Impact of a Pill Box Clinic to Improve Systolic Blood Pressure in Veterans with Uncontrolled Hypertension Taking 3 or More Antihypertensive Medications

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ABSTRACT

BACKGROUND: Two-thirds of Americans who are prescribed antihypertensive medications are not at a blood pressure (BP) goal of < 140/90 mmHg, and low adherence is identified as a primary cause of inadequate control. Improved adherence to antihypertensive medications has been shown to enhance BP control and reduce the risk of cardiovascular complications. This study investigated the effectiveness of a pill box clinic to improve BP in veterans with uncontrolled hypertension taking 3 or more antihypertensive medications.

OBJECTIVES: To (a) investigate the reduction of systolic BP by 10 mmHg from pre-intervention to post-intervention (primary outcome) and (b) investigate the percentage of patients meeting goal blood pressure—as defined by *The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure* (JNC7)—and percentage of patient adherence to antihypertensive medications (secondary outcomes).

METHODS: Patients with uncontrolled hypertension currently taking at least 3 antihypertensive medications were enrolled in this prospective pre/post study. Under the supervision of a pharmacist, each patient was provided two 7-day pill boxes to organize all antihypertensive medications. In addition, baseline BP and previous history of nonadherence were documented. Following the initial encounter, patients attended 2 follow-up appointments, at 2 and 4 weeks, for refill of pill boxes, BP measurement, and adherence assessment. A chi-square test was used for categorical outcomes and logistic regression for nominal outcomes as well as descriptive statistics, as appropriate.

RESULTS: Sixty patients were enrolled, with 50 completing appointments 1 and 2, and 45 completing all 3 appointments. Of those, 24% and 31% achieved at least a 10 mmHg reduction in systolic BP from baseline to appointments 2 and 3, respectively ($P=0.438$). Systolic BP readings for appointments 1, 2, and 3 were not statistically significant (mean [SD]: 134.1 [11.8], 131.9 [9.4], and 130.6 [11.4], respectively). Goal BP per JNC7 was achieved by 44% and 51% of patients at appointments 2 and 3, respectively, compared with baseline ($P=0.201$). All patients had ≥ 80% adherence to antihypertensive medications, assessed via pill counts at the second and third appointments.

CONCLUSION: Although results were not statistically significant, the pill box clinic resulted in clinically significant reductions in systolic BP by 10 mmHg, as well as an increased number of patients meeting prescribed BP goals.

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What is already known about this subject

- Of patients receiving antihypertensive treatment, 50% discontinue therapy within the first year of diagnosis, and of those that remain on therapy, approximately half are >80% adherent to antihypertensive medications.
- Causes of patient nonadherence to antihypertensive medications have been linked to adverse effects of antihypertensive medications, complicated drug regimens, lack of understanding about hypertension management, and absence of patient motivation.
- Measures that health care providers take to improve adherence consist of improved communication with the patient, increased educational opportunities for the patient, simplification of therapeutic regimens, more frequent clinic appointments, and the use and organization of pill boxes or reminder calendars.

What this study adds

- Results from this study indicated that pill box clinics could achieve a clinical reduction in systolic blood pressure by 10 mmHg.
- This study demonstrated that a pill box clinic conducted by pharmacists in a rural veteran population increased the number of patients meeting prescribed blood pressure goals.

