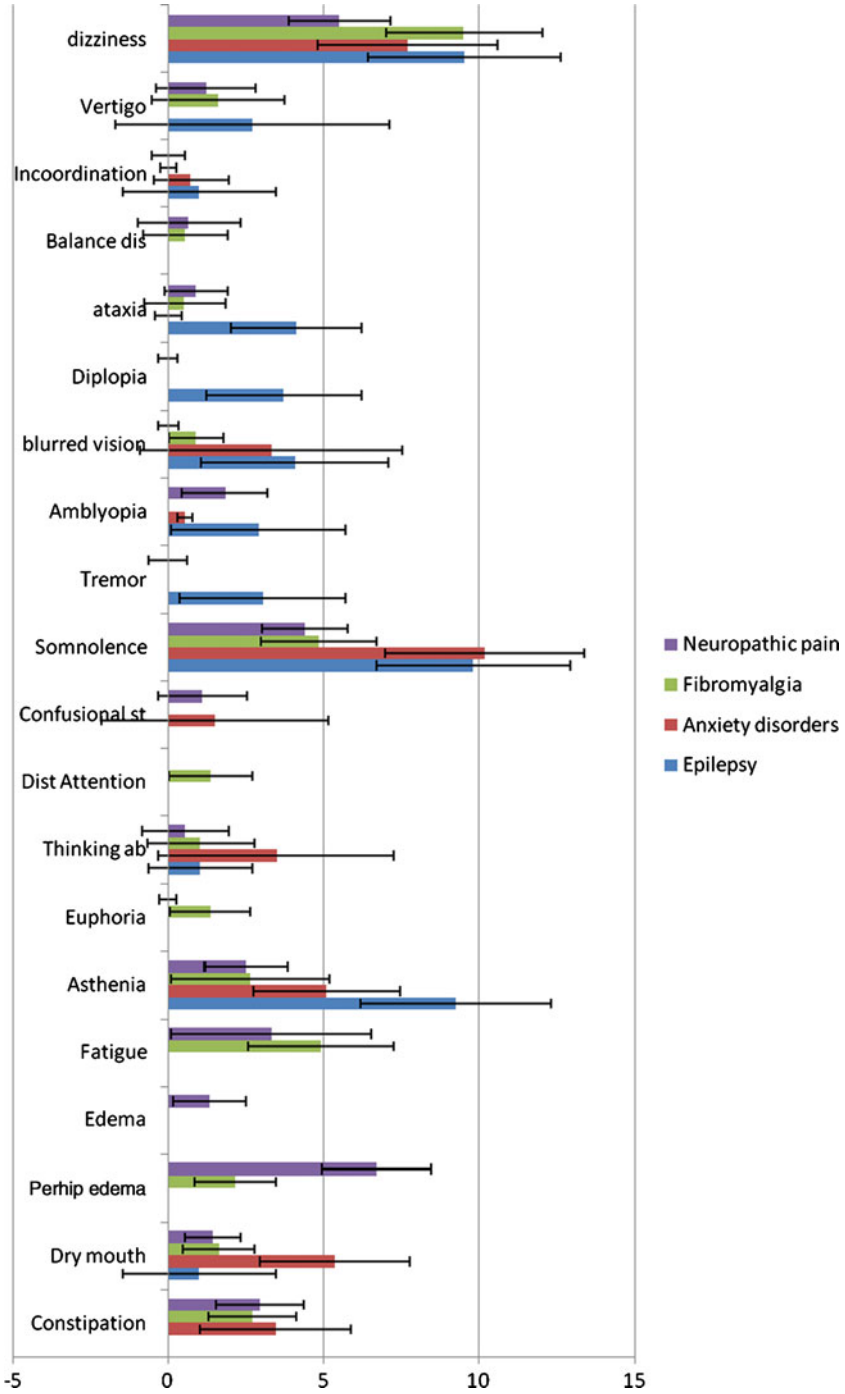

Fig. 2 Incidence of adverse events in subjects taking placebo across four distinct disorders (epilepsy, anxiety disorders, fibromyalgia, and neuropathic pain). Values are percentages with *error bars* representing the 95% CI

AEs at the outset of treatment, certain psychological characteristics (such as anxiety and depression), tendencies to somatize, or different situational/contextual factors [49, 50]. Future studies using multivariate analysis should be performed to identify which factors account for inter-disorder differences in placebo-related AEs.

To the best of our knowledge, differences in the "nocebo effect" across distinct disorders have never been previously investigated. Recent studies have assessed the extent to which the nocebo effect is influenced by the type of drug investigated in the setting of a RCT. In this respect, the AE profile of patients with migraine randomized to placebo differs in relation to whether the investigated compound is an AED, a nonsteroidal anti-inflammatory drug, or a triptan [51]. Similar findings have been observed in patients with multiple sclerosis receiving different treatments [52].

In conclusion, there are intrinsic differences in the threshold for experiencing AEs across distinct disorders. These differences may be related to the disease and also to unknown factors that might be interesting to explore in the future. However, when controlling for such variability, no differences in the risk for PGB toxicity can be detected across these disorders. Although our findings are limited to PGB, they nonetheless suggest that pooling data from studies performed in different conditions may allow an AED's tolerability profile to be fully explored.

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Appendix 1

Table 2 compares the placebo-corrected incidence of PGB AEs across four distinct disorders.

