Polypharmacy in Older Adults With Hypertension: A Comprehensive Review

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Older adults are more likely to take more than two medications for medical conditions, and polypharmacy is associated with increased risk of adverse events (fall injury, hyperkalemia and hypokalemia, heart failure, and blood pressure exacerbation), polypharmacy mismanagement, drug-drug interaction, and increased costs. Knowledge of drugs that interact with known antihypertensive agents is paramount to avoiding or reducing adverse events, hospitalizations, and health care dollars. Innovative approaches such as use of a fixed-dose combination pill, ingestible sensor system, electronic reminder system, medical audits, and the integration of a pharmacist in the care of patients should be implemented to avoid polypharmacy mismanagement. *J Clin Hypertens (Greenwich).* 2016;18:10–18. © 2015 Wiley Periodicals, Inc.

Hypertension is the most frequently diagnosed chronic medical condition among adults 65 years and older in the United States[1] and is a major risk factor for cardiovascular (CV) disease (CVD). Affecting one in three US adults,[2] hypertension is independently linked to heart failure, stroke, atherosclerotic coronary artery disease (CAD), renal failure, and death.

In addition, the prevalence of hypertension among US adults increases with age. A report from the 2013 National Center for Health Statistics (NCHS) on hypertension among adults in the United States showed that the prevalence of hypertension was 7.3% among adults aged 18 to 39 years, 32.4% among those aged 40 to 59 years, and 65% among those 60 years and older.[3] Among those 60 years and older, 86.1% were aware of their diagnosis of hypertension and 82.2% were receiving treatment for hypertension but only 50.5% had their hypertension controlled.[1,3]

Initially, there is a higher prevalence of hypertension among adult men compared with women up to approximately the age of 45 years, then the burden of hypertension balances out between the ages of 45 to 64 years, and finally among adults older than 65 years, women have a higher prevalence compared with men.[1] The US population is expected to grow by about 62 million from the year 2010 to 2030, and 50% of this growth is as a result of adults 65 years and older.[4] In 2010, older adults aged 65 years made up 13% (40 million) of the US population.[5] Therefore, the burden of hypertension is expected to rise with the rapidly growing and aging population.[6]

Although both systolic blood pressure (SBP) and diastolic blood pressure (DBP) are independent risk factors for CVD, isolated systolic hypertension (ISH) is the most common form of hypertension among older adults and is also the most common form of uncontrolled hypertension in this age group.[7] The pervasiveness of ISH in older adults is caused by age-related loss of elasticity in the arteries, particularly the larger vessels such as the aorta. The loss of distensibility in the aorta also results from progressive atherosclerosis in the vessel wall, which reduces compliance in the arterial system. In younger adults with normal arterial compliance, distensibility of the aorta during systole reduces augmentation of the pulse wave velocity and SBP. On the other hand, in older adults, lower DBP may actually represent an increase in CVD risk, manifested as predominantly ISH and an associated increase in pulse pressure caused by reduced arterial compliance and an increase in reflected pulse wave velocity.[6]

A contemporary 2015 report of 59 adults assessed the frequency of polypharmacy and potential complications among local seniors in Cuyahoga County, Ohio, with a mean age of 76.9 years. Polypharmacy was seen in 21 patients (35.6%) and was significantly associated with duplicated therapy (P=.02) and contraindicated drug combinations (P<.001).[8]

SEARCH METHOD

We performed a review of studies addressing polypharmacy in older adults with hypertension by using a comprehensive search strategy developed for PubMed. The medical subject headings and text words were: caffeine, aged and blood pressure; blood pressure, hypertension, aged and acetaminophen, cimetidine, and hypertension, ergotamine and hypertension, hypertension, erythropoietin, blood pressure and humans, gonadal steroid hormones, blood pressure, humans, hypertension and aged, glucocorticoids and blood pressure, nonsteroidal anti-inflammatory drugs and blood pressure, polypharmacy, technologies to improve adherence, grapefruit juice and hypertension, polypharmacy cost, and older adults. The electronic search was restricted to studies published before May 29, 2015. In addition, we manually searched reference lists of reviews and original study articles and our own archive.

