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Proposed Antihypertensive Medication Withdrawal Protocol

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ABSTRACT

Background

While there are extensive guidelines on the initiation of antihypertensive therapy, no widely available evidence-based guidance on antihypertensive withdrawal exists to guide clinicians. As part of a feasibility study to examine the withdrawal of antihypertensive medications in older adults with dementia, an evidence based protocol for discontinuing antihypertensive medications was developed.

Method

The research literature for evidence on antihypertensive withdrawal in older adults was reviewed. This was supplemented by review of NICE Guidance on the Management of Hypertension in Adult patients and relevant prescribing resources utilised in everyday clinical practice. Information on how antihypertensive medication should be withdrawn and the necessary monitoring required to conduct this safely was sought.

Results

The research evidence describing antihypertensive medication withdrawal in older adults was limited and predominantly observational in nature and there was a lack of clarity in the procedures and monitoring used. NICE guidance and the British National Formulary provided information on treatment initiation but not on withdrawal. To produce a withdrawal schedule therefore UK guidance for initiating therapy was reversed with additional instructions provided to account for comorbidity and overlapping medication indications. This was augmented by additional information from the research literature to produce a withdrawal protocol.

Summary

This paper presents a withdrawal protocol which has been developed based on limited research evidence. Procedures for withdrawal were adapted from UK clinical practice guidelines on medication initiation and safety data were extrapolated from prescribing guidance. Although this protocol will be tested in a feasibility study, validation by specialists, clinicians and patients is required before recommendations for practice can be made.

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BACKGROUND

There are many possible reasons to attempt to withdraw antihypertensive medication. The most obvious is when a newly introduced drug causes a side effect, when the drug is simply stopped. Another reason is the development of hypotensive symptoms due the effects of drugs given for other co-morbid conditions (such as L-Dopa preparations for Parkinson's disease), or the effects of other conditions (such as the development of orthostatic hypotension in Parkinson's disease, or the lowering of blood pressure and autonomic instability associated with the onset of dementia[1]). Another potential justification to withdraw antihypertensive medication is that between 1/3 and 1/2 of people whose blood pressures are adequately controlled on such treatment can withdraw them without a return of hypertension[2]. Withdrawing antihypertensive medication in such people could be part of an attempt to reduce the overall drug burden in people with polypharmacy and as anticipatory measure to avert the future development of hypotensive or other adverse drug events, and could be particularly suitable for people with unstable frailty states such as some people with dementia.

When planned withdrawal of antihypertensive medication is to be undertaken, particularly if undertaken as an anticipatory intervention, it is important to do this safely. This requires establishing practically how withdrawal is to be undertaken, the necessary monitoring required and identifying any potential adverse effects and how these will be detected and handled. It is also necessary to identify those in whom medication withdrawal would be considered too risky and thus who must be excluded from intervention. A specific additional concern in the treatment of hypertension is the overlap between medications which lower blood pressure, but which have been prescribed for a different indication (such as rate control for atrial fibrillation). Here any protocol for use in the older adult population must take account of other significant co-morbidity and medication indication, rather than providing blanket instructions.

Our research group undertook a feasibility study of a randomised controlled trial to withdraw antihypertensive medication in people with dementia with well-controlled hypertension[3]. As part of this study, we needed to have a safe, logical, justifiable and systematic approach to the withdrawal of antihypertensive medications. In this paper, we present the withdrawal procedure we used, and its justification.

METHODS

The withdrawal procedure was developed using the following stages.

Stage 1

A preparatory rapid review of the literature was undertaken in the form of a 'review of reviews'[4] to identify existing studies of antihypertensive withdrawal in older adults.

Stage 2

National Institute of Health and Clinical Excellence (NICE) guidance was assessed for the treatment of essential hypertension; where evidence was lacking from the literature review, the NICE guidance was applied in reverse to develop the withdrawal protocol.

Stage 3

For specific medications, the British National Formulary was consulted for advice over the duration of the withdrawal of antihypertensive drug classes and required safety/monitoring advice.

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Stage 4
Finally, a withdrawal protocol was produced indicating the order of drug withdrawal, with precautions, timing and monitoring required for each stage, in addition to specific patient considerations.

