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Review

Antihypertensive Treatment in People With Dementia

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A B S T R A C T

Background: The range and magnitude of potential benefits and harms of antihypertensive treatment in people with dementia has not been previously established.
Methods: A scoping review to identify potential domains of benefits and harms of antihypertensive therapy in people with dementia was undertaken. Systematic reviews of these domains were undertaken to examine the magnitude of the benefits or harms.
Results: Potential outcome domains identified in the 155 papers in the scoping review were cardiovascular events, falls, fractures and syncope, depression, orthostatic hypotension, behavioral disturbances, polypharmacy risks, kidney problems, sleep problems, interactions with cholinesterase inhibitors, and pain. The systematic reviews across these domains identified relatively few studies done in people with dementia, and no convincing evidence of safety, benefit, or harm across any of them.
Discussion: Given the lack of firm evidence of benefits or harm from antihypertensive therapy in people with dementia and the weak evidence for benefits in people over 80 years of age, the current presumption that the favorable evidence drawn from the treatment of nondemented people should be extrapolated to those with dementia is contentious. There is sufficient evidence to warrant particular caution and further research into treatment in this group of patients.

The World Health Organization 2012 report "Dementia: A Public Health Priority" estimated that there are 35.6 million people with dementia living at the present time worldwide.[1] About one-half of people over 50 years of age have hypertension.[2] Although the protective effects of antihypertensive treatment against cardiovascular events have been established in numerous clinical trials for different age groups,[3,4] people with dementia have been consistently excluded from these studies. Dementia is usually a condition of very old people, yet the evidence from randomized controlled trials of hypertensive therapy in people over 80 years of age shows no significant reduction in total mortality (relative risk 0.98, 95% confidence intervals 0.87–1.10).[5] Furthermore, evidence from randomized controlled trials of antihypertensive therapy in nondemented people aged over 60 shows a markedly increased rate of withdrawal from treatment because of the adverse effects of treatment (relative risk 1.71, 95% confidence intervals 1.45–2.00).[5] This vulnerability to the adverse effects of treatment might be expected to be even higher in people with dementia, further threatening the benefit to risk ratio of antihypertensive treatment. Given these concerns, it may be that the management of hypertension in people with dementia should be different from in those with normal cognition.[6] However, current guidelines for the treatment of hypertension do not provide specific advice for people with dementia.

There have been no reviews to comprehensively examine studies investigating the range of outcomes (including harmful effects) of antihypertensive treatment in people with dementia. Such work is important to clarify whether there is a case for altered guidance for the management of hypertension in people with dementia.

Methods

A 2-stage process was undertaken. In the first stage, a scoping review[7] was undertaken to identify the range of outcomes of antihypertensive treatment in people with dementia. In the second stage, systematic reviews were undertaken for each of the main areas of harmful or adverse outcomes identified in the first stage.

The authors declare no conflicts of interest.

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Stage 1: Scoping Review

Protocol

The scoping review was based on a predefined protocol to search and identify relevant research articles.

Eligibility

Inclusion. All articles reporting original research regarding the treatment of hypertension in people with dementia were included. No publication date limit was applied.

Exclusion. All studies investigating hypertension as a risk factor for dementia; effects on carers; specific nondementia diseases (eg, cancer), and rarer forms of dementia (Korsakoff's syndrome, dementia because of HIV, normal pressure hydrocephalus, Cerebral Autosomal-Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy); and animal studies and non-English language articles were excluded. As effects of antihypertensive drugs on the progression of dementia have been reviewed elsewhere,[8,9] they were excluded from the literature analysis.

Information sources

PubMed, Embase, Web of Science, and Cochrane library databases were searched.

Search

The search for articles took place from July 2012 and was updated in February 2013. Searches were limited to English language human research articles. Search terms included combinations of 'hypertension,' 'antihypertensive drug,' 'antihypertensive treatment,' or 'blood pressure' in combination with 'dementia' or 'Alzheimer's disease.'

Selection

Duplicates were removed, titles and abstracts were examined by 1 person (V.vdW.), and inclusion and exclusion criteria applied. Full text versions of the remaining papers were obtained and assessed again based on inclusion and exclusion criteria. The remaining relevant articles were used to identify the range of outcomes examined in scientific articles.

Data collection

Main outcome variables were recorded and categorized into topics.

Analysis

The number of papers examining each outcome was tabulated.

Stage 2: Systematic Reviews

Protocol

The systematic reviews were based on a predefined protocol to search and identify relevant research papers.

Eligibility

Inclusion. All articles reporting original research regarding antihypertensive treatment in people with dementia and the topic identified in stage 1 were included. No publication date limit was applied.

Exclusion. As in stage 1. Studies, which did not include antihypertensive treatment in any form in the analysis (as composite variable or individual medication classes), were also excluded.

Information sources

PubMed, Embase, Web of Science, and Cochrane library databases were searched.

Search

Articles were searched until June 2013 publication dates. Searches were limited to English language and, where possible, human research articles. Search terms for stage 2 included 'antihypertensive' or antihypertensive drug classes ('diuretics,' 'beta-blockers,' 'calcium channel blockers,' 'angiotensin receptor blockers,' and 'ACE inhibitors') in combination with 'dementia' or 'Alzheimer's disease' and the topics identified in stage 1 (Figure 1).

Selection

Duplicates were removed, titles and abstracts were examined by 1 person (V.vdW.), and inclusion and exclusion criteria applied. Full text versions of the remaining papers were obtained and assessed based on inclusion and exclusion criteria. The remaining relevant articles were included and the number of papers examining each topic was recorded.

Data collection

Methods and results were extracted to record purpose of the study, design, sample size, main measurements, and results of each study.

Analysis

Method sections of papers were examined to determine level of evidence. Results were compared and analyzed regarding the effect of antihypertensive treatment on the topic in question.

Results

Stage 1: Scoping Review

Figure 1 shows that 155 papers entered this review. Ten main outcome themes of effects of antihypertensive treatment in people with dementia emerged from the 155 papers in the scoping review (Figure 1); cardiovascular events, falls, fractures and syncope, depression, hypotension, behavioral disturbances, polypharmacy, kidney problems, sleep problems, cholinesterase inhibitors and pain. The articles identified in the last stage of the scoping review were also included into the stage 2 analysis.

Stage 2: Systematic Reviews

Table 1 shows a summary of the findings of the searches undertaken in the systematic reviews of the topics identified in the scoping review.

Cardio- and Cerebrovascular Events

In total, 4 studies examined the effects of antihypertensive medication on cardio- and cerebrovascular events in people with dementia (Table 2), with antihypertensives either as main independent variable (3 studies) or as control variable (1 study).

No randomized controlled placebo trials have been conducted in this area. In people with dementia, 2 randomized controlled trials investigated the effects of calcium channel blockers (CCBs) in an intention-to-treat, an efficacy and a safety analysis.[10–12] For both trials, main outcome was cognition but the safety analysis included cardio- and cerebrovascular events, which were reported as adverse events. The studies compared a control group against a treatment group using CCBs. Both groups were allowed to continue with unspecified antihypertensive treatment as prescribed before the beginning of the study except alpha methyldopa. The results showed that the control group had significantly more adverse (cerebrovascular) events than the treatment group.[11,12] For cardiovascular events, the trend was similar but reached significance in only one of the