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Manuscript received: April 22, 2015; **revised:** June 8, 2015; **accepted:** June 9, 2015
DOI: 10.1111/jch.12624

DISCUSSION

Polypharmacy Among Older Adults: Costs and Mismanagement

The estimated direct and indirect financial outlay for the treatment of hypertension in 2010 was $46.4 billion and this number is estimated to rise to $274 billion by 2030.[1] Moreover, as the number of associated comorbidities increases with age, so does the total aggregate of prescribed drugs. Among older adults 65 years and older, 80% and 50% have at least one and two or more chronic conditions, respectively.[9] In addition, a growing share of older adults in the United States raises concern for polypharmacy mismanagement, associated costs, drug-drug interactions, and adverse events.

According to data from the Intercontinental Marketing Services (IMS) health prescription record in 2012, 42% of older adults were taking five or more medications, increasing from five medications at age 65 to seven at age 85.[10] Moreover, approximately 13% of all older adults were taking 10 or more medications in 2012 and there was a linear relationship between the extent of polypharmacy and adverse drug events in older adults, subsequently translating into an increase in healthcare expenditures.

Polypharmacy is also a significant reason for medication nonadherence, which is associated with a vast medical and economic burden.[11,12] In addition, increase in polypharmacy may also be beneficial in controlling hypertension in older patients. A recent published analysis from the National Health and Nutrition Examination Surveys (NHANES)[13] 1988–1994, 1999–2004, and 2005–2010 confirmed that an increasing number of hypertensive medications are being utilized in older Americans. There has been a progressive increase in persons 60 years and older taking three or more BP medication from 9%±1%, to 17%±1%, to 26%±1% with each survey, respectively, associated with continuing improved BP control in older US adults.[13]

High adherence to CV medications was recently shown to significantly improve healthcare outcomes and reduce annual costs for secondary prevention of CAD.[14] Among older adults, the cost of polypharmacy mismanagement that could be avoidable in the United States is approximately $1.3 billion (range $900 million to $1.7 billion). Most of the expenses are incurred through inpatient care, emergency department visits, and hospitalizations as a result of complications and adverse drug events. Therefore, the growing share of US older adults with hypertension makes polypharmacy an increasingly relevant societal challenge.[10]

The reasons for increased adverse drug events associated with older adults are multifactorial. Older adults are more likely to be frail, have a higher likelihood of multiple comorbidities, and are more likely to incur errors with self-administration of their medications, resulting in increased nonadherence with polypharmacy. Factors associated with polypharmacy include adverse events, poor management, and tracking of medications, along with at-risk body composition and metabolic and absorption changes that occur with advancing age.[15]

Potential Drug Interactions in Older Adults and Increased BP

There are multiple medications (Table I) that cause elevated blood pressure (BP) in older adults (≥65 years).[16] In addition, there are also multiple factors that could affect BP in older adults, including tobacco use, various substances (caffeine, alcohol), and over-the-counter drugs. Among adults 65 years and older, there were 9.2% of men and 8% of women who were current smokers from 2010 to 2012.[1] Damage to the endothelial lining as a result of smoking reduces arterial compliance and changes in sympathetic nervous system activity.[17,18] These changes produce a surge in SBP that is reversible by smoking cessation. Alcohol use is also associated with elevated BP,[19] and older adults who consume caffeine may experience a slight increase in systolic and diastolic BP compared with abstinence. A meta-analysis evaluating both acute (1 to ≥3 hours) and long-term effects (2 weeks) of caffeine in patients with hypertension showed that 200 mg to 300 mg of caffeine produced a mean increase of 8.1 mm Hg (95% CI, 5.7–10.6 mm Hg) in SBP and of 5.7 mm Hg (95% CI, 4.1–7.4 mm Hg) in DBP acutely, while there was no evidence of a long-term effect on BP.[20] Transient increases in BP associated with caffeine in older adults with hypertension may not be safe.

