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Title
Pilot Study of a Somatosensory Intervention to Improve Medical Adherence in Patients with Uncontrolled Hypertension

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Abstract

Background
Essential hypertension is the most common primary diagnosis in the US, with myriad and serious sequelae inflicting significant morbidity upon individuals and economic losses upon society. Estimates of adherence to prescribed medication regimens range from 20% to 60%. Because hypertension is largely asymptomatic, patients may underestimate both the benefits of adherence and the costs of nonadherence. This novel educational intervention seeks to encourage adherent behavior by providing patients with a conscious manifestation of their disease severity through manipulation of pressurized balls.

Methods
Randomized controlled pilot trial of patients under treatment for hypertension with SBP ≥140mmHg or DBP ≥90mmHg at index visit, selected by convenience sample at a VA Primary Care Clinic. Baseline clinical, demographic, medication taking habits and motivation data obtained by surveys and chart abstraction. All subjects received a short talk on the dangers of hypertension. Intervention Group subjects simultaneously squeezed rubber balls in each hand filled to air pressures differing by the same amount that their current SBP exceeded 120mmHg. Followup medication taking habits, motivation, medication possession ratios and blood pressure measurements were determined by telephone survey, pharmacy and clinical records over 90-, 180-, 270- and 360-day time periods. Feasibility of a larger study was determined by structured interviews with a physician and nurse who employed the intervention in clinical practice.

Results
Thirty subjects were enrolled into Intervention and Control Groups of equal size. Immediate motivational impact by 7-point scale significantly favored the Intervention (6.3, $p < 0.001$ vs 4.3, $p = 0.164$). Change in self-reported adherence on an 8-point scale at 90-days favored the Intervention but was not significant (0.5, $p = 0.372$ vs -0.1, $p = 0.798$). Change in 360-day medication possession ratio favored the Intervention and approached significance (11.3%, $p = 0.088$ vs 0.7%, $p = 0.934$). Both Groups demonstrated clinically relevant improvements in MAP with greater magnitude, duration and significance for the Intervention Group through 360 days (-12.2mmHg, $p = 0.008$ vs -6.0mmHg, $p = 0.164$). Larger improvements in adherence were significantly associated with greater baseline motivation and immediate motivational impact from the intervention while longer disease experiences were associated with less improvement. Clinicians reported favorable reception from their patients and felt that the intervention represented a simple and helpful tool that they would use in everyday practice.

Conclusions
The results of this pilot trial suggest that a novel, brief educational intervention designed to provide a somatosensory manifestation of an otherwise asymptomatic disease process may show promise in promoting adherent behavior and clinically useful reductions in blood pressure in patients with poorly controlled hypertension. A larger study appears feasible and is required to confirm and investigate the statistical significance of these results.

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Introduction

Essential hypertension is the most common primary diagnosis in the United States (1). Defined in adults as a systolic blood pressure (SBP) greater than 140mmHg or diastolic (DBP) of greater than 90mmHg, high blood pressure has been linked to a myriad of disorders including stroke, heart disease, renal disease, ocular disease and aortic dissection. More than sixty-five million Americans have blood pressure high enough to warrant treatment (2-4). Worldwide estimates of hypertension prevalence approach one billion individuals resulting in 7.1 million deaths annually. The World Health Organization estimates that 62% of cerebrovascular disease and 49% of ischemic heart disease are sequelae of high blood pressure (5, 6). Other studies find that death from ischemic heart disease, kidney disease and stroke increases progressively and linearly with severity of hypertension (7, 8). The Framingham Heart Study found that normotensive sixty-five year olds who live to eighty-five have a 90% chance of becoming hypertensive in the intervening years (9). Economists estimate that the costs of hypertension in the United States alone exceed $100 billion annually (10).

