Discontinuation of antihypertensive drugs due to adverse events: a systematic review and meta-analysis
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Authors' objectives
To quantify the frequency of antihypertensive agents being discontinued due to adverse events (AEs), by a meta-analysis of the studies.

Searching
MEDLINE, Current Contents and the Cochrane Library were searched from 1990 to 1 November 1999. The search terms were reported. The search was restricted to publications in the English language. The reference lists of included studies were also searched.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials with at least 10 patients, with parallel-group designs and lasting at least one week, were eligible for inclusion. Studies that reported subgroup results from larger studies, haemodynamic physiology studies, and pharmacokinetic or pharmacodynamic studies were excluded. The study duration ranged from 1.4 weeks to 2 years.

Specific interventions included in the review
Studies of antihypertensive agents were eligible for inclusion. Combination drug trials were excluded. The classes of antihypertensive agent included in the review were diuretics, beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, calcium-channel blockers, angiotensin-receptor blockers and alpha-adrenergic blockers.

Participants included in the review
The participants were patients with essential hypertension who were otherwise well. Studies of hypertensive patients who might also have diabetes mellitus or left ventricular hypertrophy, which are common co-morbid conditions, were also included. Of the patients included in the review, 57.7% were male, the mean age was 54.3 years, 58.6% had a history of previous antihypertensive drug use, 15.7% had diabetes mellitus and 27.4% had left ventricular hypertrophy.

Outcomes assessed in the review
Trials that reported the number of patients in the treatment and placebo groups who discontinued treatment due to AEs were eligible for inclusion, as this was the primary outcome of interest. The authors also sought information on the timing of discontinuations. A secondary outcome was the frequency of patients with any adverse drug event. The authors used the following definition of adverse drug event: any noxious, unintended effect occurring at doses administered to humans for therapy that is not attributable to therapeutic failure or drug abuse. This included non-compliance and errors of administration.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The primary studies were assessed for quality using the Jadad scale, which assesses randomisation method, blinding of treatment and accounting for all patients entered and withdrawn. The authors did not state how the papers were assessed for quality, or how many reviewers performed the quality assessment.

Data extraction
The data were extracted by one investigator and agreed by a second investigator before being entered into the database.
Data were collected on the study, patient and treatment characteristics, and on the numbers of patients with AEs and discontinuations due to AEs (DAEs), overall and broken down by major organ system and the timing of DAEs. When several AEs led to discontinuation, the most severe event was recorded.

Methods of synthesis
How were the studies combined?
The treatment group frequencies of DAEs and AEs were pooled across studies and grouped by the category of antihypertensive agent. The outcomes from many studies were combined in meta-analyses using both fixed-effect and random-effects models. The results of the random-effects models were reported. The outcomes were expressed as risk differences with 95% confidence intervals (CIs).

How were differences between studies investigated?
A regression model was used to study the potential influence of study variables (e.g. location, duration, publication year and quality score) and group variables (e.g. gender distribution, mean age, concurrent diabetes mellitus and baseline left ventricular hypertrophy) on the frequency of DAEs.

Results of the review
The review included 190 studies, comprising 409 treatment groups and 28,922 patients.

The frequency of DAEs was highest with calcium-channel blockers (6.7%) then alpha-adrenergic blockers (6.0%), ACE inhibitors (4.7%), beta-blockers (4.5%), placebo (4.3%) and, finally, angiotensin-receptor blockers and diuretics (both 3.1%). The DAE risk differences relative to placebo were calculated for diuretics (0.027, 95% CI: 0.001, 0.053), beta-blockers (0.018, 95% CI: -0.008, 0.044), ACE inhibitors (0.014, 95% CI: -0.002, 0.029), calcium-channel blockers (-0.005, 95% CI: -0.022, 0.012) and angiotensin-receptor blockers (0.02, 95% CI: 0.001, 0.038). The advantage of both diuretics and angiotensin-receptor blockers relative to within-study placebo was statistically significant, (P=0.038 in both cases). The DAE event rate was not significantly different from placebo for any of the other categories of antihypertensive agent.

The range of total AE frequency among different classes of antihypertensive agents was narrow, extending from 39.3% (diuretics) to 32.3% (beta-blockers). The AE frequency with placebo was 37.3%. The frequency ranking of antihypertensive agents varied by organ system. Rankings of agents for AEs by organ system did not parallel frequency rankings of DAEs for the same organ system.

