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FULL-LENGTH ORIGINAL RESEARCH

The adverse event profile of pregabalin: A systematic review and meta-analysis of randomized controlled trials

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Summary

Purpose: Despite the widespread use of antiepileptic drugs (AEDs) across different neurologic and psychiatric disorders, no study has systematically reviewed all available randomized controlled trials (RCTs) of a given AED to fully uncover its tolerability profile.

We aimed at identifying treatment emergent adverse events (AEs) associated with pregabalin through a systematic review and meta-analysis of all available RCTs. We also assessed the association between serious AEs and pregabalin, and investigated whether pregabalin AEs display a dose–response relationship.

Methods: We searched MEDLINE, EMBASE, and Cochrane CENTRAL to February 2010 for RCTs. Additional studies were identified from reference lists of retrieved papers and from online clinical databases. We selected placebo-controlled, double-blind RCTs investigating the therapeutic effects of pregabalin in adults with any condition. Studies had to include at least 20 subjects per arm and have a duration of at least 4 weeks. AEs were assessed for their association with pregabalin after identification/exclusion of synonyms, rare AEs, and nonassessable AEs due to methodologic limitations. We used relative risks (RRs) to assess the association of any [99% confidence intervals (CIs)] or serious AEs (95% CIs) with pregabalin, and risk differences (RDs, 95% CIs) to investigate dose–response relationships of pregabalin AEs.

Key findings: Thirty-eight RCTs were included in our study. Of 39 AEs, 20 (51%) were significantly associated with pregabalin (dizziness, vertigo, incoordination, balance disorder, ataxia, diplopia, blurred vision, amblyopia, tremor, somnolence, confusional state, disturbance in attention, thinking abnormal, euphoria, asthenia, fatigue, edema, peripheral edema, dry mouth, constipation). The highest RRs were found for cognition/coordination AEs. There was no significant association between serious AEs and pregabalin. There was a selective dose–response pattern in the onset of pregabalin AEs, with certain AEs appearing at lower doses than others.

Significance: Individuals starting treatment with pregabalin are at increased risk for several AEs, particularly those affecting cognition/coordination. Pregabalin AEs appear according to a selective dose–response pattern, possibly reflecting the severity of dysfunction of distinct anatomic structures. These findings may aid clinicians in providing better patient management, and support the value of including in meta-analyses of AED tolerability profiles RCTs performed in different conditions.

KEY WORDS: Epilepsy, Antiepileptic drugs, Pregabalin, Adverse effects, Side effects, Meta-analysis.

In addition to their traditional indication in epilepsy, antiepileptic drugs (AEDs) have been used extensively over the last few years to treat a wide range of neurologic and psychiatric disorders (Johannessen Landmark, 2008). In a recent U.S. Food and Drug Administration (FDA) meta-analysis of 199 randomized controlled trials (RCTs) of 11 AEDs, less than one third were performed in epilepsy. Neuropathic pain, bipolar disorder, migraine, and anxiety accounted for almost one-half of the trials (U.S. Food and Drug Administration, 2010). Moreover, the number of indications and off-label utilizations of common AEDs is continuously growing (Rosenberg & Salzman, 2007). Therefore, providing reliable information on the tolerability and safety profiles of these agents has a broad clinical relevance.

Meta-analyses of RCTs have attempted to provide such data for several AEDs (Marson et al., 1997, 2000; Chadwick & Marson, 2000; Jette et al., 2000; Ramaratnam et al., 2000; Chaisewikul et al., 2001; Marson et al., 2001; Chadwick & Marson, 2002; Jette et al., 2002; Leach et al., 2002; Pereira et al., 2002; Chadwick & Marson 2005; Hemming et al., 2008; Jette et al., 2008; Lozsadi et al., 2008; Michael & Marson, 2008). However, due to the exclusion of any RCT performed outside of a selected disorder (in most cases epilepsy), none of these investigations had a sufficiently large

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sample size to reveal the adverse event (AE) profile of any AED. In one study, for instance, assessment was restricted to the five most commonly observed AEs (Marson et al., 1997). Including all available trials in which a certain AED was investigated would lead to a more comprehensive evaluation of the drug's tolerability and safety profiles. Moreover, considering that most of these studies include fixed-dose regimens, it would allow a better ascertainment of dose-response relationships for any AE.

Pregabalin is a suitable candidate for this type of analysis, for two main reasons: (1) it has been investigated in a large variety of conditions (e.g. pharmacoresistant epilepsy, neuropathic pain, fibromyalgia, and generalized anxiety disorder); (2) it does not display clinically significant interactions with other drugs, thereby avoiding the confounding effect of AEs due to drug–drug interactions (Ryvlin et al., 2008).

Study end points

The primary aim of this study was to identify any AEs associated with pregabalin treatment, through a systematic review and meta-analysis of available RCTs.

We additionally investigated the association between serious AEs and pregabalin treatment, and assessed whether pregabalin AEs exhibit a dose–response relationship.

