The adverse event profile of pregabalin: a systematic review and meta-analysis of randomized controlled trials
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CRD summary
The review concluded that individuals starting pregabalin treatment were at increased risk of several adverse events, particularly those affecting cognition/co-ordination, which followed a dose-response relationship. The review was generally well conducted, but the potential issues with trial quality and the small number of trials for some adverse events limit the reliability of the results.

Authors’ objectives
To determine the adverse event profile of pregabalin.

Searching
MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched to February 2010. Search terms were reported. The National Institute of Health clinical trial register and the Pharmaceutical Research and Manufacturers of America (PhRMA) clinical study results database were searched. Reference lists of retrieved articles were scanned. Summary clinical reports not available as full publications were sought via Internet searches.

Study selection
Randomised controlled trials (RCTs) that compared oral pregabalin (any dose) with placebo in adults (18 years or older) affected by different neurologic or psychiatric conditions were eligible for inclusion. Trials had to be double blind, include at least 20 participants per treatment arm, and have a treatment duration of at least four weeks. Eligible trials had to be reported as full journal publications or summary clinical trial reports; abstracts were excluded.

The included trials studied pregabalin at a dose of 150 to 600mg (in two or three daily doses), or on flexible dosing. The titration phase lasted from zero to eight weeks, with some trials using flexible titration. The type of disease treated included epilepsy, panic disorder, anxiety disorder, neuropathy, post-stroke pain, postherpetic neuralgia and fibromyalgia. Trial duration ranged from four to 14 weeks.

Two reviewers independently performed study selection and consensus was achieved by discussion.

Assessment of study quality
The authors did not state that they performed a formal quality assessment, but they did discuss double blinding, allocation concealment, and randomisation.

Data extraction
Data were extracted on adverse events, and used to calculate relative risks (RRs) and risk differences (RDs), together with 95% confidence intervals (CIs).

The authors did not state how many reviewers performed data extraction.

Methods of synthesis
A fixed-effect meta-analysis was used to calculate pooled relative risks and risk differences, together with 95% confidence intervals. Heterogeneity was assessed using $\chi^2$ and $I^2$. If significant statistical heterogeneity was detected, a random-effects model was used. Trials were analysed by dose to determine the dose-response relationship. The number needed to harm was estimated.

Results of the review
Thirty-eight RCTs (n=11,918 participants) were included in the review. All trials were double-blind, but few trials described the method of randomisation, blinding or allocation concealment.
Compared with placebo, pregabalin was associated with a statistically significantly greater risk of twenty adverse events (full list of the adverse events results were available in a separate online appendix, see Additional Data URL). The highest risk was for balance disorder (RR 8.22, 95% CI 1.75 to 38.97), followed by euphoria (RR 6.18, 95% CI 2.76 to 13.87), incoordination (RR 4.88, 95% CI 2.18 to 10.95), ataxia (RR 4.77, 95% CI 2.77 to 8.20), and oedema (RR 4.63, 95% CI 2.15 to 9.95). There was no statistically significantly increased risk of serious adverse events with pregabalin. The number needed to harm was reported as a graph, generally showing a dose-dependent pattern in the onset of adverse events, which was especially evident for balance disorder, amblyopia, confusional state, disturbance in attention, asthenia, and constipation.

There was no evidence of statistical heterogeneity in the main analyses, but there was some evidence of statistical heterogeneity in the dose-dependent analyses.

**Authors’ conclusions**
Individuals starting pregabalin were at increased risk for several adverse events, particularly those affecting cognition/co-ordination, which followed a dose-response relationship.

**CRD commentary**
Inclusion criteria for the review were clearly defined. Several relevant data sources were searched. Publication bias was not assessed, although several unpublished trials were included. Attempts were made to reduce reviewer error and bias during study selection, but the authors did not state if the same methods were used for data extraction.

The authors did not state that they undertook a formal quality assessment, but few trials described the method of randomisation, blinding or allocation concealment. Trials were combined using appropriate statistical methods. Statistical heterogeneity was assessed. Some of the adverse events were only reported by a few trials (three or less). The authors acknowledged that the definitions of adverse events may have differed.

The review was generally well conducted, but the potential issues with trial quality and the small number of trials for some adverse events limit the reliability of the pooled results.

**Implications of the review for practice and research**
**Practice:** The authors stated that these results may aid clinicians in providing better patient management.

**Research:** The authors stated that a single standardised terminology for RCTs for adverse events should be developed.

**Funding**
None.

**Bibliographic details**

**PubMedID**
21320112

**DOI**
10.1111/j.1528-1167.2010.02966.x

**Original Paper URL**

**Additional Data URL**

**Indexing Status**
Subject indexing assigned by NLM
MeSH
Analgesics /adverse effects; Anticonvulsants /adverse effects /therapeutic use; Epilepsy /drug therapy; Humans;
Neuralgia /drug therapy; Outcome Assessment (Health Care) /methods /trends; Pregabalin; Randomized Controlled
Trials as Topic /trends; gamma-Aminobutyric Acid /adverse effects /analogs & derivatives /therapeutic use

AccessionNumber
12011002578

Date bibliographic record published
21/09/2011

Date abstract record published
20/02/2012

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract
contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on
the reliability of the review and the conclusions drawn.