Pharmacotherapy of hypertension

Pharmacists can play a greater role in improving management

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Hypertension treatment and control requires a multidisciplinary approach. The convenient community location of pharmacies and the expertise of pharmacists are well suited to improving the management of hypertension. We have specifically indicated where pharmacists can improve pharmacotherapy.

Abstract

Background: Hypertension is a leading risk factor for death and disability in Canada. Pharmacists can help to improve the treatment and control of hypertension through collaboration with physicians and patients to improve pharmacotherapy.

Objective: To review appropriate pharmacotherapy for hypertension, as outlined in the recommendations of the Canadian Hypertension Education Program.

Methods: The recommendations of the Canadian Hypertension Education Program were reviewed with a view to identifying gaps in the recommendations as they apply to pharmacy practice. For some of these gaps, it was determined that pharmacists could provide further care to patients with hypertension, and opportunities for pharmacist involvement are suggested here.

Results: Initial pharmacotherapy for uncomplicated hypertension includes thiazide-type diuretics, beta-blockers for patients under 60 years of age, angiotensin-converting enzyme (ACE) inhibitors, long-acting calcium channel blockers, and angiotensin receptor blockers. For additive hypotensive action in two-drug combinations, either a diuretic or a calcium channel blocker should be combined with a beta-blocker, ACE inhibitor, or angiotensin receptor blocker. Other combinations are less effective or unproven. Areas where pharmacists must become more actively involved in the management of patients with hypertension include provision of balanced information about benefits and side effects, identification of secondary drug-induced causes of hypertension or drug interactions, and suggestion of adjustments to medication dosage for patients with renal dysfunction.

Conclusions: **There are specific and unique roles for pharmacists in the management of hypertension. Pharmacists can play a greater role in improving the pharmacological management of hypertensive patients, aided in part by regular updates to the recommendations of the Canadian Hypertension Education Program.**

Key points

- Assess the cardiovascular risk of all patients with hypertension with a view to intensifying therapy for those at highest risk and optimizing risk reduction strategies.
- Use lifestyle modification to prevent and treat hypertension as well as to reduce the requirement for pharmacotherapy.
- Individualize drug therapy on the basis of the patient's other risk factors and comorbid conditions.
- Use synergistic combinations of medications to reach therapeutic targets.
- Help patients adhere to therapy.

Hypertension is a leading risk factor for death and disability, but the burden of cardiovascular disease can be reduced by preventing hypertension and by identifying people with hypertension and reducing their blood pressure.[1,2] This article discusses the use of pharmacotherapy to reduce blood pressure. The contents of the manuscript are based on the recommendations of the Canadian Hypertension Education Program. This program systematically reviews the hypertension literature and updates treatment recommendations annually.

The 2006 recommendations (www.hypertension.ca) were used for this manuscript.

Risk assessment

Among patients with the same level of blood pressure, the risk of a cardiovascular event can

vary by a factor of more than 10.[3] The risk increases with blood pressure above 115 mmHg systolic and above 70 mmHg diastolic.[4] A variety of factors, some reversible, contribute to a person's cardiovascular risk (see box). Reducing multiple risk factors could reduce overall cardiovascular risk in a patient with hypertension by 80%, whereas reducing blood pressure (without changes in other risk factors) reduces the risk by about 25%.[5]

Although there are several methods of assessing cardiovascular risk, the use of a risk table is effective for communicating risk to patients and has been associated with a greater reduction in systolic blood pressure than is the case if no risk assessment is performed.[6] Consideration should be given to the use of lipid-lowering therapy and acetylsalicylic acid (ASA) in patients with hypertension and high cardiovascular risk.[7-9]

Major cardiovascular risk factors

- Male gender
- Age 55 years or older
- Smoking
- Obesity
- Inadequate diet (i.e., high in saturated fats and salt and low in fresh fruit and vegetables)
- Sedentary lifestyle
- Diabetes mellitus or glucose intolerance
- Dyslipidemia
- Microalbuminuria or proteinuria
- Left ventricular hypertrophy
- Overt atherosclerotic vascular disease (e.g., past myocardial infarction)
- Family history of premature cardiovascular disease (i.e., first-degree relative [male <55 years of age or female <65 years of age] with atherosclerotic vascular disease)

