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New horizons: The management of hypertension in people with dementia

ABSTRACT

The optimal management of hypertension in people with dementia is uncertain. This review explores if people with dementia experience greater adverse effects from antihypertensive medications, if cognitive function is protected or worsened by controlling blood pressure and if there are subgroups of people with dementia for whom antihypertensive therapy is more likely to be harmful.

Robust evidence is scant, trials of antihypertensive medications have generally excluded those with dementia. Observational data show changes in risk association over the life course, with high blood pressure a risk factor for cognitive decline in mid-life, whilst low blood pressure is predictive in later life. It is therefore possible that excessive blood pressure lowering in older people with dementia might harm cognition. From the existing literature there is no direct evidence of benefit or harm from treating hypertension in people with dementia.

So what practical steps can the clinician take? Assess capacity, establish patient preferences when making treatment decisions; use ambulatory monitoring to thoroughly assess blood pressure; individualise and consider deprescribing where side effects (e.g. hypotension) outweigh the benefits.

Future research might include pragmatic randomised trials of targeted deprescribing which include patient-centred outcome measures to help support decision-making and studies to address mechanistic uncertainties.

Keywords

Hypertension, dementia, deprescribing, decision making, individualise

Key points

- Randomised trials in hypertension have generally excluded people with dementia
- The relationship between cognitive decline and blood pressure is complex, with a change in risk association over the life course
- Although direct evidence is lacking for the benefits of treatment of hypertension in older adults with dementia, there is no definitive evidence that treatment is harmful
- We advise clinicians to individualise treatment whenever possible, guided by patient priorities
- Future research should include pragmatic randomised trials of targeted deprescribing studies with patient-centred outcome measures

INTRODUCTION

Why treat hypertension?

The justification to treat hypertension is based on robust trial evidence that doing so reduces the incidence of cardiovascular events, such as heart attack and stroke, without producing harms that offset these benefits[1]. Clinical trials in older people, with blood pressures (BPs) usually >160/100mmHg, have convincingly shown that the risks of myocardial infarction and stroke are reduced in those whose BP is lowered compared with those in whom it is not. A meta-analysis of 15 trials of people aged ≥60 (n=24,055) showed that treatment was associated with a relative risk (RR) for cardiovascular morbidity and mortality of 0.72 (95% CI 0.68, 0.77) and RR for total mortality of 0.90 (95% CI 0.84, 0.97)[2].

For patients to make an informed decision about whether to accept treatment, the size of the benefits and harms for them as individuals must be appropriately communicated. Not everyone who takes antihypertensive medication avoids cardiovascular events – many would not have an event without medication and some would have an event despite taking it. 125 patients with a systolic blood pressure (SBP) of 170mmHg have to be treated for five years to prevent one death[3]. Fewer (67) need to be treated to prevent a stroke[3] and fewer still (48) to prevent heart failure[4]. Antihypertensive medication can cause harm, largely through minor, non-specific drug side effects such as rashes or gastrointestinal symptoms, or those arising from the drug's mechanism of action, such as hyponatraemia from diuretics; as many as 1 in 10 patients discontinue medication for such reasons[3].

Why might the decision to treat hypertension be different for people with dementia?

A concern in the treatment of all conditions in people with dementia is that they may lose the mental capacity to make decisions about whether or not to accept treatment. So the prescriber must assess mental capacity when offering or continuing antihypertensive medication and establish the person's best interests when capacity is lacking.

People with dementia may make different choices from those without dementia, for example prioritising their current, manifest problems over the prevention of future events. They might decline treatments that they may have accepted if they did not have dementia. Interventions to promote independence were identified as the first of ten research priorities in the James Lind Alliance priority setting partnership for dementia[5]. Antihypertensive therapy offers the chance to achieve these outcomes by reducing disability from cardiovascular or cerebrovascular events which, in turn, reduce the likelihood of dependency and requirement for long-term care. However, trading-off the risk of distant events against current priorities is conceptually complex and may not be possible for some patients with cognitive impairment. The priorities for individuals are likely to vary depending on their symptoms and change as dementia progresses.