Nonsteroidal Anti-Inflammatory Drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most commonly utilized medications worldwide and nearly 20% to 30% of older adults in developed countries are prescribed NSAIDs, with this trend expecting to rise.[21] In older adults, the use of NSAIDs increase the risk of antihypertensive medication initiation by 1.5 to 1.8 times compared with nonusers.[22] Several mechanisms have been postulated for NSAID-induced BP elevation. First, NSAIDs inhibit both COX-1 and COX-2 production of prostaglandins, thereby reducing renal perfusion with resultant systemic BP elevation. Second, the COX-2 inhibitory effect of NSAIDs leads to reduced natriuresis, which results in increased sodium and water retention[23] and may worsen BP and edema in hypertensive patients.[19,24,25] Third, NSAIDs increase BP through the induction of endothelin-1 production and/or alter arachidonic acid metabolism.[26,27] In addition, several studies have shown decreased efficacy of angiotensin-converting enzyme (ACE) inhibitors in reducing BP when concomitantly used with NSAIDs through reduction of prostacyclin.[24,25,28] Gualtierotti and colleagues[29] reported a significant increase in clinic and ambulatory SBP/DBP when naproxen was used concomitantly with ramipril ($P<.01$) or valsartan ($P<.05$) but not with aliskiren.

Although in younger adults with normal renal function, the combination of NSAIDs and ACE inhibitors may be acceptable; however, in older patients, caution

TABLE I. Agents That Can Interfere With Blood Pressure Control in Older Adults

Medication	Physiologic Effect
Nonsteroidal anti-inflammatory drugs	Increase sodium and water retention Increase in blood pressure
Glucocorticoids	Dose-dependent blood pressure elevation
Sex hormones	Minimal blood pressure elevation in postmenopausal women
Acetaminophen	Small increase in blood pressure
Erythropoietin	Blood pressure elevation
Ergotamine	Worsen blood pressure and minimize the effect of antihypertensive agents
Cimetidines	Potentiate the effect of β-blockers
Grapefruit juice	May cause hypotension when used with calcium channel blockers

Data from Cooney and colleagues.[16]

should be exercised when administering these drugs concurrently, in view of an increased risk of developing difficult to control hypertension, renal failure, and hyperkalemia. Overall, NSAIDs are also known to reduce the antihypertensive efficacy of both loop and thiazide diuretics and therefore adjustment in the diuretic regimen is sometimes needed.[19]

Acetaminophen

Acetaminophen (United States) (or paracetamol in Europe) is a well-established over-the-counter analgesic used for the relief of mild to moderate pain, to reduce fever, and to treat symptoms of upper respiratory viral infections and influenza.[30] For many patients, it is the initial drug of choice and the most widely used analgesic for the treatment of chronic pain.[31,32] As a result of concerns for CV safety of NSAIDs and COX-2, acetaminophen has been the preferred analgesic used in patients with increased CV risk and hypertension.[31,33] Nevertheless, acetaminophen may elevate BP. The mechanism for acetaminophen-induced hypertension is unclear, but there are recent data suggesting a COX-2 inhibitory mechanism via a peroxidase site on prostaglandin H2 synthase and also via a COX variant centrally.[31,34,35]

In a randomized, double-blind, placebo-controlled, crossover study of 33 patients aged 60.5±8.5 years with coronary disease, 1 g of acetaminophen three times a day was associated with a significant increase in both systolic and diastolic ambulatory BP.[36] In the United Kingdom General Practice Research Database there was a nonsustained rise in SBP and DBP among older hypertensive treated patients who were using acetaminophen.[31] However, the BP changes were no different than those seen in matched nonacetaminophen-exposed patients.[31] A recent systematic review study by Turtle and colleagues[30] involving more than 140,000 patients concluded that the overall effect of acetaminophen on BP was unclear. Nevertheless, caution should be taken when prescribing acetaminophen for patients with CAD and hypertension because, based on observational data, even a small increase of 2 mm Hg in BP can be translated into a 7% and 10% increase in mortality from ischemic heart disease and stroke, respectively.[37] Overall, large randomized, placebo-controlled, double-blind studies are needed to determine the effect of long-term use of acetaminophen on BP.