Advancements in the American health care system over the last 40 years have increased awareness of the effects of hypertension and appropriate antihypertensive treatment.[1] Despite this increased awareness, more than 50 million Americans are estimated to still suffer from uncontrolled hypertension.[2,3] Two-thirds of Americans receiving treatment for hypertension did not meet the goal blood pressure (BP) of < 140/90 mmHg (millimeters of mercury) recommended by *The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure* (JNC7).[1] Contributing factors include inappropriate treatment regimens and nonadherence, of which nonadherence is proposed as the most common cause of suboptimal response to antihypertensive therapy.[4]

Studies have shown that more than 50% of patients receiving antihypertensive treatment discontinue therapy within

a year of diagnosis, and only half of patients remaining on therapy are >80% adherent to antihypertensive medications.[5,6] A prevalent factor associated with patient nonadherence to antihypertensive medications is the asymptomatic characteristic of hypertension.[7-9] Patient nonadherence to antihypertensive medications has also been linked to adverse effects of antihypertensive medications, complicated drug regimens, misunderstanding of hypertension management, and lack of patient motivation.[10] Regardless of the etiology of nonadherence, patients are less likely to achieve optimal BP control, thereby increasing the risk of complications, including heart disease, stroke, renal disease, and atherosclerotic disease.[11,12] Risk of these complications increases with age and higher baseline BP but decreases with appropriate use of antihypertensive medications as prescribed.[13,14]

A systematic review of randomized trials that evaluated the effectiveness of several measures proposed to enhance adherence revealed that adherence to all medications was improved significantly after introduction of pill boxes.[15] More specifically, demonstration of enhanced adherence and thereby improved outcomes has been reported with antiretroviral therapy, as found by Petersen et al. (2007), who assessed the relationship between pill box use and adherence to antiretroviral therapy in patients with human immunodeficiency virus (HIV) taking >3 antiretroviral medications.[16] Adherence was measured by unannounced pill counts at the place of the patient's usual residence every 3 to 6 weeks for a period of 12 months. After adjustment for confounding variables, pill box use was found to improve adherence by 4.1% to 4.5%, thus reducing the progression of HIV to AIDS by 11%. Petersen et al. proposed that patients with other chronic disease states, such as hypertension, would likely benefit from use of pill boxes, since adherence is essential for management.[16]

Another study where pill boxes demonstrated improved adherence and outcomes was completed by Nochowitz et al. (2009), who assessed the adherence of patients with a history of poor adherence to chronic warfarin therapy after introduction and organization of a 28-day pill box over a 3-month period in a pre/post study.[17] International normalized ratio (INR) was measured at the initial appointment and all follow-up appointments. Adherence to clinic appointments and time spent in therapeutic INR range significantly improved, and incidence of subtherapeutic INR significantly decreased from pre-intervention to post-intervention. Overall, a 77% improvement in both adherence and time spent in therapeutic INR range after implementing pill boxes was reported.[17]

As identified in antiretroviral and anticoagulation therapies, enhanced patient adherence improves disease state management and prevents complications. Burnier et al. (2001, 2005) demonstrated that implementation of adherence monitoring for refractory hypertension improved BP control, proving the vital role health care providers have in enhancing patient adherence.[18-19] However, we were unable to identify any published literature detailing the value of pill boxes specifically in hypertensive patients with uncontrolled BP. Because of the lack of literature available, the pill box trial was designed to evaluate the effectiveness of a pill box clinic to improve BP.

Methods

Study Design

This prospective study employed a pre/post design to evaluate the effectiveness of a pill box clinic over a 4-week period for the management of uncontrolled hypertension at a rural Veterans Affairs Medical Center (VAMC). The study complied with the Declaration of Helsinki and the International Conference on Harmonization/Good Clinical Practice Guidelines and was approved by the on-site VAMC Institutional Review Board (IRB). All study investigators were pharmacists at the VAMC during the study period.