No guidelines for the treatment of hypertension give advice for people with dementia. As with other long-term conditions, it might be assumed that evidence derived from cognitively intact populations should directly apply to those with dementia. We will examine the available evidence by considering three questions:

1. Do people with dementia experience greater adverse effects from antihypertensive medications?

2. Is cognitive function protected or worsened by controlling blood pressure?
3. Are there subgroups of people with dementia for whom antihypertensive therapy is more likely to be harmful?

1. DO PEOPLE WITH DEMENTIA EXPERIENCE GREATER ADVERSE EFFECTS FROM ANTIHYPERTENSIVE MEDICATIONS?

Antihypertensive medications are known to have side effects which commonly lead to patients stopping treatment[3]. Individuals with cognitive impairment may also experience difficulties with adherence and require simplified schedules or support with medication to reduce potential harms[6].

Over-treatment, where an individual's BP is reduced too far, can also occur. This might be because their tendency for hypertension has reduced over time since starting treatment, or because other comorbidities or medications that lower their BP have become established. This is particularly relevant in people with dementia where SBP falls[7]. A drop of 8-22mmHg in SBP and of 7-13mmHg in diastolic blood pressure (DBP) has been observed in those diagnosed with dementia compared with 2mmHg SBP and 4mmHg DBP in those without[8]. Reductions in SBP have been observed in several large cohort studies, between three[7, 8] and six[9] years before clinically-apparent dementia developed. BP has also been observed to continue to fall after diagnosis[7, 8, 10]. The magnitude of these BP changes is such that they could move an individual below the treatment threshold.

Orthostatic hypotension (OH), a common cause of falls and subsequent injury, is common in older adults[11] and may be caused or exacerbated by antihypertensive medications[12]. Withdrawal of antihypertensive medication in adults with cognitive impairment has been shown to increase recovery from OH, without associated adverse events[13]. OH is associated with cognitive impairment: it is found in 4% of people with normal cognition but 22% of those with vascular dementia[14].

Overall anticholinergic burden (ACB) could put individuals with dementia at greater risk of adverse effects from antihypertensive medications. Adverse effects associated with ACB are cognitive, such as a predisposition to delirium or the development of dementia, but also include effects such as dry mouth, constipation or urinary retention. Mild effects are seen in many commonly used antihypertensive drugs[15]. Effects are likely to be additive in the context of polypharmacy and may be disproportionate in a frail or cognitively impaired person[16, 17]. To date, there is no evidence that this theoretical risk is observed, or whether it is great enough to outweigh the benefits of antihypertensive therapy.

2. IS COGNITIVE FUNCTION PROTECTED OR WORSENED BY CONTROLLING BLOOD PRESSURE?

2.1 Pathophysiological considerations

Hypertension is a risk marker for Alzheimer's disease, associated both with the pathological features of the condition (including plaques, tangles and hippocampal atrophy) and other vascular risk factors (including obesity and diabetes)[18]. The neuropathology of dementia is complex, with mixed pathology commonly found in older adults[19]. Small vessel cerebrovascular disease combined with Alzheimer pathology appears to be a particularly potent cause of dementia[20, 21]. The treatment of hypertension should reduce progression of the pathological processes and the risk of dementia.

Hypertension causes microvascular disease, which not only predisposes to stroke but also affects "neurovascular coupling", the regulation of cerebral blood flow to match the blood supply to the demands of different brain regions[22]. The hypotension/hypoperfusion damage hypothesis posits that episodes of poor cerebral perfusion due to hypotension worsens deep white matter ischaemia[23] and increases progression of dementia [24-26]. This might include hypotension during intercurrent illness, or interventions such as cardiac bypass[27], or possibly as a result of antihypertensive therapy. Current clinical practice varies in the continuation or withholding of established treatment for chronic conditions, such as hypertension, during acute illness and further evidence is required to guide practice.