Thresholds for therapy

Virtually all patients can benefit from lifestyle modification. If patients are at low risk and blood pressure is less than 160/100 mmHg, initiating lifestyle modifications alone is reasonable. Several trials have shown that certain groups of high-risk patients, including those with vascular disease (e.g., past myocardial infarction or ischemic heart disease, stroke or transient ischemic attack, congestive heart failure) or diabetes mellitus combined with additional cardiovascular risk factors, benefit from blood pressure reduction by pharmacotherapy even if their blood pressure is normal.[10-12] For other patients, thresholds for initiation for antihypertensive therapy are as follows:[7]

- For patients without any additional cardiovascular risks (less than 10% of patients with hypertension), drug therapy should be initiated if the blood pressure is sustained above 160 mmHg systolic or 100 mmHg diastolic.
- For patients with additional risk factors, treatment can be initiated if blood pressure is sustained above 140 mmHg systolic or 90 mmHg diastolic.
- For patients with diabetes or renal disease, treatment should be initiated if the blood pressure is sustained above 130 mmHg systolic or 80 mmHg diastolic.

BP targets during pharmacotherapy

For most patients, blood pressure should be reduced to less than 140 mmHg systolic and less than 90 mmHg diastolic.[7] For patients with renal disease or diabetes, the blood pressure target is less than 130 mmHg systolic and less than 80 mmHg diastolic.

Initial pharmacotherapy of uncomplicated hypertension

The reduction in frequency of cardiovascular events in patients with uncomplicated hypertension depends on the degree of reduction in blood pressure and not on the specific class of antihypertensive medication used.[7,13-15] Initial therapy should be selected from classes of drugs proven to reduce cardiovascular events. These include low-dose thiazide-type diuretics, beta-blockers in patients less than 60 years of age, angiotensin-converting enzyme (ACE) inhibitors, long-acting calcium channel blockers, and angiotensin receptor blockers. Beta-blockers are less effective in those over 60 years of age.[7,9,16-18] Beta-blockers administered as monotherapy have not been proven to reduce cardiovascular events in patients with hypertension and therefore should not be selected as initial therapy.[7,19]

Patients with compelling indications for specific pharmacotherapy

Table 1 outlines initial therapeutic options for patients, with specific indications for pharmacotherapy.

Patients with diabetes are generally at very high cardiovascular risk,[20] and there are substantial morbidity and mortality benefits from intensive lowering of blood pressure in these patients.[20,21] The threshold for initiation of therapy is 130/80 mmHg, and the therapeutic target is less than 130/80 mmHg.[7] First-line therapy should consist of an ACE inhibitor or an angiotensin receptor blocker. If there is no proteinuria, a thiazide-type diuretic or a long-acting dihydropyridine calcium channel blocker would be suitable as an alternative first-line therapy. Most patients, however, require combinations of first-line drugs.

Combining antihypertensive drugs

It is generally more effective to combine two drugs at low to moderate dose than to maximize the dose of a single drug. Most patients with hypertension need two or more antihypertensive drugs to achieve the target blood pressures.[22] Most drug combinations should include a diuretic.[8,20]