The primary outcome was reduction of systolic BP (SBP) by 10 mmHg from pre-intervention to post-intervention. Secondary outcomes were percentage of patients meeting goal BP as defined by JNC7 and patient adherence to antihypertensive medications. Goal BP was defined as <130/80 mmHg for patients with a diagnosis of diabetes mellitus (DM) and <140/90 mmHg for all other patients. Patient adherence to antihypertensive medications was assessed at the 2 follow-up appointments from pill counts conducted by a pharmacist. Antihypertensive medication adherence was calculated using the medication possession ratio (MPR), a comparison of the number of doses the patient missed and the number of prescribed doses during a defined time.[20] MPR is equivalent to the number of doses taken over a specified time period, divided by the number of doses prescribed over the same time period. An MPR of ≥80% was considered adherent, as is standard in clinical practice.[21]

Based on pharmacokinetics of antihypertensive medications, lack of need for laboratory evaluation, and a sole purpose to evaluate change in BP with implementation of pill box use, we decided that a change in BP could be evaluated within a matter of weeks rather than months. Therefore, the duration of this study was approximately 4 weeks.

Participant Selection

Potentially eligible study patients were identified (a) from an onsite database of patients with a BP reading above goal per JNC7 in the previous 6 months and (b) through referrals from the pharmacist-managed cardiovascular risk reduction clinic between September 2010 and July 2013. Inclusion and exclusion criteria were employed to determine whether patients identified from the onsite database and the cardiovascular risk reduction clinic were eligible for participation.

Patients were contacted via mailed letter or in person, if determined to be preliminarily eligible for enrollment. If the patient was deemed eligible for enrollment per discussion with the pharmacist and was willing to participate, an appointment was scheduled to obtain patient consent. Patients were consented with VAMC IRB-approved consent forms prior to participation. Patients were terminated from the study if any of the following occurred: adjustment of antihypertensive medication regimen, admission to the emergency department or hospital for a cardiovascular-related event, or failure to follow directions of the study to eliminate variables that could impact BP control and misrepresent results.

Inclusion criteria for the study were diagnosis of hypertension for at least 1 year, current treatment with 3 or more antihypertensive medications, and 3 consecutive BP readings above goal per JNC7 in the previous 6 months at outpatient appointments within the VAMC facility. Antihypertensive medications were defined as any medication with the potential to lower BP, including the following classes: alpha$_1$ blocker, angiotensin-converting enzyme inhibitor, angiotensin II receptor blocker, beta blocker, calcium channel blocker, central alpha$_2$-agonist, direct arterial vasodilator, direct renin inhibitor, diuretic, and peripheral adrenergic antagonist.

Exclusion criteria for the study were aged >80 years, dementia (including Alzheimer's disease), impaired vision or legal blindness, illiteracy without management of medications by a caregiver, enrollment in Home Based Primary Care, current use of a pill box, antihypertensive medication prescribed by a non-VAMC provider, current prescription of a medication known to increase BP, scheduled appointment within the study period where antihypertensive therapy could potentially be modified, and BP reading >180/110 mmHg within the previous 6 months. Management of medications by a caregiver was determined via verbal questioning during appointment 1 and documented if confirmed by patient and caregiver. Medication profiles, including non-VAMC medication lists, were reviewed to determine whether patient was on medications known to increase BP, such as cyclosporine, nonsteroidal anti-inflammatory drugs, decongestants, and ephedra. Patients were also questioned regarding over-the-counter medication use during the first appointment.

Intervention Procedures

Patients enrolled in the study attended 3 appointments at the on-site pill box clinic. Baseline characteristics obtained were age, sex, number of antihypertensive medications, antihypertensive medication classes, comorbidities, diagnosis of nonadherence, and management of medications by caregiver.

At the first appointment, patients received two 7-day multislot pill boxes to organize antihypertensive medications. Antihypertensive medications, brought in by the patient, were verified by the pharmacist using the patient's electronic medical record. After verification, the patient or patient caregiver organized the antihypertensive medications in both pill boxes. Appropriate filling of the pill boxes was confirmed by the pharmacist. If initial pill box fill by patient or patient caregiver was inaccurate, compared with prescription instructions, the pharmacist demonstrated appropriate filling measures by reading instructions on the prescription vial and prompting the patient or patient caregiver to refill the pill box. Two post-intervention appointments at the pill box clinic were conducted at 2-week intervals to assess BP and adherence. During study visits, no educational interventions were implemented. To eliminate confounders, patients were not educated on health conditions or medications, encouraged to complete home-based monitoring, or make lifestyle modifications, as typically completed in a hypertension encounter.