The insidious and insensible nature of hypertension makes the disease easy for the patient to miss, minimize or deny. Approximately 30% of hypertensive adults are unaware of their condition. More than 40% of hypertensive individuals are not under treatment and an estimated 53% of patients do not have their SBP controlled to less than 140mmHg (11). The efficacy of antihypertensive medicines in reducing blood pressure and the incidence of clinical sequelae when taken appropriately is well documented (12, 13). Failure to attain recommended targets can be due to many different phenomena including

poor adherence to hypertensive medication and prescribed medical regimes, a problem which is particularly prevalent in asymptomatic and chronic diseases (14, 15). Of those who are under treatment, estimates of adherence with antihypertensive medical regimes range from 20 to 60% (16-21). Recommendations regarding lifestyle modification are even less likely to be followed with estimates of adherence ranging from 20% to 30% (22). An estimated 15% of nonelective hospital admissions are due to poor medical adherence (23) and the US Chamber of Commerce estimates the cost of poor antihypertensive medical adherence at $13 to 15 billion per year (24). Thus, effective approaches to improve adherence have the potential to significantly affect morbidity and mortality in patients and decrease health care costs.

"Adherence" and "compliance" are synonyms, classically defined as the extent to which a patient's behaviors coincide with health care providers' recommendations for health and medical advice (25). Recently, medical practitioners and researchers have shifted away from use of compliance, in favor of adherence in order to better recognize the patient's responsibility, agency and involvement in therapeutic decisions and encompass their ability and willingness to abide by a prescribed therapeutic regimen (26). Nonadherence is typically characterized as purposeful or incidental. Purposeful nonadherence refers to willful departure from the recommendations of the physician, for example "I just don't think I need medication." Incidental nonadherence involves unintentional and nonsystematic departures from the prescribed treatment plan, for example "I ran out of/lost my pills" (15, 27). Forgetfulness and discomfort with side effects are consistently found to be the most prevalent explanation for incidental and

purposeful antihypertensive nonadherence respectively (18, 28, 29). Estimates of these components' contributions to aggregate nonadherence vary, but one study's findings of 42% incidental and 15% purposeful are representative of values commonly found in the literature (15). Poor adherence manifests along a spectrum: the patient may fail to take any medication, may discontinue prematurely or may take medication in a manner that deviates from the prescription (30).

A significant body of work evaluates factors associated with poor adherence. Certain demographic and clinical variables have been shown to be inconsistently associated with compliance levels: age, gender, race, education, employment status, socio-economic status, presence or absence of symptoms, quality of followup, complexity and duration of regimen, side effects and certain comorbidities (15, 31-34). In addition, investigators have examined the impact of financial, psychosocial and behavioral factors such as cost of medication, level of insight into illness, belief in the benefit of treatment, fear of dependence on drugs, fear or intolerance of side effects, religious beliefs, knowledge about hypertension, support networks, quality of therapeutic alliance, access to and satisfaction with the healthcare system, depression, internal versus external perceived loci of control and alcohol use (35-39).

In fact, when a patient weighs their personal experience with a drug's beneficial and deleterious effects, costs and their understanding of the risks associated with nonadherence, it may seem rational to forgo their medication (14, 40). Studies have found that nonadherent patients are usually able to justify their actions through rational

arguments that take into account their symptoms, side-effects and personal circumstances (29). The fact that these arguments are often predicated on misunderstanding of a drug's purpose, side effects or symptomatic target does not lessen their weight in the decision making process. This rationalist approach is given an analytic framework in the Health Belief Model (HBM) which posits that people seek to avoid illness if the treatment is perceived to be less deleterious than the illness itself as assessed along four core beliefs: 1) motivation - degree of interest in and concern about their health; 2) susceptibility - perceptions of vulnerability to sequelae; 3) severity - perceptions concerning the seriousness of the consequences of nonadherence and; 4) benefits and costs - evaluation of the treatment's efficacy balanced against barriers such as cost and side effects (41). In the words of one patient, "I mean, it seems to me that like everything else it was a question of balancing the risks. You always have risks if you have long term medication because in a sense you become dependent on it, but on the other hand if you don't take them, then you risk... heart problems and strokes and all the other things which happen as a result of high blood pressure" (42). In the HBM framework, the decision to forego the prescribed therapy is simply the result of the patient's personal weighting of these often nebulous factors.