Glucocorticoids

Glucocorticoids are widely used for the treatment of several medical conditions such as rheumatologic, immunologic, and autoimmune diseases. Although glucocorticoid-induced hypertension is a widely recognized concern, the mechanism for the BP elevation is not clearly understood. The significant activation of mineralocorticoid receptors by excess glucocorticoid plays a role, but it is not the only pathway for BP elevation in this setting.[38,39]

Older patients treated with synthetic corticosteroids are even more sensitive to BP elevation and this increase in BP is dose-dependent. At least 20% of patients treated with synthetic corticosteroids develop hypertension, and BP up to 15 mm Hg in 24 hours can occur with higher steroid dosages.[40] Azole antifungal agents, such as ketoconazole, inhibit the enzyme cytochrome P450 14-alpha-demethylase and limit the enzymatic degradation of steroids, leading to mineralocorticoid-related hypertension. If both drugs are used, then discontinuation of one or the other may be warranted or additional antihypertensive therapy may be needed.[34]

Sex Hormones

Postmenopausal oral estrogen replacement therapy may increase SBP by 1 mm Hg to 2 mm Hg but will rarely cause severe hypertension.[40] In a prospective randomized placebo-controlled estradiol study, Steiner and colleagues[41] concluded that estradiol increases SBP in younger postmenopausal women, while having the opposite effect in older postmenopausal women. A semisynthetic androgen (danazol), used in the treatment of endometriosis and hereditary angioedema, has been reported to induce hypertension and fluid retention.[40] On the other hand, a National Institutes of Health–supported clinical trial has been designed to determine the treatment outcome (walking, vitality, sexual function, memory, blood count, and CV risk) of testosterone supplementation in men 65 years and older (NCT00799617).

Erythropoietin

Recombinant erythropoietin (EPO) is used for the management of anemia in end-stage renal disease with/without associated hemodialysis. Despite its success in improving anemia, EPO has been reported to develop or worsen hypertension in 20% to 30% of dialysis patients treated with EPO, thereby disrupting EPO therapy.[42] There are several mechanisms involved in EPO-induced hypertension. First, EPO causes activation of the local renin-angiotensin system, thereby leading to increased vasoconstrictor response to catecholamines.[43,44] In addition, EPO can cause vasoconstriction via increase in endothelin-1[45] and causes contraction of vascular smooth muscle cells via increased cytoplasmic calcium concentration.[46] Finally, EPO may raise BP by attenuating the effect of nitric oxide and cyclic guanosine monophosphate production in the endothelium.[42] Interestingly, Schulz and colleagues[47] concluded that an EPO polymorphism is more frequently found in patients with hypertension and is associated with higher BP level. Recombinant EPO is sometimes needed for treatment of anemia in patients with end-stage renal disease and concomitant hypertension. Despite the negative effect of EPO on BP, it should not be avoided; instead, additional antihypertensive agents could be added or additional blood volume be removed during hemodialysis, as tolerated.

Ergotamine

Ergotamine, used in the acute treatment of migraine since 1926, is structurally similar to endogenous catecholamine. At therapeutic doses, it may cause BP elevation, and prolonged use can lead to arterial spasm, claudication, and gangrene in some patients.[48,49] In a small, randomized, double-blinded, placebo-controlled crossover study in patients with a mean age of 28 years, 2 mg of oral ergotamine alone was associated with a statistically significant 6.9-mm Hg increase in DBP and a nonsignificant increase in SBP of 3.3 mm Hg.[50] In older patients with hypertension, prolonged usage of ergotamine should be avoided as it could worsen BP and minimize the effect of antihypertensive medications.

AGENTS THAT INCREASE ANTIHYPERTENSIVE EFFECT OF β-BLOCKERS AND CCBS

Cimetidine

Cimetidine is commonly used among older adults and its combination with lipid-soluble β-blockers such as carvedilol, labetolol, metoprolol, and propanolol can potentiate the β-blocker effect. These lipid-soluble β-blockers are metabolized via the CYP2D6, and inhibition of this enzyme with cimetidine reduces the breakdown of the β-blockers.[19] Cimetidine should be avoided if possible in elderly patients treated with lipid-soluble β-blockers or dose-reduced when concomitant cimeditine use is indicated.

Grapefruit Juice and Antihypertensive Therapy

Grapefruit juice, an inhibitor of the CYP3A4 enzyme, interacts with several CV drugs[51] commonly used in older adults including the calcium channel blockers (CCBs) and certain HMG-CoA reductase inhibitors (lovastatin, simvastatin, and atorvastatin). The most extensively studied of these drugs are the dihydropyridine CCBs, particularly felodipine,[52] nifedipine, and amlodipine.[51] Grapefruit juice has been shown to triple the mean plasma concentration area under the curve of felodipine.[53] Grapefruit juice also interacts with nondihydropyridines, increasing drug area under the curve for diltiazem and verapamil to 110% and 143%, respectively. Extensive intake of grapefruit juice should be avoided or limited in older patients who are taking CCBs and the above-mentioned statins in order to avoid serious potential adverse events such as hypotension, arrhythmias, and rhabdomyolysis.