Methods

Criteria for considering studies for this review

Types of studies

We included only randomized, placebo-controlled, double-blind trials investigating the therapeutic effects of pregabalin in adults with different neurologic and psychiatric disorders. We further limited our analysis to studies that recruited at least 20 subjects per arm and had a duration of at least 4 weeks. Full journal publication or summary clinical trial reports were required, with brief abstracts not included. All other study types, including nonrandomized trials, case reports, or clinical observations, were excluded.

Types of participants

Subjects were aged 18 years or older and affected by different neurologic or psychiatric conditions, including epilepsy, neuropathic pain, fibromyalgia, and generalized anxiety disorder.

Types of interventions

Oral treatment with pregabalin at any dose was the intervention. Studies had to include a placebo arm.

Search methods for identification of studies

Studies were identified by several methods. RCTs of pregabalin (and key brand name: Lyrica) were identified using: MEDLINE (PubMed) from 1990 to February 2010; EMBASE (Ovid), from 1990 to February 2010; and Cochrane CENTRAL issue 2, 2010. Additional studies were sought in reference lists of retrieved papers, and by searching the Internet for summary clinical trial reports not available as full publications. The National Institutes of Health (NIH) clinical trial registry (http://www.clinicaltrial.gov) and the PhRMA clinical study results database (http://www.clinicalstudyresults.org) were also interrogated for trial results of pregabalin (Lyrica) in all conditions. Search strategies for MEDLINE, EMBASE, and Cochrane CENTRAL are available in Appendix S1.

Eligibility was determined by reading each study identified by the search. All studies were read independently by two authors (GZ and LS) and agreement was reached after discussion.

Strategy for the analysis of adverse events

Selection of adverse events

Relevant AEs were selected by using the following three-step strategy: (1) identification of synonyms, which were grouped under one main term; (2) identification and subsequent exclusion of treatment emergent AEs not frequently signaled in clinical studies, that is, AEs observed in <10 subjects among those treated with pregabalin or placebo; and (3) identification and subsequent exclusion of any other AEs the assessment of which was impeded by a nonuniform acquisition of data in clinical trials.

After selecting those AEs to be included in our analyses, we extracted the frequency of each AE from the pregabalin and placebo groups of each study that met inclusion criteria. This information was recorded into a separate data extraction sheet.

Statistical analysis

All analyses were performed using RevMan (2008).

Statistical heterogeneity was assessed using the I^2 test, with an $I^2 > 70\%$ indicating heterogeneity. A chi-square test for heterogeneity was also used. Provided no significant clinical or statistical heterogeneity was present, the analyses used a fixed-effect model. In cases where I^2 was >70%, random-effect model was used.

We estimated: (1) relative risks (RRs) to assess the association of any or serious AEs with pregabalin treatment; and (2) risk differences (RDs) to investigate dose–response relationships of pregabalin AEs. For the latter analysis, we selected only those studies in which subjects were randomized to fixed-dose regimens (150, 300, 450, and 600 mg/day), and excluded studies or study arms using flexible-dose regimens, since in these studies it is not possible to assign the appearance of an AE to a precise drug dose.

To ease interpretation of dose–response relationships, each RD estimate was complemented by the computation of the number needed to harm (NNH).

When assessing the association of any AE with pregabalin treatment, the confidence intervals (CIs) of RRs were set at 99%. This conservative approach was aimed at minimizing the error rate without reducing the probability of an adequate individualization of AEs. For all other analyses, 95% CIs were used.

Results

Description of studies

Results of the search

Our search yielded 86 potentially eligible RCTs, 19 of which were unpublished studies identified in the PhRMA clinical study results database. From this initial screening, we excluded non–double-blind studies, abstracts, active-controlled studies, double-blind studies in which pregabalin was administered only for a few days in subjects undergoing surgery, and studies performed on healthy volunteers. Fifty-three randomized, placebo-controlled, double-blind studies in which pregabalin was administered to subjects with various conditions were carefully evaluated (Fig. 1), and 38 were ultimately selected for our analysis on the criteria stated (see Types of studies). Main clinical characteristics of selected studies are reported in Table 1.

For a detailed description of included and excluded studies see Appendix S2.

Included studies

The 38 studies included a total of 11,918 subjects, 8,235 of whom were randomized to pregabalin and 3,683 to placebo. Nineteen studies were performed in neuropathic pain, four in fibromyalgia, six in pharmacoresistant epilepsy, six in generalized anxiety disorder, two in social anxiety disorder, and one in panic disorder. Ten studies used flexible-dose regimens, with pregabalin doses usually increased up to 600 mg/day. In 25 studies, after a titration phase of variable duration, pregabalin doses were fixed. Three studies included both flexible and fixed-dose arms. Study duration varied from 4–14 weeks.