RESULTS

Stage 1: Literature review

The findings from our rapid review have been published fully elsewhere[2]. In summary, the literature to date suggested that between 27-52% of patients whose blood pressures were currently well-controlled may be able to withdraw medication without return of long term hypertension. There was limited information on the procedures used for withdrawing medications and monitoring individuals thereafter. However, common issues identified were both the high risk of 'withdrawal failure' in the immediate few weeks following withdrawal and the need for long-term monitoring to detect the return of hypertension. The identified studies in the older adult population were predominantly observational cohort designs. We recommended that a formal systematic review of all antihypertensive withdrawal literature be performed, not limited to the older adult population.

Stage 2: Hypertension Guidance

The 2011 edition of the National Institute for Health and Clinical Excellence (NICE) Guidelines[5] advocated the following approach for the management of essential hypertension in adult patients:

- 1st line: Initiate a Calcium-Channel Blocker (CCB) (unless not tolerated, patient has oedema or evidence of heart failure or a high risk of heart failure when they advocate starting with thiazide-like diuretic)
- 2nd line: Add an ACE inhibitor (ACE-i) or Angiotensin II receptor blocker (ARB)
- 3rd line: Add a Thiazide-like diuretic
- 4th line: Consider further diuretic (e.g. Spironolactone), or α-blocker or β-blocker

Thereafter, they advised seeking specialist advice if blood pressure is not controlled. For those aged over 80 years, they advised the same antihypertensive drug treatment as people aged 55-80 years, taking into account any comorbidities. Their clinic blood pressure target was below 140/90mmHg in people aged under 80 years and below 150/90mmHg in people aged 80 years and over for treated hypertension.

Stage 3: Information from the British National Formulary

The antihypertensive section of the British National Formulary was reviewed and a summary table (Table 1 *Antihypertensive medication and proposed duration of withdrawal*

Drug Class	Duration of Action	Proposed total duration for withdrawal

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Amlodipine	Terminal half-life: 35-50 hours.	Nelson schedule
ACE inhibitors	24 hours (maximum effects of continued treatment apparent after 3-4 weeks)	2-4 weeks
Angiotensin receptor blockers	A range of values for different drugs	2 weeks
Thiazides and thiazide-like-agents	12-18 hours	Nelson schedule
Spironolactone	2.8-11.2 hours Action persists for at least 24 hours	Nelson schedule
α-blockers	BP Effects last 24 hours	1-2 weeks
β-blockers	A range of values for different drugs	1-2 weeks
Aliskiren	Steady state 5-7 days	2 weeks
Methyldopa		48 hours
Clonidine	Half-life 23 hours	2-4 weeks
Moxonidine	90% excreted within 24 hours	3 weeks

Monitoring Requirements

When arranging planned medication withdrawal, there are certain effects which can be anticipated. Of particular relevance to the withdrawal of antihypertensive drugs are: heart failure, palpitations, tachycardia, angina, myocardial infarction and recurrent hypertension[8]. In Nelson 2003[7], 43% of patients in whom antihypertensive medications were withdrawn had to re-start treatment, with cardiac failure, recurrent hypertension and arrhythmia being cited as reasons for recommencement.

The only published monitoring regimen following withdrawal was described by Nelson 2002: where weekly visits for two weeks, fortnightly for two months, then monthly for six months then six monthly indefinitely[9] were used.

Table ***2*** summarises the published stopping safety criteria which were taken as indicative of the failure of drug withdrawal. Many were conducted before the outcome of recent major blood pressure trials and thus the values they described may no longer be acceptable to current practicing clinicians. The 2011 NICE Guidelines specified a threshold for initiating antihypertensive treatment in those >80 years old in the presence of specified risk factors, of >150/90mmHg and for those with Stage 2 Hypertension of 160/100 or greater[5].

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Although clinic-based blood pressure measurement forms the usual approach, there is some evidence of alternative strategies. Alsop and MacMahon used 24-hour ambulatory blood pressure monitoring after six weeks for all participants who had antihypertensive drugs stopped[10]. Beltman *et al.* highlighted the potential superiority of ambulatory blood pressure monitoring in assessing blood pressure eight weeks following antihypertensive withdrawal[11]. The 2011 NICE guidelines encouraged greater use of 24-hour blood pressure monitoring or if not available home readings to guide diagnosis and treatment[5].) of withdrawal information, by antihypertensive class, was generated. Where a proposed duration of withdrawal is listed, in table 1, this has originated from the proposed time interval at which the British National Formulary or the Electronic Medicines Compendium[6] advised a dose can be increased or when withdrawal is known to occur.