This weighting process emphasizes the importance of sufficient understanding of illness in forming an accurate assessment of the severity of the disease and costs of nonadherence such that they are not underestimated. Lack of knowledge of the symptoms (or lack thereof), basic pathophysiology and treatment regarding disease compromises the adherence decision and thus the success of outpatient therapy (43). In

this regard, hypertension presents a particular challenge because the cues of pain and discomfort that normally prompt people to seek and follow the advice of a medical professional are absent. In addition, medical treatments for hypertension lack the negative reinforcement of conscious symptom alleviation that can help drive adherence for other maladies. As a result, treatment is encouraged through appeals to abstract health advantages, long-term benefits and decreased risk of future disease (29). Both the risks of nonadherence and the benefits of treatment are remote and abstract while the side effects and cost of medication are quite real and concrete. Studies comparing beta-blockers prescribed for angina and hypertension found significantly lower adherence rates for hypertension despite the fact that both diseases are associated with substantial cardiac morbidity (44, 45). Other studies concluded that patients who perceive hypertension as a symptomatic disease have higher rates of medical adherence (15).

Patient motivation also plays a role in adherence behavior and is interwoven with the concepts of knowledge of costs and benefits of treatment and disease insight. One widely-studied framework of motivation and competence, Self-Determination Theory (SDT), posits that different kinds of motivation underlie health behaviors and thus outcomes and exist along a continuum of autonomy (46). Autonomous, self-derived forms of motivation (e.g. “I take my hypertension pills because I believe it is the best thing for my health”) are associated with positive health behaviors including medical adherence. Interventions shown to increase autonomous forms of motivation are associated with better health outcomes (47-49). In contrast, “controlled” or externally derived motivations (e.g. “I take my hypertension pills because others would be upset

with me if I didn't") are linked to poorer adherence and well-being (50). Because autonomy and agency are key to successful behavioral change, SDT further proposes that health interventions require a process of proactive internalization in which people take in and integrate the motivations and competencies initially reinforced by an external source (e.g. physician, family members or the media) (46, 47). This process of internalization opens up opportunities for interventions seeking to improve the health behaviors of the poorly adherent hypertensive patient.

Given the diversity of barriers to adherence, it is unsurprising that an optimal intervention for its improvement remains elusive. Scholars have produced more than fifty well-designed RCTs exploring methods to increase antihypertensive adherence rates (51). These studies can be broadly categorized into four approaches: 1) patient education, 2) simplification of dosing regimens, 3) patient motivation, support and reminders and, 4) complex initiatives including more than one of these approaches. These interventions employ diverse modalities including: lecture, interactive and programmed instruction sessions (52-55), worksite access to medical advice (56, 57), self-monitoring of blood pressure (54, 56, 58), psychological counseling (49), reward systems (56, 58), home visits or phone calls from care providers or researchers (53, 59, 60), and special reminder medicine packaging (43) among many others. Design and implementation of antihypertensive intervention studies are highly heterogeneous and their efficacy varies widely. For example, dose simplification studies have resulted in relative improvements of 8% (61) to 19.6% (62) as measured by pill count and electronic monitoring

respectively. Studies of behavioral interventions cite improvements from 5% (53) to 12% (63) by self-report and pill count.

Studies of the effects of educational efforts regarding hypertension's dangers, progression and sequelae on adherence have produced mixed results. Some investigators have found that the predictive value of higher levels of disease knowledge is strongest with short-term rather than long-term treatments (64). Several studies find that frequent blood pressure monitoring (a form of recurrent information as to disease severity) is associated with both adherence and with return to a drug regimen for nonadherent patients (23, 65). Researchers have found that for patients with chronic conditions, the adherence levels of newly diagnosed patients were more likely to respond positively to educational efforts than those with longer disease experiences (66). Often, educational efforts must challenge well-entrenched beliefs that are at odds with the diagnosis, for example "I can't have hypertension because I don't feel stressed", or "I can't be sick because I don't feel sick" (67, 68).

Meta-analyses have identified intervention types that appear to have a "significant" (but widely varying) impact on increasing patient adherence and improving clinical outcomes (69-73). Although not amounting to a consensus among researchers, several reviews cite improvements following multi-approach, patient-specific interventions (69, 71, 72, 74). Researchers have repeatedly found that successful interventions typically involve longitudinal application of combinations of approaches and modalities. For example, in an analysis of 16 educational interventions using indirect adherence metrics, the average

effect size almost doubled when a behavioral component was added (71). Unfortunately, multi-approach and longitudinal, multi-contact initiatives tend to be complex, time consuming and expensive. As a result, reviewers cite the need for work on simpler, more cost-effective interventions capable of being efficiently integrated into routine clinical practice (75).