BP measurement was obtained using the CAS Medical System Monitor (CASMED, Branford, CT). If the BP was above goal per JNC7, BP was rechecked manually by the pharmacist. If 2 readings were obtained, the reading with the lower BP was recorded. To ensure accuracy of BP measurement, the following procedures were implemented for the study: confirmation of antihypertensive medication administration prior to appointment, selection of appropriate cuff size based on circumference of the upper arm, and confirmation the patient was in a seated position for at least 5 minutes prior to measurement.

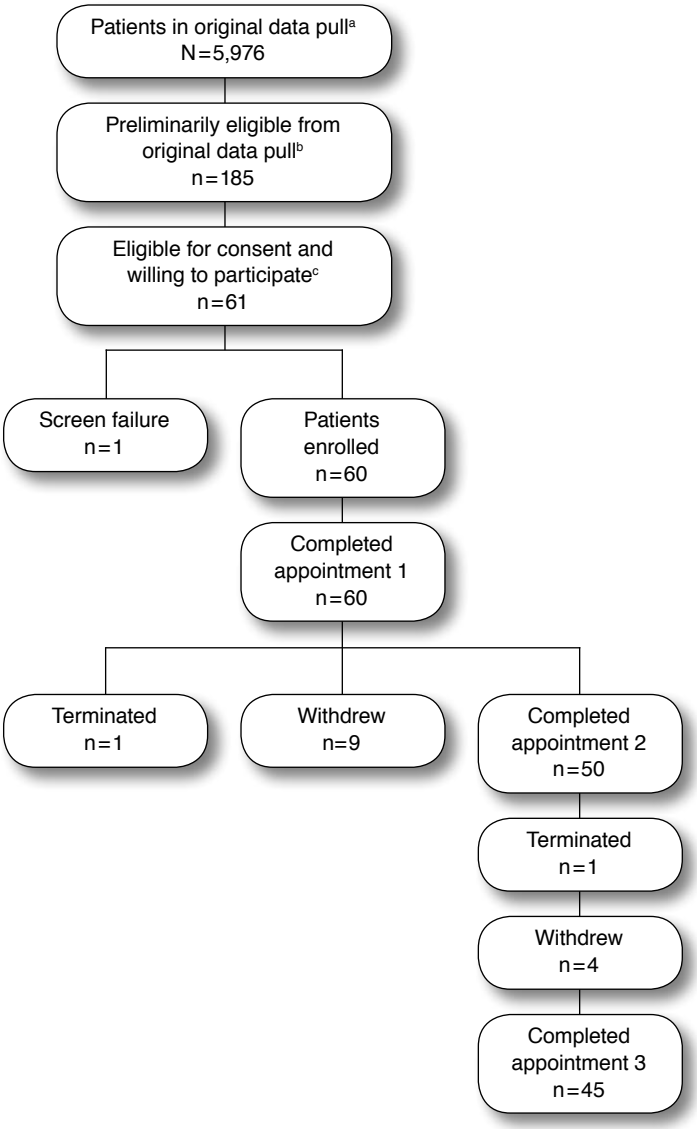
Statistical Analysis

Enrollment of 50 patients was estimated to provide 80% power to detect a 10 mmHg decrease in SBP from pre-intervention to post-intervention. Sixty patients were then enrolled to account for patients lost in follow-up. A chi-square test was used for categorical outcomes, including the primary outcome, whether SBP decreased by 10 mmHg from pre-intervention to post-intervention, and the secondary outcome, the percentage of patients meeting BP goal. Descriptive statistics such as arithmetic mean and standard deviation were reported for patient demographics and other clinical variables examined in the study. Logistic regression analysis was performed on the nominal outcome variables at the second and third appointments. The input variables used in the logistic regression models were number of antihypertensive medications, gender, and comorbidities, including DM, heart failure, and dyslipidemia. A *P* value less than 0.05 was considered significant.