Excluded studies

From 53 potentially eligible RCTs, 15 studies (Anon, 2005c,d; Arnold et al., 2007; De Haas et al., 2007; Houghton et al., 2007; Zesiewicz et al., 2007; Anon., 2008a,c; Crofford et al., 2008; Feltner et al., 2008; Anon., 2009c,d,f; Ferrara et al., 2009; Kasper et al., 2009) were excluded from our analysis due to additional limitations (see Fig. 1). Reasons for exclusion included: lack of AE data, non-suitable study designs for AE analysis, ≤20 subjects on

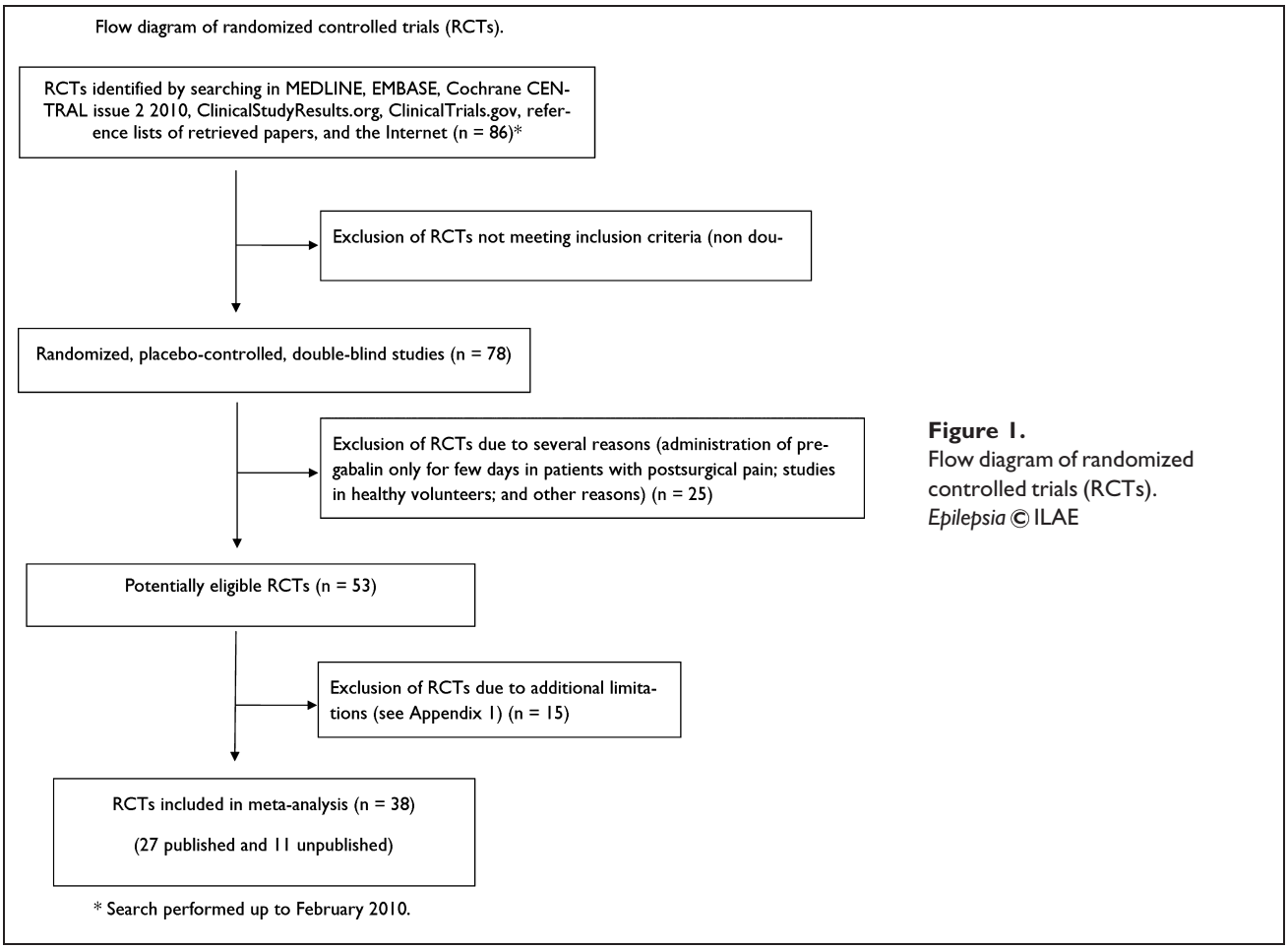

Figure 1.
Flow diagram of randomized controlled trials (RCTs).
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Table 1. Characteristics of studies included in our analysis