The Medical Research Council has provided guidance stressing the importance of pilot work to refine the design of adherence interventions prior to embarking on a definitive trial (76). As such, the aim of this project is to address the utility and feasibility of a full scale study to add a simple, brief, patient-specific somatosensory component to the experience of hypertension, a disease where conscious sensory feedback is otherwise unavailable. Searches of the literature (PubMed.org on December 12, 2012) and patent filings (patft.uspto.gov on December 15, 2012) identified no similar device for the education of hypertensive patients and no documentation of a similar intervention. Review of 618 manuscript titles returned for the following searches of the PubMed Database resulted in no similar inquiries: somatosensory AND intervention; somatosensory AND intervention AND hypertension; conscious AND intervention AND hypertension; *symptomatic AND intervention AND hypertension.

The contemplated intervention may provide a novel, fast, safe, inexpensive and easily performed opportunity to educate patients during the office visit with inexpensively fabricated equipment. Providing immediacy, tangibility and urgency to the patient's condition - with feedback specifically calibrated to their degree of illness in the moment -

may give impetus to greater levels of medical adherence through better understanding of disease severity and increased levels of autonomous motivation. In keeping with the recommendations of prior adherence improvement trials, the current inquiry implemented a combination of previously studied metrics to capture the effects of the proposed intervention on antihypertensive adherence (18, 30, 74).

Hypothesis

Patients with poorly controlled essential hypertension who simultaneously and repeatedly squeeze two rubber bladders, inflated to pressures differing by the same amount that the patient's current systolic blood pressure exceeds its ideal level, will exhibit better adherence to anti-hypertensive medication regimes than patients who receive no such intervention as measured by self-report at index session and 90-day followup.

Aims

Demonstrate utility of a full-scale study through exploration of any effect on the primary outcome of self-reported medical adherence and secondary outcomes including change in medication possession ratios, blood pressure and motivation.

Demonstrate feasibility of a full-scale study through implementation of control and intervention sessions, as well as interviews with clinicians who enrolled patients and employed the intervention in the course of routine primary care practice.

Methods

Overview

This randomized, controlled pilot study tested a five minute in-office intervention consisting of a tactile, patient-specific representation of high blood pressure in a sample of patients with poorly controlled essential hypertension. The intervention was performed using a device conceived, designed and fabricated by the co-investigator. Approval for the study was granted by the Human Subjects Subcommittee (HSS/IRB) of the Veterans' Affairs Connecticut Healthcare System of West Haven (VACT) and the Human Investigation Committee (HIC) of the Yale School of Medicine. The study was performed under the supervision of an Associate Professor of Internal Medicine who is an attending physician in the Clinic and served as Principal Investigator.

Inclusion and exclusion criteria

Eligible patients included any patient over eighteen years old treated at the VACT Primary Care Clinic between June 15, 2010 and August 15, 2010 with diagnosis of essential hypertension by ICD-9 in the patient's Problem List and SBP at check-in of ≥140mmHg or DBP of ≥90mmHg and an active prescription for medications from the following classes: diuretics, beta blockers, ACE inhibitors, angiotensin II receptor blockers, calcium channel blockers, alpha blockers, combined alpha and beta blockers, central agonists, peripheral adrenergic inhibitors, vasodilators and sympathetic inhibitors. Included patients must have been able to provide a current home address and phone number.

Ineligible patients included those under eighteen years old, no diagnosis of essential hypertension prior to index session, no home address or phone, pregnant, incompetent to consent, non-English speaking, unable to perform the intervention, unable or not expecting to attend followup appointment, and those with any comorbidities that would raise the risk or pain associated with the mild physical exertion necessary to perform the intervention: history of myocardial infarction, history of stroke, history of congestive heart failure, on supplementary oxygen, upper extremity arthritis, upper extremity vascular compromise, or recent upper extremity surgery. Patients were also excluded if the care provider felt that the patient should not participate for any reason. Exclusion of patients with history of advanced vascular compromise or atherosclerotic disease was intended to minimize the possibility of adverse events related to effort expended during the intervention.