POTENTIAL RISKS OF HIGH BP OVERTREATMENT IN OLDER ADULTS

Fall Risk

The CV benefits of antihypertensive treatment among older adults have been clearly illustrated in multiple randomized controlled clinical trials.[54] Despite the reduction in CV events, treatment with antihypertensive medications among older adults carries potential risk for fall and injury. Tinetti and colleagues[55] recently evaluated the risk of fall injury in a cohort of 4961 older adults (with or without antihypertensive medications) with a mean age of 80 years followed for a period of 3 years. They reported a 9% risk of serious fall injury (hip fractures, head injuries, major joint dislocation), and antihypertensive medication use was associated with an increased risk of experiencing a serious fall injury. In addition, multiple comorbidities as well as a history of falls were associated with increased risk of fall injuries.[55] Nevertheless, recent analysis of major studies with intensive BP reduction in older patients, including the Action to Control Cardiovascular Risk in Diabetes (ACCORD) and Secondary Prevention of Small Subcortical Strokes (SPS3) trials, did not confirm this concern.[56,57]

The Possible J-Curve Effect

Historically, elevated BP in older adults was considered a compensatory mechanism in the setting of increased vascular resistance, with no BP intervention necessary.[58] Modern hypertension treatment trials, however, confirm the beneficial CV outcomes with BP reduction in older adults.[59–61] On the other hand, the possible J-curve effect suggests that overly robust DBP reduction in patients with CV risk factors was associated with an increased incidence of myocardial infarction.[62] Coronary blood flow occurs during diastole, and it remains unclear at what BP threshold coronary hypoperfusion occurs with associated adverse CV events, especially in

very high-risk patients. Nevertheless, there is evidence both in favor and against the J-curve theory.[63,64]

Vulnerable groups potentially at highest risk for the J-curve effect include older women with hypertension, persons with diabetes and coronary disease, and frail older patients. Increasingly, when defining treatment target for high BP, consideration of potential harm of overtreatment is being given to these vulnerable groups.[65]

GOALS AND THERAPEUTIC BP TARGETS IN OLDER PERSONS

The recently published 2014 evidence-based guideline for the management of high BP in adults report from the panel members appointed to the Eighth Joint National Committee (JNC 8)[66] made a significant change in goal BP for older patients in the last National Heart, Lung, and Blood Institute–sponsored report, JNC 7.[67] The 2014 guideline suggests changing the BP target of <140/90 mm Hg to a target of <150/90 mm Hg in adults 60 years and older. The new recommended BP target was based on a rigorous analysis of evidence from six main randomized clinical trials: the Hypertension in the Very Elderly Trial (HYVET), the Systolic Hypertension in Europe (Syst-Eur) trial, the Systolic Hypertension in the Elderly Program (SHEP), the Japanese Trial to Assess Optimal Systolic Blood Pressure in Elderly Hypertensive Patients (JATOS), the Valsartan in Elderly Isolated Systolic Hypertension (VALISH) trial, and the Italian Study on the Cardiovascular Effects of Systolic Blood Pressure Control (CARDIO-SIS).[66] The HYVET study showed that among patients 80 years and older, a BP target of <150/80 mm Hg was associated with a statistically significant reduced risk of stroke, heart failure, and death from any cause.[68] Similarly, the SHEP study demonstrated a 36% reduction in stroke among hypertensive treated patients 60 years and older with a target SBP <155 mm Hg.[69] The average BP achieved in the treatment arm of the SHEP trial was 143 mm Hg. The JATOS trial on the other hand showed no statistically significant benefit of an SBP target <140 mm Hg in the primary endpoints of CVD and renal failure in patients 65 years and older.[70] The VALISH trial also showed no statistically significant difference in CV event reduction in patients 70 years and older with an SBP <140 mm Hg or >140 mm Hg to <150 mm Hg.[71] The JATOS and VALISH trials, in Japanese patients, may not adequately reflect the higher CVD risk of the US population. Based on these six studies, the 2014 guideline reported a lack of strong evidence to support the previously lower SBP target goal of <140 mm Hg for patients 60 years and older.