Author	Disease	Study duration (weeks)	Titration phase	Drug regimen	150 mg (n)	300 mg (n)	450 mg (n)	600 mg (n)	Flexible dose (n)
Anon. 2005a	Panic disorder	10	1–2 w	BID	90[a]		85[b]		
Anon. 2005b	Partial epilepsy	17	1 w	BID					152
Anon. 2007a	Diabetic neuropathy	9	2 w	TID				86	
Anon. 2007b	GAD	9	1 w	BID-TID					177
Anon. 2007c	Diabetic neuropathy	13	1 w	BID		153		152	
Anon. 2007d	Diabetic neuropathy	14	6 w	BID					271
Anon. 2008b	Fibromyalgia	14	2 w	BID		183	182	186	
Anon. 2008d	HIV neuropathy	15	1–2 w	BID					151
Anon. 2009a	Neuropathic pain	8	4 w	BID					127
Anon. 2009b	Central poststroke pain	12	4 w	BID					110
Anon. 2009e	Postherpetic neuralgia	13	1 w	BID	86	89		97	
Arezzo 2008	Diabetic neuropathy	13	1 w	BID				82	
Arnold 2008	Fibromyalgia	14	1–2 w[c]	BID		183	190	188	
Arroyo 2004	Partial epilepsy	12	4–8 d	TID	99			92	
Beydoun 2005	Partial epilepsy	12	8 d	BID-TID				103 111	
Crofford 2005	Fibromyalgia	8	0–3 d	TID	132	134	132		
Dworkin 2003	Postherpetic neuralgia	9	1 w[d]	TID				89	
Elger 2005	Partial epilepsy	12	0–1 w	BID				137	131
Feltner 2003	GAD	4	1 w	TID	70			67	
French 2003[e]	Partial epilepsy	12	0 d	BID	86	90		89	
Freynhagen 2005	Neuropathic pain	12	1 w	BID				132	141
Lee 2009	Partial epilepsy	12	Up to 8 w	BID					119
Lesser 2004[f]	Diabetic neuropathy	5	0–1 w	TID		81		82	
Mease 2008	Fibromyalgia	13	1 w	BID		185	183	190	
Montgomery 2006	GAD	8	5–7 d	BID			97[b]	110	
Montgomery 2008	GAD	8	Up to 6 w	BID-TID					177
Pande 2004	SAD	10	6 d	TID	42			47	
Pande 2003	GAD	4	6 d	TID	69			70	
Pohl 2005	GAD	6	4 d	BID TID	78[a]		89[b] 88		
Richter 2005	Diabetic neuropathy	6	2 w	BID	79			82	
Rickels 2005	GAD	4	Up to 7 d	TID		91	90	89	
Rosenstock 2004	Diabetic neuropathy	8	0	TID		76			
Sabatoski 2004	Postherpetic neuralgia	7	1 w	TID	81	76			
Siddall 2006	Central neuropathic pain	12	Flexible	BID					70
Stacey 2008	Postherpetic neuralgia	4	Fixed 0 flexible 2 w	BID		88			91
Tölle 2008	Diabetic neuropathy	12	1 w	BID	99	99		101	
van Seventer 2006	Postherpetic neuralgia	13	1 w	BID	87	98		90	
Vranken 2008	Central neuropathic pain	4	4 w	BID					20

[a]On 200 mg/day.
[b]On 400 mg/day.
[c]Varied according to treatment arm.
[d]Up to 600 mg/day according to creatinine values.
[e]Included an arm treated with 50 mg/day (data not shown).
[f]Included an arm treated with 75 mg/day (data not shown).
GAD, generalized anxiety disorder; SAD, social anxiety disorder; w, weeks; d, days.

pregabalin treatment, nonstable doses of other concomitant drugs during the double-blind phase, and short study duration (Appendix S2).

Risk of bias in included studies

Although all studies were reported to be randomized, placebo-controlled, and double-blind, no full details were generally given on the randomization generation scheme, allocation concealment, and blinding. However, the risk of bias in the analysis of treatment-emergent AEs was considered to be very low because many studies were multicenter and performed in a relatively large population of patients.

Description of adverse events in included studies

Results of the search

In the 38 studies included in our analysis, we found 87 AEs occurring with pregabalin treatment. After identification of synonyms, rare AEs, and other nonassessable AEs,

39 AEs (45% of the initial sample) were investigated in fixed-effect meta-analyses for their association with pregabalin (Fig. 2).

Synonyms

Of the 87 AEs, 11 (12.6%) were considered as synonyms of an another AE: accidental injury as a synonym of contusion; abnormal gait of ataxia; confusion of confusional state; coordination abnormal of incoordination; euphoric mood of euphoria; generalized edema of edema; myasthenia of asthenia; and flu syndrome, pharyngitis, nasopharyngitis, and rhinitis of upper respiratory tract infection (RTI). These synonyms were merged with their corresponding AEs in all analyses.

Nonfrequently observed adverse events

Thirty-four AEs (enlarged abdomen, abdominal pain, anorgasmia, anxiety, blood glucose increase, creatinine clearance decrease, cognitive performance, conjunctivitis, convulsion, decreased libido, depersonalization, depressed level of consciousness, depression, disorientation, dyspepsia, eczema, feeling drunk, feeling abnormal, flatulence, hyperglycemia, hypertension, hyperthermia, joint swelling, insomnia, lethargy, malaise, neuralgia, overdose, decreased reflexes, sleep disorder, speech disorder, sweating, thirst, and urinary incontinence), 39.1% of the initial sample, occurred in <10 subjects assigned to pregabalin or placebo, and were, therefore, excluded from our analysis.