For optimal reduction of blood pressure in

TABLE 1 Considerations in the individualization of antihypertensive therapy

Patient's condition	Initial therapy	Second-line therapy	Notes and/or cautions
Hypertension without compelling indications for other medications	Thiazide diuretics, beta-blockers (for patients < 60 years of age), ACE inhibitors (in non-Black patients), ARBs, or long-acting CCBs (consider ASA and/or statins in selected patients)	Combinations of first-line drugs	Alpha-blockers are not recommended as initial monotherapy. Beta-blockers are not recommended as initial monotherapy in those over 60 years of age. Hypokalemia should be avoided in those who are receiving diuretics. ACE inhibitors are not recommended as initial monotherapy for Black patients. ACE inhibitors and ARBs are contraindicated in women of childbearing potential.
Isolated systolic hypertension without other compelling indications	Thiazide diuretics, ARBs, or long-acting dihydropyridine CCBs	Combinations of first-line drugs	Hypokalemia should be avoided in people receiving diuretics
Diabetes mellitus with nephropathy	ACE inhibitors or ARBs	Addition of one or more of thiazide diuretics, cardioselective beta-blockers, or long-acting CCBs or use of combination of ARB and ACE inhibitor	
Diabetes mellitus without nephropathy	ACE inhibitors, ARBs, thiazide diuretics, or long-acting calcium channel blockers	Combination of first-line drugs or addition of cardioselective beta-blockers	
Angina	Beta-blockers (strongly consider adding ACE inhibitors)	Long-acting CCBs	Avoid short-acting nifedipine
Prior myocardial infarction	Beta-blockers and ACE inhibitors (ARBs if intolerant of ACE inhibitors)	Combinations of additional agents	
Heart failure	ACE inhibitors (ARBs if intolerant of ACE inhibitors), beta-blockers, and spironolactone in selected patients	ARBs or hydralazine/isosorbide dinitrate (thiazide or loop diuretics as additive therapy)	Avoid nondihydropyridine CCBs
Past cerebrovascular accident or TIA	Combinations of ACE inhibitor and diuretic		Blood pressure reduction reduces recurrence of cerebrovascular events
Chronic kidney disease	ACE inhibitors (diuretics as additive therapy)	Combinations of additional agents (ARBs if intolerant of ACE inhibitors)	Avoid ACE inhibitors and ARBs if bilateral renal artery stenosis is present
Left ventricular hypertrophy	ACE inhibitors, ARBs, CCBs, thiazide diuretics (beta-blockers for patients <60 years of age)		Avoid hydralazine and minoxidil
Peripheral arterial disease	Does not affect treatment recommendations		Avoid beta-blockers for patients with severe disease
Dyslipidemia	Does not affect treatment recommendations		

ACE = angiotensin-converting enzyme, ARB = angiotensin receptor blocker, CCB = calcium channel blocker, ASA = acetylsalicylic acid, TIA = transient ischemic attack.

patients requiring combination therapy, diuretics or calcium channel blockers should be combined with an ACE inhibitor, an angiotensin receptor blocker, or a beta-blocker. For other two-drug combinations, less-than-additive hypotensive effects have been observed and there has been controversy about whether the combination has additive hypotensive effects.[23]

Adherence

Lack of adherence to therapy, a significant problem, is discussed elsewhere (p. S18). For all patients receiving antihypertensive therapy, adherence should be assessed at each visit to the pharmacy. If nonadherence is identified, the pharmacist should attempt to ascertain the reasons and should work with the patient and the physician to optimize blood pressure control by improving adherence.

Resistant hypertension

As noted above, most patients need at least two drugs to lower blood pressure to targets levels.[8,20,22] Hypertension that is not controlled with three or more medications is known as resistant hypertension. The prevalence of white coat effect (isolated office hypertension) is higher in patients with resistant hypertension. Assessing blood pressure in the pharmacy or carefully instructing the

patient about self-measurement and advising a validated self-measurement device can help (see p. S12). Ambulatory blood pressure monitoring can also be used to assess white coat effect.

Lack of adherence to therapy is another reason for resistant hypertension. Secondary hypertension is more common in patients with resistant hypertension, as are obesity and sleep apnea. In many cases resistant hypertension is caused by lifestyle (e.g., weight gain, reduced physical activity, increased salt intake, excessive alcohol intake). Drugs that increase blood pressure (e.g., nonsteroidal anti-inflammatory drugs [NSAIDs]) or drugs (e.g., phenytoin) or herbal preparations (e.g., St. John's wort) that induce the metabolism of antihypertensive drugs can also cause resistant hypertension.

The cause of resistant hypertension should be identified if possible. If the pharmacist becomes aware of long-term use of over-the-counter NSAIDs or alternative therapies such as St. John's wort, it is important to educate the patient about the potential impact of these agents on blood pressure control and to notify the patient's physician. If possible, the therapeutic regime for resistant hypertension should include a diuretic, an angiotensin receptor blocker or ACE inhibitor, a vasodilator (e.g., long-acting calcium channel blocker), and a beta-blocker. Caution should be used in combining non-dihydropyridine calcium channel blockers with beta-blockers. In many patients, hypertension responds well to a high dose of diuretics, so such a regimen should be instituted as a therapeutic trial. In some patients, there is a response to spironolactone even if hyperaldosteronism is absent. In resistant hypertension, moderate to high doses of drugs are used, but the aim is to use long-acting, once-daily medications in a simplified medication regime, if possible.