Results

Review of the on-site database showed that 5,976 patients at the facility had a BP measurement above goal per JNC7, documented within the previous 6 months (Figure 1). Of those patients, 185 were identified as preliminarily eligible to participate in the pill box trial. The preliminarily eligible patients, and patients deemed eligible in the pharmacist-managed cardiovascular risk reduction clinic, underwent discussion with a

FIGURE 1 Selection of Patients



[a]*With an above-goal blood pressure reading in previous 6 months.*
[b]*Eligible for participation upon review of electronic medical record.*
[c]*Eligible for enrollment after discussion with pharmacist and willing to participate.*

TABLE 1 Baseline Characteristics

Number of patients	60
Age, years	
Mean ± SD	62 ± 6.18
Gender, n (%)	
Male	58 (96.7)
Female	2 (3.3)
Race, n (%)	
Caucasian	40 (66.7)
African-American	16 (26.7)
Other	2 (3.3)
Not disclosed	2 (3.3)
Antihypertensive medications	
Mean ± SD	3.8 ± 1.22
Antihypertensive drug class, n (%)	
ACE-I	36 (60.0)
ARB	19 (31.7)
Beta blocker	41 (68.3)
Calcium channel blocker	47 (78.3)
Thiazide diuretic	33 (55.0)
Aldosterone antagonist	4 (6.7)
Combination	3 (5.0)
Other[a]	43 (71.7)
Diagnosed comorbidity, n (%)	
DM	50 (83.3)
Dyslipidemia	44 (73.3)
CHF or HF	6 (10.0)
CAD	14 (23.3)
CKD	11 (18.3)
PVD	3 (5.0)
BP goal, n (%)[b]	
< 130/80 mmHg	50 (83.3)
< 140/90 mmHg	10 (16.7)
Patient nonadherence diagnosis, n (%)	2 (3.3)
Management of medications by caregiver, n (%)	3 (5.0)

[a]*Alpha$_1$ blocker, direct arterial vasodilator, direct renin inhibitor, loop diuretic, peripheral adrenergic antagonist.*
[b]*From the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.*[1]
ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; BP = blood pressure; CAD = coronary artery disease; CDK = chronic kidney disease; CHF = congestive heart failure; DM = diabetes mellitus; HF = heart failure; PVD = peripheral vascular disease; SD = standard deviation.

pharmacist to determine full eligibility. After determination of full eligibility by the pharmacist, 61 patients expressed willingness to participate. Following consent, 1 patient opted not to participate in the pill box trial, resulting in 1 screen failure and a total enrolled population of 60 patients, including 2 female and 18 minority patients. Thirteen patients withdrew from the study, and 2 patients were removed prior to completion. This exclusion included 1 patient terminated due to cardiovascular-related hospitalization and 1 terminated due to potential adverse effect with syncope, resulting in an emergency department visit. Baseline characteristics were collected for the 60 enrolled patients (Table 1). The mean age of study participants was 62 years, ranging from 46 to 76 years. More than 83% of the population had a concomitant diagnosis of DM and a BP goal of < 130/80 mmHg, while the remaining 17% of participants had a goal of < 140/90 mmHg per JNC7. Only 5% of patients had documentation of medications being managed by a caregiver. The number of antihypertensive medications patients were taking at study enrollment ranged from 3 to 7, with a mean of 3.8. The mean baseline SBP was 142 mmHg and mean baseline

TABLE 2 Primary Outcome

Appointment	SBP	(SD)
1	134.1	(11.8)
2	131.9	(9.4)
3	130.6	(11.4)

SBP = systolic blood pressure; SD = standard deviation.