Other adverse events

Weight gain is an established AE of pregabalin, occurring in about one fourth of treated patients (Ryvlin et al., 2008). However, weight gain assessment varies considerably across studies. In the 38 studies included in our analysis, some reported the proportion of subjects who gained weight throughout the study. Others calculated the mean weight

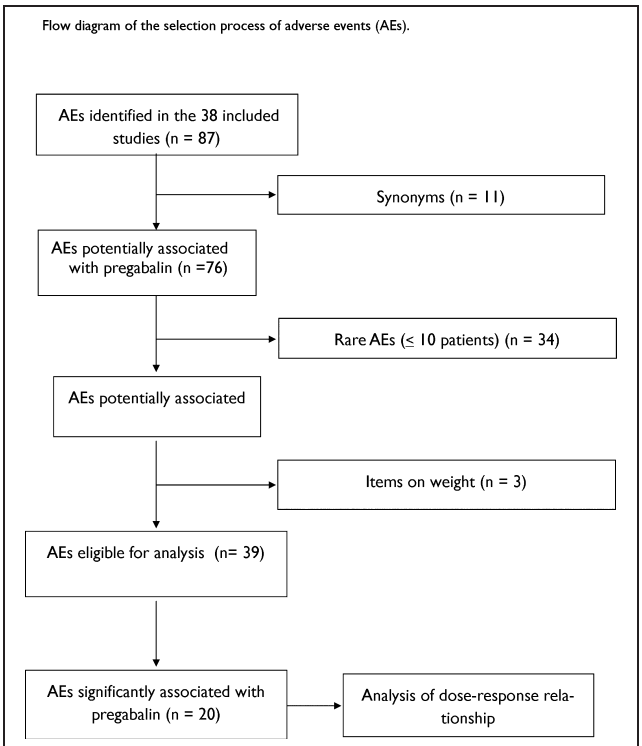

Figure 2.
Flow diagram of the selection process of adverse events (AEs).
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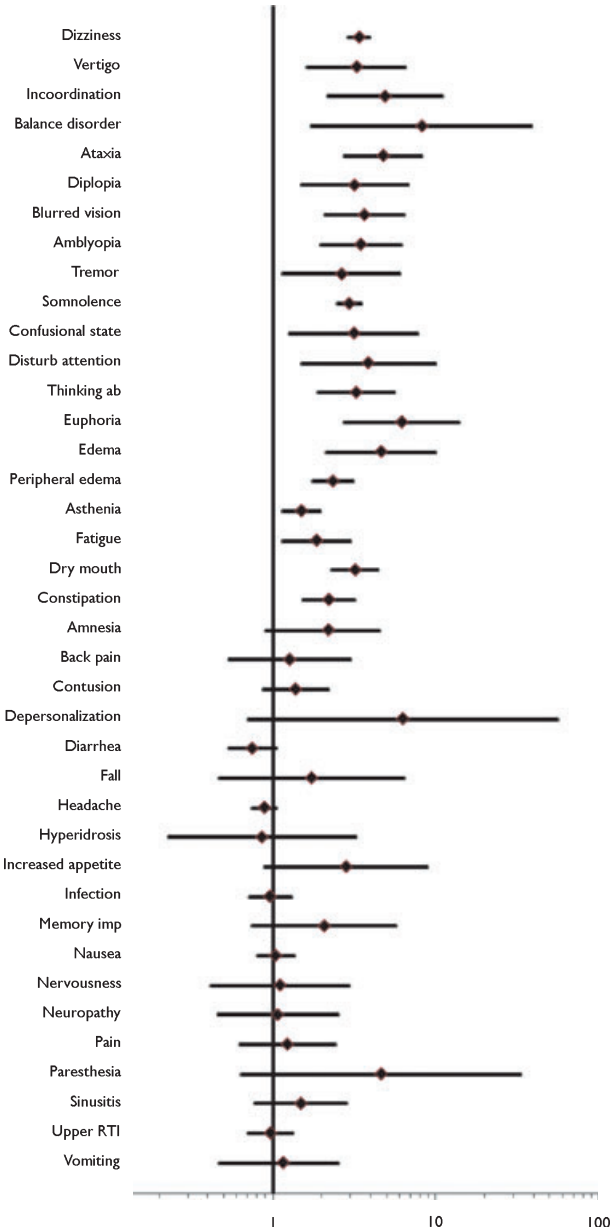

Figure 3.
Relative risks (99% CI) of adverse events (n = 39) eligible for assessment of the association with pregabalin treatment.
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increase of enrolled subjects. Because these methodologic discrepancies seriously impeded an accurate assessment of this AE, we decided to disregard in our analysis the following items: weight gain, increased weight, and weight change.

Meta-analyses results

Adverse events associated with pregabalin

Analysis of data showed no evidence of heterogeneity (I^2 between 0% and 60%). Therefore, a fixed-effect model was used in all cases.

As illustrated in Fig. 3, 20 of the 39 (51%) analyzed AEs were significantly associated with pregabalin treatment. The highest RR (95% CI) was found for balance disorder 8.22 (1.75 to 38.57), followed by euphoria 6.18 (2.76 to 13.87), incoordination 4.88 (2.18 to 10.95), ataxia 4.77 (2.77 to 8.20), and edema 4.63 (2.15 to 9.95). A detailed description of these results is available in Appendix S3.