This controversial recommendation has been objected to by some societal groups,[72] and a recently published report from the minority committee of the 2014 guideline led by Wright and colleagues[73] proposed that the higher BP target for an age threshold of 60 years and older with less aggressive treatment was not uniformly accepted and lacks consistency. The concern is that increasing the goals for many of the more than 36 million Americans who are 60 years and older and have hypertension will result in a disproportionately negative impact on African American patients, women, and patients with chronic kidney disease and cerebrovascular disease. Moreover, hypertension is the largest most significant contributor of a 5.4-year decrease in life expectancy in African Americans compared with Caucasians.[74] Nevertheless, among adults 80 years and older, overtreatment is a valid concern and some epidemiologic studies suggest that there is an inverse relationship with BP and death.[75–77] Overall, there is general consensus for the BP treatment target goal of 150/90 mm Hg in people 80 years and older, which is well supported by the HYVET trial.[68]

The Systolic Blood Pressure Intervention Trial (SPRINT) is currently in the follow-up phase evaluating the significance of intensive (SBP <120 mm Hg) vs standard (SBP <140 mm Hg) BP in adults with hypertension, excluding diabetic patients and including patients with chronic kidney disease, age older than 80 years, nonfatal heart failure, and nonmyocardial infarction acute coronary syndrome (NCT01206062).

INNOVATIVE APPROACHES TO ADDRESS POLYPHARMACY IN HYPERTENSION AND CVD

Patients with hypertension take multiple medications for the treatment of other comorbid conditions (eg, hyperlipidemia, diabetes mellitus, peripheral arterial disease, coronary artery disease, and chronic kidney disease). According to a meta-analysis involving 376,162 patients, the adherence to CV medications at 24 months was 57%.[78] The authors in this meta-analysis noted no difference in adherence between the drug classes. Therefore, side effects of the individual drugs were not the reason for the reduction in adherence. There are several approaches to the management of polypharmacy. A recent Cochrane systematic review sought to determine which interventions, alone or in combination, are effective in improving the appropriate use of polypharmacy and reducing medication-related problems in older people. The studies reviewed were not conclusive in determining which approaches appeared beneficial in terms of reducing inappropriate prescribing.[79]

Fixed-Dosed Combination Pill Using Evidence-Based Medications

The concept of using a polypill has emerged as an enticing strategy to improve adherence and compliance and reduce cost in patients requiring multiple medications to reach goal therapy and improve CV outcomes.[12] Patients with hypertension are likely to be taking antiplatelets, β-andrenergic blockers, ACE inhibitors, angiotensin receptor blockers (ARBs), or statins in addition to their concurrent antihypertensive medications.

In a recently published review by Castellano and colleagues,[12] the authors categorized four important

reasons for medication nonadherence: patient-, illness-, provider-, and system-related factors. Clinical data from large randomized trials assessing the benefit of a fixed-dosed combination pill are lacking although multiple smaller trials that have evaluated both primary and secondary prevention of CVD using evidence-based CV medications were shown to improve treatment adherence and risk factor control. The recently published Fixed-Dose Combination Drug for Secondary Cardiovascular Prevention (FOCUS) study[11] is the first trial to analyze the impact of a polypill strategy on adherence in patients with post–myocardial infarction. The study was conducted in two phases. In the first phase, the risk for nonadherence was independently associated with younger age, depression, being on a complex medication regimen, poorer health insurance coverage, and a lower level of social support.[11] In phase 2 of the study, the authors showed approximately a 10%-point increase in adherence when the fixed-dose combination pill (containing aspirin 100 mg, simvastatin 40 mg, and ramipril 2.5 mg, 5 mg, or 10 mg) was compared with the three drugs given separately. The first approved polypill formulation (acetylsalicylic acid 100 mg, simvastatin 20 mg, and ramipril 2.5/5 mg) has been commercialized in Argentina, Dominican Republic, El Salvador, Honduras, Mexico, and Nicaragua. The second formulation (acetylsalicylic acid 100 mg, atorvastatin 20 mg, and ramipril 2.5/5 mg) has been approved by various agencies in Europe.[12,80]