As regards OH, direct research is scarce but the Irish Longitudinal Study of Ageing observed OH to be a significant predictor of the conversion of mild cognitive impairment to dementia (HR 2.77, 95% CI 1.02 to 7.50)[28]. An alternative explanation is that autonomic changes including OH are simply markers of impending dementia rather than its cause. Further confounding the issue, OH is known to be strongly associated with hypertension (OR 4.38, 95% CI 2.14 – 10.08)[29]. Nevertheless, it is possible that the treatment of hypertension, if it further reduced the capability to control cerebral perfusion, could increase the chance of dementia or increase its progression.

2.2 Epidemiological considerations

The epidemiology of BP and cognitive decline is also complicated and changes across the life-course, with evidence that both high and low BPs are associated with the development of cognitive impairment[30]. In mid-life, hypertension is a risk factor for dementia[8], whilst in older age hypotension is associated with greater risk[30]. It is possible that the latter observation represents disease effects, as BP is observed to fall prior to dementia diagnosis in those who were previously hypertensive[31]. The Milan Geriatrics 75+ Cohort study[32] found that higher BPs among older outpatients were associated with higher levels of cognitive function (10mmHg increase in SBP associated with 0.26 point (95% CI 0.13 to 0.40) rise in MMSE score; median BP of cohort 145/80mmHg). The PARTAGE study, conducted on French and Italian nursing home residents (mean MMSE 23), found higher mortality in those with low SBP (defined as <130mmHg) receiving multiple BP-lowering medications (HR 1.78 95% CI 1.34 to 2.37), after adjustment for cardiovascular comorbidities[33]. For individuals with established cognitive impairment, recent cross-sectional data identified an association between low daytime SBP (< 128mmHg) and greater decline in MMSE score (mean -2.8 [SD 3.8]), in those treated with antihypertensive medications[34].

Traditional epidemiological studies as described above assume that average BP is the determinant of risk and that episodic rises are less significant as BP varies throughout the day and night as a natural phenomenon[35]. There is, however, growing evidence of the risks associated with blood pressure variability (BPV), defined as "the overall variability during a period of time, or the average absolute difference between adjacent readings"[36]. Observational data and secondary re-analyses of clinical trials show that those who experience greater degrees of BPV, over short (within 24 hours) or long (day to day, month to month) periods, are at greater risk of cardiovascular morbidity and mortality[35]. Higher levels of BPV have been associated both with poor cognitive performance and structural brain abnormalities on MRI[37]. There is currently no consensus on how to define BPV or how to adapt management strategies for individual patients[38]. The effects of treating hypertension may include alterations in BPV that could in theory alter the risk of developing dementia or affect its progression.

2.3 Trial evidence

A Cochrane review considering cognitive function found no convincing evidence that BP lowering in patients with hypertension protects against cognitive decline – in individuals without cerebrovascular disease[39]. As with all Cochrane reviews, it relied on the available randomised controlled trial evidence which was limited to four studies that were affected by significant losses to follow-up and contamination[39]. Randomised controlled trials are not well suited to investigate the development of dementia because of the long interval that may elapse between starting antihypertensive therapy and subsequent development of dementia. For individuals with established dementia, the evidence on the treatment of hypertension is limited and the heterogeneity of the studies included precludes meta-analysis to quantify effects[40].

3. ARE THERE SUB-GROUPS OF PEOPLE WITH DEMENTIA FOR WHOM ANTIHYPERTENSIVE MEDICATION IS MORE LIKELY TO BE HARMFUL?

3.1 Extreme old age

Epidemiological studies have demonstrated that the relationship between BP and adverse outcomes is non-linear. In middle and early old age, a J-shaped relationship between total and cardiovascular mortality and DBP has been established, whether or not individuals are receiving anti-hypertensive agents[41]. In those ≥85 years, the relationship between BP and mortality changes[42] such that people with lower SBP (<150mmHg) have a higher mortality than those with higher BP (>150mmHg) (HR 2.5 95% CI 1.7 to 3.5)[43]. It is not clear whether the lower mortality risk in the very old is a reflection of underlying pathology caused by previous high BP.