A meta-analysis of risk difference of DAE frequency in placebo-controlled monotherapy trials supported the frequency rankings of the DAE frequency, as computed by class of antihypertensive agent in the treatment groups. Tests for heterogeneity were not significant in any instance for these meta-analyses. The risk of DAEs was greater in placebo groups than for same-study beta-blocker, ACE inhibitor, diuretic or angiotensin-receptor blocker groups, of which the latter two reached statistical significance. However, for studies of calcium-channel blockers, the risk of DAE was higher for the calcium-channel blocker group than for the placebo group, but it was not statistically significant.

A meta-analysis of the risk difference of DAE frequency in active comparison trials showed statistical significance for four comparisons: diuretics versus calcium-channel blockers, beta-blockers versus calcium-channel blockers, angiotensin-receptor blockers versus ACE inhibitors, and ACE inhibitors versus alpha-adrenergic blockers. In each case, the latter drug group had a significantly higher frequency of DAEs than the former.

When stratifying groups by study duration of 1 month or less versus more than 1 month, the results differed by drug class. In ACE inhibitor, calcium-channel blocker and placebo groups the frequency of DAEs more than doubled from short- to long-term studies, suggesting that not all DAEs with these drugs occur in the first month. Little difference was seen in DAE frequency between short- and long-term studies for beta-blocker, angiotensin-receptor blocker and alpha-adrenergic blocker groups. The overall DAE frequency was 4.0% in fixed-dosage studies and 5.4% in dose-titration studies.

The analysis of variance procedure, undertaken to assess the impact of covariates on DAE frequency, showed that covariates of interest relating to the study were geographic location, year of study and quality score. This was explained...
by the differences in reporting practices. For patient characteristics, only concurrent left ventricular hypertrophy had a significant effect on the frequency of DAEs in the model containing all covariates. However, when studied in a univariate model, significance was not present.

The average Jadad quality score was 3.2 (range: 1 to 5), with 80% of the studies scoring 3 or higher.

**Authors’ conclusions**
The authors stated that data are greatly needed to support considerations of drug toxicity and impact on quality of life when selecting drug therapies, especially for chronic asymptomatic conditions such as hypertension. The authors believed that, despite the limitations of current literature, this review provides the best available evidence on the frequency of DAEs in patients with essential hypertension who are otherwise well and are receiving single-agent antihypertensive therapy.

**CRD commentary**
The review was based on a well-defined question, with clearly stated inclusion criteria relating to the study design, participants, intervention and outcomes of interest. However, the authors acknowledged that a major limitation of their review was the heterogeneity of rules used by investigators for reporting AES. In addition, although DAEs were reported more clearly than AES, the lack of reporting the actual timing of DAEs relative to drug initiation was a limitation. The authors searched three electronic databases and manually searched reference lists, but no attempts were made to identify unpublished studies. Also, only English language studies were included, which may have resulted in the exclusion of other relevant studies. Study selection bias was not assessed.

The primary studies were assessed for quality using a published checklist. However, the authors did not report the processes by which quality was assessed or the studies were selected for the review, which could allow the introduction of errors and reviewer bias. The data extraction was performed by one investigator and agreed by a second investigator. Due to the large number of trials included in the review, it would not have been appropriate to provide comprehensive data on the individual trials. The data synthesis appears to have been appropriate.

Overall, the review appears to have been well conducted and the authors’ conclusions are supported. However, only studies including participants without other co-morbid conditions (other than diabetes mellitus and left ventricular hypertrophy) were included in the review, therefore, the results are not generalisable to hypertensive patients with other co-morbidities.

**Implications of the review for practice and research**
Practice: The authors stated that the varying frequency of DAEs across drug classes should be considered when choosing drugs for patients with essential hypertension.

Research: The authors did not state any implications for further research.

**Bibliographic details**

**PubMedID**
11718500

**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Antihypertensive Agents /administration & dosage /adverse effects /therapeutic use; Data Interpretation, Statistical;
Female; Humans; Hypertension /drug therapy; Male; Middle Aged; Randomized Controlled Trials as Topic; Regression Analysis; Time Factors; Treatment Outcome

AccessionNumber
12001002145

Date bibliographic record published
31/03/2004

Date abstract record published
31/03/2004

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.