Funding

The co-investigator received $5,244 from a National Institutes of Health NHLBI Research Fellowship.

Conflicts of interest

The co-investigator and Yale University are co-holders of a provisional patent on the design of the device.

Prior presentation

Preliminary results were reported at the AMA Medical Student Research Symposium in 2010.

Recruitment and setting

Investigators recruited a convenience sample of patients presenting for regularly scheduled or acute primary care visits at the VACT Primary Care Clinic from June 15 through August 15, 2010.

Every morning, a clinical room and a roster of the day's patients were made available to the co-investigator. The co-investigator pre-screened patients with diagnoses of essential hypertension and active prescriptions for antihypertensive medication via chart review using the VA Computerized Patient Record System (CPRS). Prior to being seen by their physician, all patients underwent evaluation by a staff healthcare provider including assessment of vital signs. If the SBP recorded at check-in was ≥140mmHg or DBP ≥90mmHg and no exclusions were present, the co-investigator placed a note in the patient's file indicating that they appeared to qualify for the study and asking the treating physician to discuss study participation if time permitted. If the patient indicated interest, the caretaker introduced the patient to the co-investigator at the conclusion of the primary care visit. The co-investigator then confirmed that the inclusion and exclusion criteria were met. Subjects then participated in the informed consent process as guided by the co-investigator.

Randomization

Upon completion of the consent process and after any questions were addressed, the subjects were randomized and assigned to one of two Groups - Intervention or Control - according to a pregenerated list of 0's and 1's using the Excel =RAND() function. For practical reasons, the co-investigator could not be blinded to Group assignment as they delivered the intervention and also collected, entered and analyzed the data. Moreover, the subject's active participation precluded their blinding to whether or not they received the intervention.

Groups

All patients from both Groups underwent the same session at index visit including filling out surveys, listening to an educational script on the dangers of uncontrolled hypertension and followup as outlined below. The Intervention Group received the somatosensory pressure demonstration during the index visit whereas the Control Group did not.

Demographic questionnaire and baseline clinical data

Subjects from both the Control and Intervention Groups underwent a short investigator-administered demographic survey including questions on age, gender, race and marital status. Subjects were also asked to provide contact information (address and telephone number) for followup. Additional patient profile data were later abstracted from the chart including date of hypertension diagnosis, comorbidities, number of medications and number of antihypertensive medications. The number of index hypertension medications was calculated by taking the average number of active scripts for the 30 days preceding the index visit.

Motivation and adherence habits questionnaires

Subjects were then prompted to complete a series of Likert-scale and yes/no questions to the best of their ability. Research staff left the room for 5 minutes; if subjects required any clarification, it was given by the co-investigator before proceeding to the next stage of the session. Self-administration of the questionnaires was intended to reduce observer bias.

Subjects first completed the Treatment Self-Regulation Questionnaire (TSRQ) (Image 1, left), a twelve-item questionnaire designed to assess baseline motivation levels. The TSRQ is a theoretically derived scale that assesses the degree and origin of motivation possessed by patients contemplating medical treatment or healthy behavior. The questionnaire was developed by the NIH Behavioral Change Consortium (77, 78) and has been widely employed to gauge "controlled" and "autonomous" or "internal" motivation. It has been validated across several settings and health behaviors (50, 79-83). The wording of the generic questionnaire was modified to provide relevance to antihypertensive medical adherence. Subjects used a 7-point Likert scale to rate their agreement with each item describing the reasons they would take their hypertension medications as prescribed to them (1 = not true at all, 7 = very true) for a total possible score of 84 evenly divided between autonomous and controlled metrics.

Prior studies have found that autonomous motivation in initiating behaviors is associated with greater sense of perceived competence in carrying out those behaviors and with

positive health behaviors including adherence to medication regimens (48, 83, 84). One study of HIV antiretroviral adherence found autonomous components of the TSRQ associated with better dose timing but not with dose adherence (84). Another inquiry concluded that positive changes in autonomous motivation were found to predict improvement in glycemic control for patients with chronic diabetes (48).