Screening tips

Some drugs and substances can increase blood pressure or interfere with the effectiveness of antihypertensive drugs. These include:

- Nonsteroidal anti-inflammatory drugs, including COX II inhibitors
- Corticosteroids (glucocorticoid, mineralocorticoid) and anabolic steroids
- Oral contraceptives (and other estrogen-containing preparations)
- Sympathomimetic drugs
- Cyclosporine and tacrolimus
- Erythropoietin
- Monoamine oxidase inhibitors (especially nonselective)
- Licorice extracts
- St. John's wort
- Thyroxine (in excess)

Special issues for the pharmacist

Antihypertensive drugs and side effects

Antihypertensive drugs have a reputation for causing side effects. Most of this evidence is from older studies that used very high doses or drugs that are now obsolete. Studies performed in the past two decades have demonstrated that low-dose diuretics, moderate-dose beta-blockers, long-acting calcium channel blockers, ACE inhibitors, and angiotensin receptor blockers have very few side effects relative to placebo and improve the quality of life of treated patients.[24-28] The side effects reported in patient information handouts have often been disproved by large randomized controlled trials. Drug monographs usually mention all the adverse symptoms a patient might experience while taking either the active agent or placebo in clinical trials, which reflect the common ailments seen in patient populations, not necessarily adverse effects of the agent. Giving patients long lists of unproven side effects may undermine adherence and patients' faith in drug therapy and is therefore not justifiable. It is important that the pharmacist stress the benefit of drug therapy and the relative safety of the agent selected and that he/she indicate that the most common outcome is blood pressure control without side effects.

Drugs that cause hypertension

Several drugs and other substances can cause hypertension or interfere with the reduction of blood pressure in those with hypertension (see box). NSAIDs represent a particular problem in this regard. Up to 25% of patients over 65 years of age receive NSAID prescriptions each year, but these drugs increase blood pressure, interfere with antihypertensive medications, and can interact with drugs that interrupt the renin–angiotensin–aldosterone axis (i.e., ACE inhibitors and angiotensin receptor blockers), thus causing renal impairment and hyperkalemia. Nonpharmacologic therapy (e.g., exercise), use of the lowest possible NSAID dose, and substitution of acetaminophen can reduce this problem.

Drug interactions

Antihypertensive drugs that are eliminated primarily through metabolic pathways may accumulate if these pathways are inhibited by other agents. This may result in side effects or hypotension because of increased drug bioavailability or drug accumulation. Grapefruit juice is a potent inhibitor of the metabolism of some antihypertensive drugs, especially some calcium channel blockers. The antihypertensive effectiveness of drugs that are hepatically metabolized may be reduced or eliminated by drugs that induce their metabolism. Common inducers of metabolism include barbiturates, phenytoin, and rifampin. St. John's wort, a commonly used herbal preparation,

also causes significant induction of hepatic metabolism and can interact with antihypertensive drugs. Pharmacists should check patients' drug profiles regularly for prescribed drugs that are hepatically metabolized to determine the potential for interactions with other drugs, grapefruit juice, and St. John's wort. If the pharmacist notes a lack of blood pressure control and an interacting therapeutic regimen, he/she should communicate with the prescribing physician to discuss therapeutic options.

Renal clearance of drugs

Many antihypertensive drugs are cleared from the body by the kidneys. In clinical practice drug doses are typically not adjusted to account for renal dysfunction. For patients receiving renally cleared drugs, pharmacists should routinely ask about kidney disease and notify the physician if the doses prescribed are higher than those recommended for patients with renal dysfunction.

Conclusion

Antihypertensive pharmacotherapy is an effective way to reduce cardiovascular morbidity and mortality. There are specific and unique opportunities for pharmacists to improve hypertension management, including providing evidence-based information regarding drug side effects, screening for hypertension-inducing drugs and drug interactions, and ensuring patients with altered clearance of drugs are dosed appropriately. Pharmacists can play a greater role in improving the pharmacological management of hypertensive patients, aided in part by regular updates to the recommendations of the Canadian Hypertension Education Program. ■

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