Serious adverse events associated with pregabalin

Serious AEs were reported in 21 (55%) of the 38 studies, resulting in a total of 6,588 subjects, 4,382 of whom randomized to pregabalin and 2,206 to placebo. The RR (95% CI) for experiencing a serious AE on pregabalin compared to placebo was 1.02 (0.77 to 1.36). In the majority of cases, reported serious AEs were a heterogeneous number of events, and only in 16 studies was it clearly specified whether the observed serious AE was considered associated or not associated with the experimental drug. When specified, serious AEs considered related with pregabalin were: somnolence in three patients, ataxia, peripheral edema, ventricular extrasystoles, accidental injury or fall in two, spasticity due to drug withdrawal, increased anxiety, fractured arm secondary to a fall, chest pain, subacute myocardial infarction, hypotension, transient loss of consciousness, asthenia, and encephalopathy in one patient, respectively. One further patient had edema, hypervolemia, and reduced platelet count. In patients treated with placebo, serious AEs that were considered related to the treatment were: coronary artery disorder, ventricular extrasystoles, attack of unconsciousness, manic reaction, and prostate cancer.

Analysis of dose–effect responses for pregabalin adverse events

Of the 38 studies, 10 were excluded from this part of the analysis due to utilization of flexible-dose regimens. Three other studies included both flexible- and fixed-dose arms, and we excluded the flexible-dose groups. Two studies included 200 and 400 mg/day arms, which were merged for the purposes of this analysis with the 150 and 450 mg/day arms, respectively. Therefore, the sample eligible for this analysis amounted to 28 studies. In these analyses, heterogeneity ($I^2 > 70\%$) was found in some cases and a random effect model was adopted for euphoria at 150 mg/day, ataxia and edema at 300 mg/day, fatigue at 450 mg/day, and somnolence and edema at 600 mg/day.

RDs (95% Cis) for the 20 pregabalin AEs at different doses are shown in Table 2. There was a selective dose-dependent pattern in the onset of AEs, with five AEs first presenting at 150 mg/day (dizziness, ataxia, somnolence, edema, and dry mouth), 11 at 300 mg/day (vertigo,

Table 2. Adverse effects significantly associated with pregabalin

Adverse effect	150 mg/day 150 mg	300 mg/day 300 mg	450 mg/day 450 mg	600 mg/day 600 mg
Dizziness	0.08 (0.05 to 0.10)	0.21 (0.19 to 0.24)	0.29 (0.25 to 0.32)	0.30 (0.27 to 0.32)
Vertigo	0.02 (−0.01 to 0.05)[a]	0.05 (0.02 to 0.07)	0.03 (0.00 to 0.07)	0.06 (0.04 to 0.08)
Incoordination	0.00 (−0.01 to 0.02)	0.03 (0.01 to 0.04)	0.07 (0.05 to 0.09)	0.07 (0.05 to 0.10)
Balance disorder	nv	0.01 (−0.00 to 0.03)	0.09 (0.05 to 0.13)[a]	0.06 (0.03 to 0.09)
Ataxia	0.03 (0.00 to 0.05)	0.04 (0.00 to 0.08)[b]	0.04 (0.01 to 0.07)[a]	0.11 (0.09 to 0.13)
Diplopia	0.00 (−0.02 to 0.03)	0.02 (−0.00 to 0.04)	nv	0.07 (0.05 to 0.10)
Blurred vision	0.02 (−0.02 to 0.05)	0.04 (0.02 to 0.05)	0.06 (0.04 to 0.08)	0.07 (0.05 to 0.09)
Amblyopia	0.01 (−0.01 to 0.03)	0.03 (0.00 to 0.06)	0.05 (−0.00 to 0.10)[a]	0.07 (0.05 to 0.09)
Tremor	0.00 (−0.03 to 0.04)	0.02 (−0.01 to 0.06)	nv	0.06 (0.02 to 0.10)
Somnolence	0.07 (0.04 to 0.10)	0.14 (0.12 to 0.16)	0.16 (0.14 to 0.19)	0.17 (0.13 to 0.21)[b]
Confusional state	0.01 (−0.01 to 0.03)	0.03 (0.01 to 0.05)	0.05 (0.01 to 0.09)[a]	0.04 (0.01 to 0.07)
Disturb attention	nv	0.04 (0.01 to 0.06)	0.05 (0.02 to 0.08)	0.06 (0.03 to 0.09)
Thinking abnormal	0.02 (−0.01 to 0.04)	0.04 (0.01 to 0.06)	0.06 (0.04 to 0.09)	0.08 (0.05 to 0.10)
Euphoria	0.05 (−0.06 to 0.15)[b]	0.04 (0.02 to 0.06)	0.07 (0.05 to 0.09)	0.06 (0.03 to 0.08)
Edema	0.05 (0.01 to 0.08)	0.08 (−0.02 to 0.18)[b]	nv	0.07 (0.01 to 0.13)[b]
Peripheral edema	0.02 (−0.00 to 0.05)	0.05 (0.03 to 0.07)	0.04 (0.02 to 0.06)	0.08 (0.06 to 0.10)
Asthenia	0.01 (−0.02 to 0.03)	0.02 (0.00 to 0.04)	0.03 (0.01 to 0.06)	0.04 (0.02 to 0.06)
Fatigue	nv	0.02 (−0.00 to 0.05)	0.05 (0.03 to 0.12)[b]	0.03 (0.00 to 0.06)
Dry mouth	0.04 (0.02 to 0.06)	0.05 (0.03 to 0.06)	0.08 (0.06 to 0.10)	0.07 (0.05 to 0.08)
Constipation	0.02 (−0.01 to 0.05)	0.03 (0.01 to 0.04)	0.04 (0.02 to 0.06)	0.04 (0.03 to 0.06)

Risk difference (CI 95%) at various pregabalin dosages. Fixed effect model has been used otherwise differently specified.
[a]Only one study nv, not evaluable (no data available for that dose).
[b]Random effect model used.