Questions 1-6 of the TSRQ relate to autonomous forms of motivation in which behavior finds its antecedents in volition and choice. Questions 1-3 focus on "identification" wherein behavior is positively endorsed and valued by the individual. Questions 4-6 relate to "integration" in which a behavior is perceived as being part of the larger self and connected to broader values and goals.

Questions 7-12 consider controlled types of motivation. Items 7 and 8 explore "introjected" regulation in which behaviors are performed to avoid feelings of guilt. Questions 9-12 consider "external" motivation which drives behaviors performed in order to obtain a reward or to avoid negative consequences (50, 64).

Subjects were then prompted to complete the Morisky Medication Adherence Scale (MMAS) (Image 1, right), an eight-item questionnaire designed to assess baseline adherence levels (85). The questionnaire was recently developed as an improvement upon a widely used four-item assessment (86) and has been shown to have a strong, graded and statistically significantly association with anti-hypertensive medical adherence as measured by electronic Medication Event Monitoring System (MEMS) and

pharmacy refill records (87). These studies also confirm the predictive validity of the MMAS for adequate blood pressure control (85, 87).

Each of the eight items measures a specific medication taking behavior and not a determinant of adherence such as motivation. Each question is scored 1 for "no" and 0 for "yes" with the exception of question 5 which is reverse coded and question 8 which uses a 5-point Likert scale and is coded fractionally. Aggregate scores for the MMAS are typically segregated into three levels of adherence: a perfect score of 8 corresponds to "high" adherence, 6 to < 8 indicates "medium" adherence, and a score of < 6 is associated with "low" adherence. The primary validation study for the MMAS found that 67.2% of low adherers had uncontrolled blood pressure compared to 55.2% and 43.3% of medium and high adherers respectively. The same study found that scores of 6 or greater had 93% sensitivity and 53% specificity for adequately controlled blood pressure (85).

The use of questionnaires was thought to provide a compromise between simpler but less reliable assessments such as interviews and more complex or invasive methods that may be more accurate (22, 88, 89). Although easy and cheap, interviews are subject to distortion due to socially desirable answers, approval-seeking, variable interviewer experience, phrasing and interpersonal dynamics. Self-administered questionnaires have the advantages of prior validation, ease of administration and the possibility of providing explanations for adherence behavior (as opposed to pharmacy data). Disadvantages of this approach include discontinuity of the data and the fact that the accuracy of the results depend on the instrument chosen (30). MMAS questions are phrased in the negative to

counter the tendency of patients to respond to questions in healthcare settings in the affirmative (89).

Although considered the gold standard for indirect adherence measurement, electronic monitoring of pill usage via MEMS (30) was not practical due to cost. Direct measures of adherence such as blood tests for drug or metabolite levels, biological markers or direct observation of the subject receiving medications were not feasible with the resources available to the investigators and are subject to their own disadvantages (90).

Image 1. Motivation (TSRQ) questionnaire (left), adherence (MMAS) questionnaire (right)

For each item, please circle the number from 1 to 7 that best expresses your beliefs:

1. I take my high blood pressure medications because it is very important for being as healthy as possible.								
Not true at all	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**Very true**
2. I take my high blood pressure medications because it is the best thing for my health.								
Not true at all	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**Very true**
3. I take my high blood pressure medications because I want to take responsibility for my own health.								
Not true at all	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**Very true**
4. I take my high blood pressure medications because it is a choice I really want to make.								
Not true at all	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**Very true**
5. I take my high blood pressure medications because it is very important for many aspects of my life.								
Not true at all	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**Very true**
6. I take my high blood pressure medications because it is consistent with my life goals.								
Not true at all	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**Very true**
7. I take my high blood pressure medications because I would feel guilty or ashamed of myself if I didn't.								
Not true at all	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**Very true**
8. I take my high blood pressure medications because I would feel bad about myself if I didn't.								
Not true at all	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**Very true**
9. I take my high blood pressure medications because I feel pressure from others (family, friends, care providers, etc) to take them.								
Not true at all	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**Very true**
10. I take my high blood pressure medications because others (family, friends, care providers, etc) would be upset with me if I didn't.								
Not true at all	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**Very true**
11. I take my high blood pressure medications because I want others (family, friends, care providers, etc) to see I can do it.								
Not true at all	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**Very true**
12. I take my high blood pressure medications because I want others (family, friends, care providers, etc) to approve of me.								
Not true at all	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**Very true**