diastolic BP (DBP) was 80 mmHg. The study found that 24% of patients had a SBP decrease of 10 mmHg or more at the second appointment, while 31% of patients had a similar SBP decrease of 10 mmHg at the third appointment, achieving the primary outcome. There was no statistical difference in the response between the 2 appointments ($P = 0.438$). SBP readings for appointments 1, 2, and 3 were not statistically significant (mean [standard deviation]: 134.1 [11.8], 131.9 [9.4], and 130.6 [11.4], respectively) as shown in Table 2. At appointment 2, 44% of patients met goal BP, while 51.1% met goal BP at appointment 3. However, the margin of difference between the 2 appointments was not significant ($P = 0.201$). All patients had ≥80% adherence to antihypertensive medications, assessed via pill counts at the second and third appointments. The logistic regression analysis showed that 3 factors were of significance to explain meeting BP goal at appointment 2. These were race ($P = 0.0164$), number of antihypertensive medications ($P = 0.0392$), and comorbidity heart failure ($P = 0.0287$, $R^2 = 0.5649$). Of patients meeting BP goal at appointment 3, comorbidity DM was the only factor significantly associated with the outcome ($P = 0.0045$, $R^2 = 0.6954$) as detailed in Table 3.

Discussion

While statistical significance was not achieved in the primary or secondary outcomes assessed in the pill box trial, the data revealed a numeric reduction in SBP from baseline. In addition, the percentage of patients achieving goal BP increased from baseline. This increase in percentage suggests that in a veteran population, BP goals are more likely to be met when antihypertensive medications are organized in a pill box, and use of the pill box is monitored by a pharmacist.

Modest reductions in SBP can have significant impact on reducing risk of cardiovascular events. Reduction of SBP by 5 mmHg decreases mortality due to stroke and coronary heart disease by 14% and 9%, respectively.[22] Presumably, greater cardiovascular benefit is reported with further reduction of BP. SBP reduction of 12 mmHg over 10 years in patients with stage 1 hypertension (SBP 140 to 149 mmHg and DBP 90 to 99 mmHg) and cardiovascular risk factors prevents 1 cardiovascular disease event for every 11 patients. In patients with stage 2 hypertension (SBP > 160 mmHg and DBP > 100 mmHg) and cardiovascular risk factors, the same SBP reduction prevents 1 cardiovascular disease event for every 7 patients.[23] In the pill box trial, 42% of patients achieved a 5 mmHg SBP reduction, and 22% achieved a 12 mmHg reduction from baseline. In the current study, findings are clinically significant, as SBP reduction is known to improve morbidity outcomes by reduction of cardiovascular events, and continued use of a pill box over a lifetime would likely yield benefits spanning much greater than the 4 weeks observed in the pill box trial.

TABLE 3 Logistic Regression of Secondary Outcome, Meeting Goal BP

	Nparam	DF	L-R Chi-square	Prob > Chi-square
Appointment 2				
Race	9	9	20.255	0.0164[a]
Gender	3	3	2.945	0.4002
Number of anti-HTN medications	3	3	8.356	0.0392[a]
DM	3	3	2.057	0.5606
HF	3	3	9.046	0.0287[a]
Dyslipidemia	3	3	4.874	0.1812
Other (CAD, CKD)	15	15	24.450	0.0578
Appointment 3				
Race	12	12	15.778	0.2016
Gender	4	4	5.591	0.2318
Number of anti-HTN medications	4	4	3.575	0.4666
DM	4	4	15.097	0.0045[a]
HF	4	4	2.720	0.6057
Dyslipidemia	4	4	7.102	0.1306
Other (CAD, CKD)	20	20	31.123	0.5350

[a]*Statistically significant.*

CAD = coronary artery disease; CKD = chronic kidney disease; DF = degrees of freedom; DM = diabetes mellitus; HF = heart failure; HTN = hypertension; L-R = likelihood ratio; Nparam = number of parameters; Prob = probability.