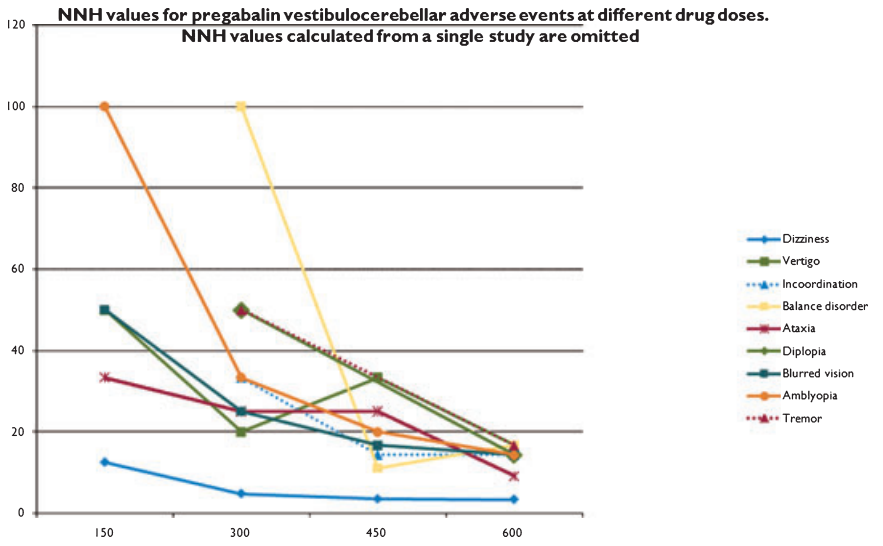

Figure 4.
NNH values for pregabalin vestibulocerebellar adverse events at different drug doses. NNH values calculated from a single study are omitted.
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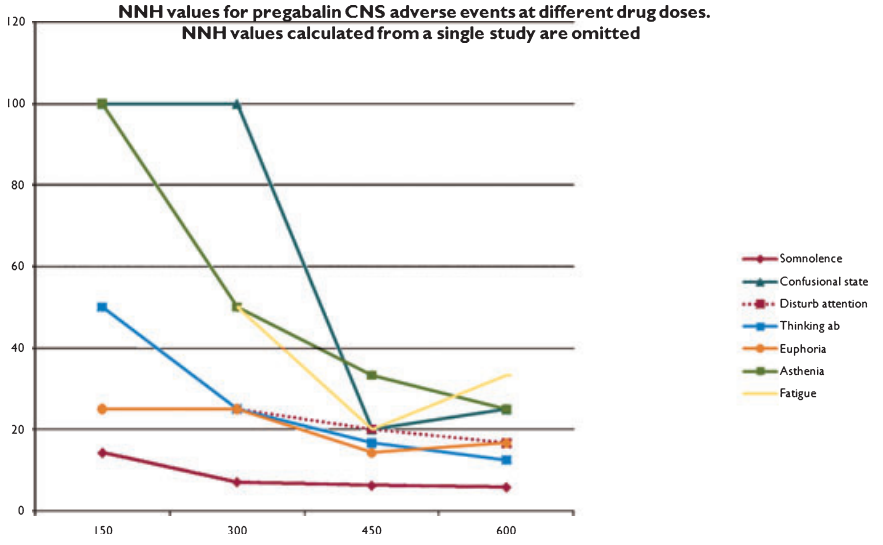

Figure 5.
NNH values for pregabalin CNS adverse events at different drug doses. NNH values calculated from a single study are omitted.
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incoordination, blurred vision, amblyopia, confusional state, disturbance in attention, thinking abnormal, euphoria, asthenia, peripheral edema, and constipation), 2 at 450 mg/day (balance disorder and fatigue), and 2 at 600 mg/day (diplopia and tremor). Further details are given in Appendix S4.

NNH values for each AE at different pregabalin doses are illustrated in Figs 4–6. Most AEs displayed a clear dose–response relationship, this being particularly evident for balance disorder, amblyopia, confusional state, disturbance in attention, asthenia, and constipation.

Discussion

We found 20 AEs significantly associated with pregabalin treatment. Most (16 of 20; 80%) were cognition/coordination AEs, which a recent study found to be the strongest determinant of impaired health-related quality of life in people taking AEDs (Perucca et al., 2009). Of these 16 AEs, 9 indicate involvement of vestibulocerebellar/brainstem structures (dizziness, vertigo, incoordination, balance disorder, ataxia, tremor, diplopia, blurred vision, and amblyopia), whereas 7 are related to higher cortical functions (euphoria, disturbance in attention, thinking abnormal, somnolence, confusional state, asthenia, and fatigue). A cause–effect relationship between cognition/coordination AEs and pregabalin treatment was further supported by inspection of the 10 highest RRs, nine of which were found to belong to this AE class (Appendix S3). Finally, all these AEs shared a clear dose–response relationship. The occurrence of this AE class may be attributed directly to the primary mode of action of pregabalin. Pregabalin inhibits the