For each item, please circle the answer that best expresses your beliefs:

1. Do you sometimes forget to take your high blood pressure pills?				
Yes				**No**
2. Over the past two weeks, were there any days when you did not take your high blood pressure medicine?				
Yes				**No**
3. Have you ever cut back or stopped taking your high blood pressure medicine without telling your doctor because you felt worse when you took it?				
Yes				**No**
4. When you travel or leave home, do you sometimes forget to bring along your high blood pressure medicine?				
Yes				**No**
5. Did you take your high blood pressure medicine yesterday?				
Yes				**No**
6. When you feel like your blood pressure is under control, do you sometimes stop taking your medicine?				
Yes				**No**
7. Do you ever feel hassled about sticking to your blood pressure treatment plan?				
Yes				**No**
8. How often do you have difficulty remembering to take all your blood pressure medication?				
Never	**Almost never**	**Sometimes**	**Quite often**	**Always**

Informational script - the importance of BP management

Following completion of the questionnaires, the co-investigator delivered a short, scripted talk on the importance of hypertension management derived from the American Heart Association publication *What is High Blood Pressure?*

> "High blood pressure means the pressure in your arteries is elevated. Blood pressure is the force of blood pushing against blood vessel walls. No one knows exactly what causes most cases of high blood pressure. It usually can't be cured, but it can be controlled. High blood pressure usually has no symptoms. So many people have it and don't know it.
>
> Not treating high blood pressure is dangerous. High blood pressure increases the risk of heart attack and stroke and can damage your kidneys. You can live a healthier life if you treat and control it. Things that you can do to help control your blood pressure include taking your medicine the way your doctor tells you.
>
> Some medicines, help relax and open up your blood vessels so blood can flow through better. Other medicines keep your body from holding too much water and salt or help your heart beat more slowly and with less force." (91)

Intervention

Subjects randomized to the Intervention Group then participated in a session intended to provide tactile feedback demonstrating the difference between the subject's blood pressure as measured at check-in and the target pressure recommended by their doctor. Tactile feedback was provided by two rubber balls constructed out of commonly available sphygmomanometers in which the cuff's nylon covering was removed and the rubber bladder stuffed inside the distal portion of a cotton sock and secured with zip-ties, resulting in an inflatable ball of roughly spherical shape (Image 2). Upon inflation to the desired pressure, the rubber hoses leading to the bulb and gauge were clamped using hemostats to prevent air leakage.

One rubber ball was inflated to 20mmHg (the Reference Ball). A second ball was inflated to 20mmHg plus the difference between the patient's current SBP and their ideal SBP (the Hypertensive Ball). For example, if the patient's SBP measured at check-in was 160mmHg and their ideal SBP is 120mmHg, the Hypertensive Ball was inflated to 20 + (160 - 120) = 60mmHg. The subject was then informed that the difference between the two balls was equal to the difference between their actual blood pressure and "where your doctor thinks it should be".

The subject was then asked to take one ball in each hand and squeeze them both repeatedly and simultaneously until one arm felt fatigued or for one minute, whichever occurred first. The co-investigator monitored the time using a wristwatch. In informal testing, noticeable unilateral fatigue was reached at approximately 30 squeezes over 20 seconds with a Hypertensive Ball pressure of 60mmHg and a Reference Ball pressure of 20mmHg.

Intervention script - extra workload on the heart

The co-investigator then discussed with the Intervention subject the analogy of this fatigue with the added work that is being demanded of their heart due to the same extra pressure against which it is constantly and unceasingly working. The script emphasized that the difference in work/fatigue that their arms are experiencing is the same as the difference between the resistance that healthy blood pressure would present to their heart and its current burden. Furthermore, while their arm can send conscious signals of fatigue, stop working and recuperate, the heart's signals of pain and fatigue do not rise to the level of consciousness and it does not get to rest.