It may be that the survival benefits of antihypertensive therapy do not extend into extreme old age. A sub-analysis of the meta-analysis of 15 trials of people aged >60 (referred to earlier) showed that treatment was not associated with reduced mortality in those aged >85[2].

The Systolic Blood Pressure Intervention Trial (SPRINT) included a pre-planned sub-group analysis of the population ≥75[44]. SPRINT found lower rates of events (including acute coronary syndrome, myocardial infarction, decompensated heart failure and stroke) in those who had intensive BP lowering targeted to <120mmHg compared with those targeted to <140mmHg (HR 0.66, 95% CI 0.51 to 0.85)[44]. There was no accompanying increase in serious adverse events (HR 0.99, 95% CI 0.89 to 1.11)[44]. The study excluded those with diabetes, heart failure, standing BP <110mmHg, stroke and dementia and this limits its generalisability. It does, however, provide evidence for the safety of reducing BP in a carefully selected cohort[44] and indicates that more intensive treatment reduces events likely to cause symptomatic distress and/or lead to hospitalisation.

3.2 Frailty

Frailty commonly accompanies dementia. For people with frailty, the risk of adverse drug reactions may be particularly high, and mortality and other major events may be less governed by a single risk factor (such as hypertension) and so less likely to benefit from single risk factor interventions (such as BP lowering). The presence of frailty may affect the prognostic implications of hypertension[45]. Odden and colleagues found that walking speed (a simple measure of frailty) modified the association of hypertension with mortality such that hypertension conferred a survival advantage in those unable to complete the walk test, while in faster walkers the inverse was the case[46].

Most hypertension trials were conducted before the frailty syndrome was reliably characterised, so it was not routinely measured as a co-variate. Further, it is likely that as older people who enter randomised controlled trials tend to be relatively robust, the findings may not generalise to older people with frailty. A secondary analysis of the HYpertension in the Very Elderly Trial (HYVET) generated a frailty index from baseline trial variables and used this to examine whether frailty modified the relationship between antihypertensive treatment and adverse outcomes[47], concluding that it did not. This finding was also seen in the SPRINT trial, which incorporated frailty assessment at baseline assessment[44]. Importantly, mortality rates in both studies were low (7% over three years in SPRINT and 11% over two years in HYVET). Both studies excluded patients from care homes and those with an established diagnosis of dementia, limiting the applicability of the findings to more severely frail or demented people.

CLINICAL ADVICE AND RESEARCH RECOMMENDATIONS

We have reviewed the management of hypertension in people with dementia and for each of our three questions there was a lack of direct evidence. However, just as there is no definitive evidence of benefit, neither is there of its being harmful.

Clinical advice

Assess carefully

In addition to assessing usual vascular risk factors, ambulatory blood pressure monitoring (ABPM) should be attempted, to exclude white-coat hypertension and prolonged hypotension which may contribute to cerebral hypoperfusion. Co-morbidities should be taken into account and symptomatic orthostatic hypertension should be sought. Guidelines for hypertension management now require the use of home BP and ABPM to diagnose hypertension and to monitor treatment effects[48]. Ambulatory measures provide more reliable indicators of usual BP[49] and predict outcomes more accurately than clinic measures[50]. Ambulatory monitoring has been found to be tolerable at least in mild to moderate dementia[51].

Guidelines

This review finds no reason not to adhere to current clinical guidelines. Those of the European Society of Hypertension and European Society of Cardiology[52] recommend reducing SBP in older people to 140-150mmHg . These guidelines contain the caveat that people >80 years of age should be in good physical and mental condition prior to treatment initiation, although this health state is not further defined. The guidelines of the National Institute for Health and Care Excellence[48] advise a target BP of 140/90mmHg for those aged <80 and 150/90mmHg for people aged ≥80.

Medication choice

One way to reduce medication burden is to select those which have complementary effects, e.g. to prescribe a β-blocker for the treatment of hypertension if the individual also requires treatment for atrial fibrillation, or to utilise the BP-lowering effects of nitrates or amlodipine also used in the treatment of angina.