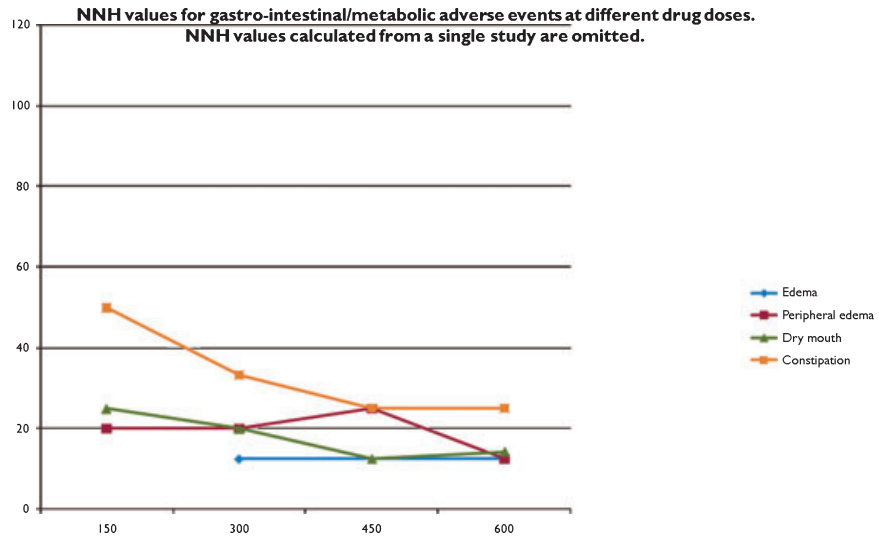

Figure 6.
NNH values for gastrointestinal/metabolic adverse events at different drug doses. NNH values calculated from a single study are omitted.
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depolarization-dependent calcium influx at P-, Q-, and N-type voltage-gated calcium channels, resulting in decreased neurotransmitters release (Ben-Menachem, 2004). The highest level of expression of these channels has been found in the cerebellum and in the hippocampus, and their dysfunction or decreased activity has been linked to ataxia (Zhuchenko et al., 1997; Liao et al., 2008) and cognitive impairment (Nakagawasai et al., 2010).

The remaining four AEs indicate gastrointestinal/metabolic dysfunction (edema, peripheral edema, dry mouth, and constipation). As opposed to the cognition/coordination class, these AEs were slightly less common and did not display a clear dose–response relationship (except for constipation). The pathogenesis of these AEs is unclear and should be elucidated in future studies.

There was a dose-dependent pattern in the onset of pregabalin AEs, with certain AEs appearing at lower doses than others. An example is provided by amblyopia, blurred vision, and diplopia. As discussed previously, these AEs are likely to result from brainstem involvement and displayed a clear dose–response relationship. However, amblyopia and blurred vision appeared at 300 mg/day, and were accompanied by diplopia only at 600 mg/day. It is possible that the onset of the two former AEs corresponds to a milder brainstem dysfunction than that observed with higher doses, particularly with the occurrence of diplopia. Similar considerations can be extended to other AEs, and suggest that different AEs can be clinically significant biomarkers of the severity of dysfunction of distinct anatomic structures.

In this study, serious AEs were not more frequent with pregabalin compared to placebo. Although randomized, double-blind, placebo-controlled trials are not the optimal design to evaluate these AEs, our findings nevertheless corroborate the results of other investigations of the safety profile of pregabalin (Ryvlin et al., 2010).

Our study has several limitations. Although RCTs allow direct comparisons of AE rates between an investigated compound and placebo, as well as an accurate analysis of dose–response relationships for any identified AE, their short duration hampers the assessment of long-term toxicity. Moreover, different terms may be used in different RCTs to describe a given AE, which may result in its exclusion from all analyses, as in our case with weight gain. Collective efforts should be made to develop a single standardized terminology for RCTs of AEDs.

We have already noted that pregabalin seems to be devoid of pharmacokinetic interactions. However pharmacodynamic interactions may still influence drug tolerability and appearance of some AEs, and their relation with the experimental drug dose may also be modified by total drug load. In the examined RCTs, most often pregabalin was administered on monotherapy (patients with anxiety disorders, neuropathic pain, or fibromyalgia), whereas patients with epilepsy received this drug as add-on treatment. Finally, in the present meta-analysis, we did not control for the underlying disease, which might have altered drug's toxicity profile; however, these effects will be evaluated in a subsequent study.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. MEDLINE (PubMed), EMBASE (OVID), and Cochrane CENTRAL search strategies.

Appendix S2. Characteristics of studies identified trough a search in MEDLINE, EMBASE, Cochrane CENTRAL issue 2 2010, ClinicalStudyResults.org, ClinicalTrials.gov, reference lists of retrieved papers, and the Internet.

Appendix S3. Fixed-effects meta-analyses to assess the association of any adverse event with pregabalin treatment.

Appendix S4. Adverse effects significantly associated with pregabalin at different doses.

Data S1. Brief summary.

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