Table 2 Comparison of the placebo-corrected incidence of pregabalin adverse events (AEs) across four distinct disorders. Values are risk differences (95% CI)

AEs	Epilepsy	Anxiety disorders	Fibromyalgia	Neuropathic pain
Vestibulocerebellar AEs				
Dizziness	0.28 (0.23–0.34)	0.27 (0.21–0.32)	0.36 (0.31–0.41)	0.26 (0.19–0.33)
Vertigo	0.11 (0.04–0.18)	nr	0.06 (0.02–0.10)	0.04 (0.02–0.07)
Incoordination	0.09 (0.03–0.16)	0.09 (0.00–0.17)	0.05 (0.02–0.09)	0.03 (−0.01 to 0.08)
Balance disorder	nr	nr	0.06 (0.03–0.10)	0.05 (0.01–0.09)
Ataxia	0.15 (0.11–0.19)	0.09 (0.03–0.14)	0.06 (0.03–0.10)	0.09 (0.06–0.12)
Diplopia	0.09 (0.05–0.13)	nr	nr	0.05 (0.01–0.08)
Blurred vision	0.06 (0.01–0.11)	0.06 (−0.01 to 0.13)	0.08 (0.06–0.10)	0.07 (0.02–0.11)
Amblyopia	0.09 (0.05–0.13)	0.09 (0.05–0.14)	nr	0.05 (0.03–0.08)
Tremor	0.08 (0.03–0.13)	nr	nr	0.02 (−0.02 to 0.06)
Other CNS AEs (vigilance, cognition, and mood)				
Somnolence	0.16 (0.11–0.21)	0.25 (0.14–0.37)	0.18 (0.14–0.22)	0.14 (0.09–0.20)
Confusional state	nr	0.00 (−0.04 to 0.04)	nr	0.05 (0.02–0.08)
Disturbance in attention	nr	nr	0.06 (0.03–0.09)	nr
Thinking abnormal	0.09 (0.03–0.15)	0.13 (0.05–0.20)	0.08 (0.04–0.12)	0.04 (0.00–0.07)
Euphoria	nr	nr	0.06 (0.03–0.09)	0.04 (0.01–0.08)
Asthenia	0.05 (0.00–0. 09)	0.02 (−0.01 to 0.05)	0.03 (0.01–0.07)	0.05 (0.03–0.08)
Fatigue	nr	nr	0.03 (0.00–0.07)	0.03 (−0.02 to 0.07)
Gastrointestinal/metabolic AEs				
Edema	nr	nr	nr	0.07 (0.01–0.13)
Peripheral edema	nr	nr	0.08 (0.05–0.10)	0.09 (0.06–0.12)
Dry mouth	0.09 (0.00–0.18)	0.08 (0.04–0.12)	0.08 (0.05–0.10)	0.06 (0.04–0.08)
Constipation	nr	0.02 (−0.01 to 0.06)	0.05 (0.03–0.08)	0.05 (0.02–0.07)

n/r Not reported

Appendix 2

Table 3 presents the incidence of adverse events (AEs) in subjects taking placebo across four distinct disorders.

Table 3 Incidence of adverse events (AEs) in subjects taking placebo across four distinct disorders (epilepsy, anxiety disorders, fibromyalgia, and neuropathic pain). Values are percentages (95% CI)

AEs	Epilepsy	Anxiety disorders	Fibromyalgia	Neuropathic pain
Vestibulocerebellar AEs				
Dizziness	9.51 (6.38–12.64)	7.7 (4.91–10.6)	9.5 (7.0–12.0)	5.5 (3.93–7.12)
Vertigo	2.7 (−1.69 to 7.1)	nr	1.6 (−0.47 to 3.73)	1.2 (−0.36 to 2.8)
Incoordination	1 (−1.45 to 3.45)	0.73 (−0.46 to 1.93)	0 (−0.26 to 0.26)	0 (−0.54 to 0.54)
Balance disorder	nr	nr	0.54 (−0.79 to 1.88)	0.66 (−0.96 to 2.3)
Ataxia	4.1 (1.9–6.2)	0 (−0.43 to 0.43)	0.52 (−0.76 to 1.82)	0.9 (−0.9 to 1.9)
Diplopia	3.7 (1.3–6.2)	nr	nr	0 (−0.3 to 0.3)
Blurred vision	4.06 (1.05–7.07)	3.30 (−0.92 to 7.51)	0.90 (0.02–1.77)	0 (−0.33 to 0.33)
Amblyopia	2.9 (0.1–5.7)	0.55 (−0.8 to 0.8)	nr	1.82 (0.46–3.18)
Tremor	3.04 (0.39–5.7)	nr	nr	0 (−0.62 to 0.62)
Other CNS AEs (vigilance, cognition, and mood)				
Somnolence	9.8 (6.61–12.9)	10.16 (6.96–13.35)	4.83 (2.97–6.70)	4.38 (3.02–5.75)
Confusional state	nr	1.49 (−2.16 to 5.14)	nr	3.09 (−0.32 to 2.51)
Disturbance in attention	nr	nr	1.35 (0.00–2.68)	nr
Thinking abnormal	1.02 (−1.5 to 3.5)	3.48 (−0.30 to 7.26)	1.05 (−0.66 to 2.76)	0.56 (−0.82 to 1.94)
Euphoria	nr	nr	1.34 (0.04–2.63)	0 (−0.27 to 0.27)
Asthenia	9.24 (6.14–12.3)	5.08 (2.72–7.44)	2.63 (0.09–5.17)	2.49 (1.16–3.82)
Fatigue	nr	nr	4.89 (2.55–7.23)	3.31 (0.13–6.5)
Gastrointestinal/metabolic AEs				
Edema	nr	nr	nr	1.32 (0.16–2.49)
Peripheral edema	nr	nr	2.15 (0.86–3.44)	6.69 (4.94–8.44)
Dry mouth	1 (−1.45 to 3.45)	5.35 (2.93–7.76)	1.61 (0.48–2.75)	1.43 (0.57–2.30)
Constipation	nr	3.44 (1.04–5.85)	2.69 (1.26–4.12)	2.93 (1.51–4.34)

nr Not reported

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