One hypothesis concerns whether different classes of antihypertensive medications could have different effects on cognition. A recent meta-analysis incorporating ten randomised trials and observational studies found use of renin-angiotensin-aldosterone system blocking medications was associated with a reduced risk of dementia (RR 0.84; 95% CI 0.76 to 0.92)[53]. A meta-analysis of 15 studies found that diuretic medications were associated with reduced dementia risk (HR 0.83, 95% CI 0.76 to 0.91), after adjustment for other potential confounders and in preference to non-diuretic medications[54]. The mechanism for these observed differences is not fully understood and the large trials in this area were not designed to look specifically at differences in drug classes[55].

Deprescribing

Deprescribing is "the process of tapering or stopping drugs, aimed at minimising polypharmacy and improving patient outcome"[56]. Primary care is best placed to review and deprescribe, outwith episodes of acute illness and where deprescribing is commenced in hospital, careful communication of rationale and treatment objectives is essential. Reviews may include education around medication indications, communication of the risks and benefits, and establishment of the individual's goals. The outcome of such reviews may lead to relaxation of BP targets, change in prescriptions or medication withdrawal. If a side effect is suspected, a trial of dose reduction or drug withdrawal (a "drug holiday") can be illuminating and could result in re-starting, changing or withdrawal. It can be difficult to attribute non-specific symptoms to antihypertensive medications without a trial of their withdrawal. However, the avoidance of symptoms such as constipation or ankle oedema can be very helpful to patients. Such trials can have reciprocal benefits: they can reduce harm from a drug reaction but they can also reassure that the drug is not to blame, enabling alternative explanations to be sought.

Individuals with 'controlled' BP may no longer require treatment. If the person is no longer hypertensive then they have little to gain from treatment, but would remain at risk of side effects. It is unclear what proportion of treated, normotensive people with dementia might be able to withdraw safely. In studies of people without dementia this ranged from 20-85%[57], although different thresholds were used to define 'acceptable' BP. However, in half the cases of initially successful withdrawal, hypertension returned after ten weeks[57], so monitoring is required. If medication withdrawal is attempted, β-blockers should be withdrawn gradually in case they are masking otherwise controlled angina or rhythm disturbances and when ACE-inhibitors are withdrawn, patients should be monitored for signs of heart failure[58].

Patients and their carers may express a desire to stop or reduce medications. This presents the opportunity for dialogue about goals of care and how these are served by current treatments. Even those who do not have the capacity to understand complex risk-benefit information may express views, such as wishing to reduce tablet burden or avoid specific symptoms, which clinicians should acknowledge. Open and honest communication about risks and uncertainties can facilitate individualised, shared decision-making[59].

The final reason to review medication is in cases of advanced illness due to the progression of dementia or other comorbidities. It is important that, where advanced dementia is present, this is acknowledged and treatment adapted in consultation with the patient and carers to provide a holistic, palliative approach[60] as would be done in any other life-limiting condition.

Ethical practice

When a patient with dementia develops hypertension, it is necessary to assess their mental capacity to decide whether to prescribe treatment. When capacity is lacking, a process to establish best interests is required. It is important to respect a preference against treatment even if there are incentives to prescribe, just as it is important not to deny patients the opportunity to take drugs that may benefit them. The consent process is a continuing one, not a single event. It is important to revisit the decision to offer treatment in case a patient's declared preference or their best interests have changed.

Conclusions and future research

This review sought to examine the evidence around the management of hypertension for individuals with dementia. Framing our analysis around three questions we identified a lack of direct evidence of both benefit and harm and specific areas which require additional research. Many of the uncertainties - around hypoperfusion, orthostatic hypotension, cerebral blood flow and BPV - could be addressed in mechanistic studies, for example using transcranial doppler imaging. Secondly, the feasibility, acceptability and safety of deprescribing in specific sub-groups (such as those with low BPs on treatment, care home residents, etc.) should be studied in a pragmatic randomised controlled trial. These should examine a broad range of patient-centred outcomes including functional performance and quality of life to help provide evidence to support decision-making.

CONFLICTS OF INTEREST

The authors report there are no conflicts of interest to declare.

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