Where there was no specific guidance for an antihypertensive class, a default withdrawal schedule was proposed. This was based upon the work of Nelson *et al.*[7], who described a withdrawal regimen of half-dose reduction at weekly intervals with weekly assessments, until the lowest licensed dose was reached following which the drug was stopped.

Table 1 Antihypertensive medication and proposed duration of withdrawal

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Table 2 Antihypertensive stopping criteria applied by previous studies

Study	Blood Pressure Withdrawal Stopping Criteria	Other criteria
Alsop and MacMahon[10]	Three or more systolic ≥160 or diastolic ≥90 Mean daytime >134/81 (24 hour Ambulatory)	Nil
Ekbom *et al*. 1994[12]	Supine BP 180-230 systolic or 105-120 diastolic on three separate occasions	Nil
Lernfelt [13]	Systolic BP >200 or diastolic >105	Nil
Myers[14]	>180 systolic and 110 diastolic on two consecutive visits, at least one week	Nil

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	apart	
Nelson 2002[9]	Seated systolic ≥160 or diastolic ≥90 with systolic ≥140	GP choice to restart before 12 month follow-up (individual clinical choice)
Nelson 2003[7]	Seated systolic ≥160 or diastolic ≥90 with systolic ≥140	Patient or physician withdrawing consent
TONE Investigators[15]	Sustained BP ≥150/90	Clinical cardiovascular event Decision by participant/physician to resume BP medication

SUMMARY

The evidence base reviewed was predominantly observational in nature and suggested that 27-52% of older people could safely have antihypertensive medications withdrawn and remain normotensive at one year follow-up[2]. However, no gold standard withdrawal protocol was described or was available for use. From the evidence described a reasonable recommendation was that drug dosages are halved at weekly intervals until the lowest available dose and then stopped. This should be accompanied by weekly monitoring of blood pressure and clinical review for the development of withdrawal side effects such as fluid retention.

None of the available data reported on how to approach antihypertensive medication withdrawal in older people with dementia, and so generalising to this population of specific interest needs to be done with caution. However, our review of the literature indicated that once dementia has developed, there is no data on hypertension treatment outcomes in people with dementia[16], and that there is uncertainty over the potential harms.

The proposed antihypertensive withdrawal regime in Figure 1 incorporated the research evidence, NICE guidance and best clinical practice as described in the British National Formulary, and so represented our best approach to develop a withdrawal regime for use in our feasibility study, in which its feasibility and acceptability was to be tested.

Prior to more widespread use, it requires validation by clinicians with specialist knowledge in the field, general practitioners, carers and patients, and further development using a consensus approach. This might comprise further systematic reviews of all the relevant literature including all international and specialist guidelines in relation to hypertension in older adults, and the development of a withdrawal guideline using an iterative consensus approach, such as a Delphi technique.