The European Society of Hypertension and European Society of Cardiology recommend ACE inhibitor-thiazide diuretic, ARB-thiazide diuretic, ACE inhibitor-CCB, ARB-CCB, and CCB-thiazide diuretics as preferred combinations for management of hypertension.[81] Both societies favor the use of a fixed-dose or single-pill combination because it reduces pill burden and improves long-term adherence. A meta-analysis of about 40,000 patients with hypertension showed that a single-pill combination regimen was associated with improved adherence, persistence, and lower all-cause healthcare cost when compared with a free equivalent regimen.[82] In patients with hypertension, using a single-pill combination significantly reduces BP, reduces side effects, improves adherence, reduces healthcare cost, and potentially improves CV outcomes.[72,83,84]

Technologies to Improve Adherence

Ingestible Sensor System. Nonadherence may respond to innovative approaches such as utilizing an Ingestible Sensor System (ISS), a direct and reliable method of identifying drug use. The ISS technology is composed of an ingestible event marker (IEM) and an adhesive personal monitor (APM) that is affixed to the torso. A microsensor on the IEM becomes activated after ingestion and then transmits a signal to the APM. Using Bluetooth technology, data are transferred and stored in a smartphone. The detection accuracy, usability, and safety of ISS was studied in an uncontrolled pilot study involving 20 post–renal transplant patients with a mean follow-up period of 9.2 weeks.[85] There was 100% positive detection accuracy in 34 directly observed ingestions. Adherence was noted to be 99.4%. The ISS was well-tolerated, with seven reported skin reactions (two discontinuations because of rash) and two patients discontinued therapy because of diarrhea. The ISS technology could be particularly beneficial in monitoring of antiplatelet adherence post–myocardial infarction, especially in individuals with nonadherent behavior.

Electronic Reminder System. New technologies such as the Internet, cellular telephone, and automated voice advances can be used to notify patients to take medications and to monitor adherence from remote locations. The utilization of innovative medical technology such as automated filling of prescription medications has been shown to improve adherence and reduce polypharmacy and medication errors. Mobile phone applications could be used to facilitate communication between prescribers, pharmacists, and patients about medication changes and reminders.

Keep it Simple Approach. The most effective antihypertensive medications with the least drug-drug interactions should be initially prescribed. Medications and

TABLE II. SAIL and TIDE Mnemonics to Help Avoid Polypharmacy

SAIL	
S	Prescribing a Simple drug regimen; once-daily vs twice-daily dosing
A	Understanding potential drug Adverse effects
I	Provide clear Indication and therapeutic goal for each prescription
L	Provide a List of the names and dosage of each medication to the patient and a copy placed in the chart
TIDE	
T	When meeting with patients, allow Time to address medication issues
I	Understanding Individual variability, pharmacodynamics, and pharmacokinetics when prescribing medications
D	Review all medications to avoid potential Drug-drug interactions
E	Provide Education to the patient, significant others, and families on the drugs and nondrugs and potential adverse-related events

Data from Werder and Preskorn.[86]

herbal supplements without a proven indication should be reviewed and if necessary removed from the patient's medication list. For example, as a simple tool, Werder and Preskorn (Table II) used the mnemonic "SAIL" (Simple drug regimen, understanding of potential Adverse effects, clear Indication for prescription, List of the names, and dosage of each medication should be placed in chart and handed to patients).[86]

Medical Audits. Investing in medical audits that target older adults who are more likely to be taking multiple medications may decrease harmful outcomes. These medical audits should be mandated in order to have a meaningful impact on outcome. There should be financial incentives such as result-based financing or pay-for-performance to institutions that utilize these audits to improve medication error and reduce nonadherence.

CONCLUSIONS

Older adults on treatment for high BP are more likely to take more than two medications, and polypharmacy in this age group is associated with increased risk of adverse events (fall injury, hyperkalemia and hypokalemia, heart failure, and BP exacerbation), polypharmacy mismanagement, drug-drug interaction, and increased costs. Knowledge of drugs that interact with known antihypertensive agents is paramount to avoid or reduce adverse events, hospitalizations, and healthcare dollars. The use of innovative approaches such as use of a fixed-dose combination pill, ingestible sensor system, electronic reminder system, medical audits, and the integration of a pharmacist in the care of patients should be implemented to avoid polypharmacy mismanagement.

Disclosures: The authors have no conflicts of interest to disclose.

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