We also recognized advantages afforded by the design of the pill box trial beyond the distribution of pill boxes and organization of antihypertensive medications in the boxes. All pill box filling in the trial was supervised by a pharmacist, since we believed the effectiveness of pill boxes to be related to appropriate filling. The pharmacist supervision and the frequent follow-up appointments—every 2 weeks assessing patient adherence—likely contributed to the beneficial outcomes reported.

While the clinical efficacy of adherence programs is well documented in the literature, cost analysis is necessary for widespread implementation of pill box clinics in clinical practice. Identification of a positive relationship between cost of intervention and relative impact on adherence has been reported, validating the financial benefit of improved adherence.[24,25] Most published studies to date have used pharmacists in the interventions, but we propose that other health care providers could facilitate pill box filling, as opposed to a strictly pharmacist-driven effort, in order to increase overall cost efficiency.

Limitations

Limitations of the trial that may have affected the results and contributed to the absence of statistical significance include the population recruited and the trial design. First, the population recruited may not be easily extrapolated to a general population, since the majority of patients were Caucasian males more than 80% of whom were diagnosed with DM. Having this large percentage of patients with DM potentially resulted in difficulty demonstrating a robust BP reduction because of the lower BP goal of <130/80 mmHg. Also of note, patients willing to participate in a clinical trial may be considered more motivated and therefore more adherent to antihypertensive medications in comparison to a broader population. Finally, as is customary, patients were made aware of the objectives of the trial when they consented, which could have increased adherence to antihypertensive medications during the study period.

We also recognized aspects of the trial design as limitations. First, the exclusion of patients with a BP reading >180/110 mmHg in the previous 6 months was used because such patients would be candidates for antihypertensive medication changes during the study, which was predefined as a factor leading to termination. In retrospect, this criterion may have excluded patients who were nonadherent to antihypertensive medications and could have benefited from the trial. Second, since the trial evaluated adherence to antihypertensive medications specifically, per trial design, no other medications could be added to the pill boxes. This restriction may have made medication management more cumbersome during the study duration, since medications other than antihypertensive medications would be located somewhere besides the pill boxes. Third, during appointments, if 2 BP readings were obtained, the lowest reading was recorded and analyzed at conclusion of the study. We recognize this selection of the lower reading is not a recommended practice via guidelines, but it is clinical practice at the participating VAMC facility. Finally, with literature published since the original design of the pill box trial, BP goals in current clinical practice may differ. During the initial design of the trial, JNC7 was the preferred guideline for establishing BP goals at the facility, and using that guideline, goals of <130/80 mmHg for patients with DM, and <140/90 mmHg for all other patients, were implemented. Publication of the *American Diabetes Association Standards of Medical Care in Diabetes 2013* recommended a different BP goal for patients with DM, <140/80 mmHg, which was adopted into clinical practice at the facility.[26] An amendment to the trial protocol was considered to adjust goals, but it was determined to affect the statistical analysis and therefore declined. During the writing of the manuscript for this article, additional BP recommendations were published in JNC8. In light of that change, the goals set in the pill box trial are not likely to be the same as goals currently used in clinical practice, given the new evidence, but we believe that pill boxes are beneficial in the treatment of hypertension, regardless of the BP goal.

Despite these limitations, we continue to support use of a pill box, monitored by a health care provider via clinic or other means, to improve overall adherence and outcomes in patients with uncontrolled hypertension. As even modest reductions in SBP have been shown to improve hypertension outcomes, we propose that total care of the patient is improved and addition of unnecessary antihypertensive therapy is reduced with implementation of pill boxes.

Conclusion

Although results were not statistically significant, the pill box clinic resulted in clinically significant reductions in SBP by 10 mmHg, as well as an increased number of patients meeting prescribed BP goals. The findings from this pre/post prospective study suggest BP goals are more likely to be met when antihypertensive medications are organized in a pill box, and use of the pill box is monitored by a pharmacist.

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