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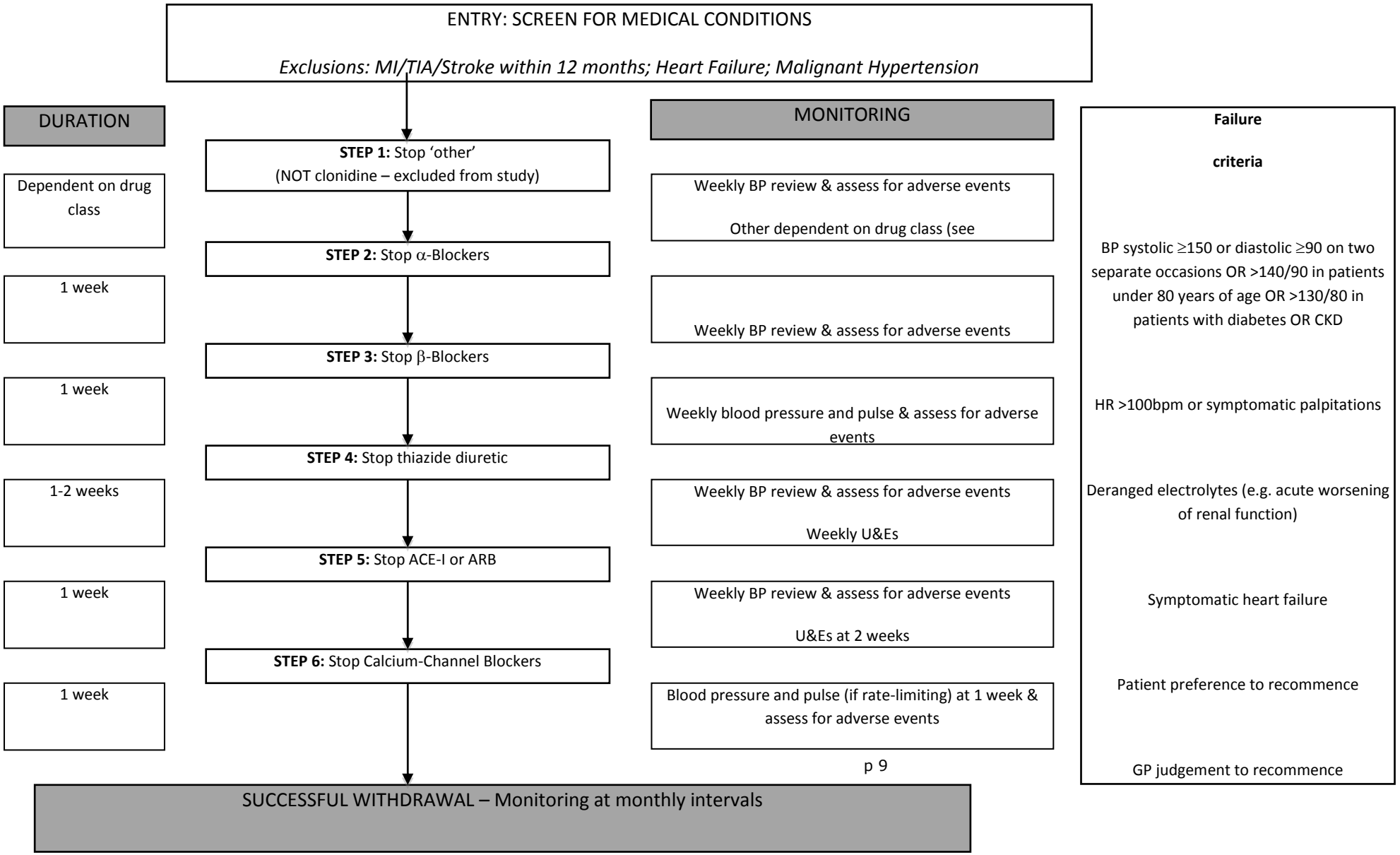
Figure 1 Draft antihypertensive withdrawal protocol to be used in conjunction with Table 3



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Individual patient considerations

As every patient is different, there will need to be scope for individualised decision making, but the withdrawal protocol above acts as an initial guide. For example, in someone in whom constipation is a big issue, the removal of calcium channel blockers first might be considered, as these drugs are known to cause constipation. This assessment will be undertaken by the 'withdrawal nurse' in consultation with the senior clinicians in the study team and the patient's GP. The learning from individual patient decision will be collated and can be used to inform the final protocol, which will hopefully cover most eventualities in due course.

N.B loop diuretics are not to be withdrawn as part of this protocol, even if it is thought that they are being used for hypertension

Table 3 Modifications to withdrawal protocol based on individual patient factors

Medical condition	Modification to protocol
Atrial Fibrillation	Assess rate-limiting therapy • If on digoxin – proceed as per protocol • If on β-blocker – omit Step 3, consider stopping if Step 6 achieved
Bradycardia	If the pulse is slow and there is no history of atrial fibrillation nor palpitations, consider removing beta-blockers first
Constipation	If constipation a problems, consider withdrawing calcium channel blocker first, as this class of drugs associated with constipation
Heart Failure	Omit Step 4, consider stopping if Step 6 achieved
Leg oedema	If no heart failure, consider withdrawing calcium channel blocker first, as this class of drugs associated with leg oedema
Prostatism	Omit Step 2, consider stopping if Step 6 achieved
Myocardial Infarction within past six months	Excluded from study
TIA/Stroke within past six months	Excluded from study
(Diabetic) nephropathy	If on ACE-I for renal protection, then exclude ACE-I from withdrawal regimen

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Table 4 Other BP Medications not covered by protocol [from Electronic Medicines Compendium (eMC)]

Drug	Withdrawal	Monitoring
Aliskerin	Monitor BP and U&Es at three weeks	BP and U&Es
Methyldopa	Monitor BP and urinary symptoms at 1 week	BP and urinary symptoms
Clonidine	Not to be manipulated as part of this study because of safety concerns	
Moxonidine	Monitor BP at three weeks	BP only

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COMPETING INTERESTS

None of the authors have any conflicts of interest that might bias this work.

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