> "The difference between the bladder pressures is equal to the difference between your blood pressure right now and where your doctor thinks it should be. In about half a minute, you were able to feel the difference in work that your arm had to exert working against the higher pressure. You heart has to do the same thing, day in and day out without a break. Your arm can send signals to your brain saying that it's tired and so it gets to rest. But while your heart is working harder, you don't experience the fatigue at a conscious level. The medications that your doctor has prescribed for you will help lower the amount of work that your heart has to do."

The use of scripts for conveying information to subjects was intended to ensure consistency of delivery between sessions.

Image 2. The intervention device consisted of two modified sphygmomanometers with the inflatable bladders repurposed to expand within a spherical cotton sleeve (photo taken by the author using a digital camera)

Assessment of immediate motivational impact

All Intervention and Control subjects were then asked the following question: "On a scale of 1 to 7 with 1 being much less motivated and 7 being much more motivated, how

has this session changed your motivation to take your blood pressure medication?" A score of 4 represented "no change in motivation". This question was conceived by the investigators as a way of evaluating patients' "gut" reaction to the session outside of any more durable changes in motivation or behavior. It was also considered a way of collecting viable motivation data in case of outsized losses to followup.

Demographic, TSRQ, MMAS data and immediate motivational scores were recorded by the co-investigator on a deidentified Excel spreadsheet stored on a secure VACT server. All original paper documents including consents and questionnaires were stored in a locked cabinet in the principal investigator's locked office.

Followup and chart abstraction

Subjects were contacted 90 days following the index session for readministration of the TSRQ and MMAS via telephone. If the subject was not available, a message was left requesting a callback. If the subject did not call back within 72 hours, another attempt was made. A maximum of three such attempts were made per subject after which the subject was deemed lost to followup. During these calls both the TSRQ and MMAS questionnaires were administered by the co-investigator for comparison to those of the index session.

Followup blood pressure data from all patients were abstracted from CPRS from regularly scheduled Clinic appointments within +/- 15 days of 90, 180, 270 and 360 days following the index session. Patients with recent hypertension diagnoses typically

receive check ups every four to six weeks to determine drug tolerance, efficacy, adherence and to address any of the patient's questions or concerns. Adjustments to treatment regimen are frequently made at this time. For patients with long-established hypertension, appointments every three to six months are typical of the course of care. "BP check" appointments are also common and while not a full visit, constituted opportunities to gather outcome data. If no such visit was recorded within the appropriate date range, the subject was considered lost to followup for that period. Patients could be lost to followup for one period but have a qualifying visit for a later period. For example, several subjects had no qualifying visit 270 days after the index session, but did have a "yearly" visit at 360 days.

In keeping with prior studies, subjects' pharmacy data were extracted to determine the Medication Possession Ratio (MPR) for the 360-day periods preceding and following the index session (87, 92-94). The VA maintains electronic records of prescriptions written by clinicians ("scripts") and patient pharmacy activity ("fills"). The co-investigator abstracted script data from CPRS including data on all hypertension medications for each subject with active date ranges in 2009, 2010 or 2011. The abstracted fields included medication name, pill count, dosage instructions, start date and end date of the script. Fill data consisted of blocks of dates defined by the date on which the patient filled a prescription for a hypertension medication (either in person or via mail) plus the number of days supplied as implied by the pill count and dosage instructions (e.g.: "½ tablet three times per day"). The resulting sets of date ranges allowed for comparison between the

number of antihypertensive scripts written and filled for any date between 1/1/2009 and 12/31/2011 for each subject.

If a subject had a script that covered a given day and had not filled that script, the resulting score would be 0 for the medication for that day. Conversely, if the fill data indicated that a subject was in possession of the medication on that day, the score would be 1. A given day's Medication Possession Ratio (MPR) was the sum of such values divided by the total number of scripts covering that day. For example, if a patient had 4 antihypertensive scripts whose valid dates covered a given day and on that day the patient's fill data indicated possession of only 3 medications, the MPR for that day would be 0.75. Outcome MPR measures were then computed using the average of such ratios over the 360 days preceding and following the index visit.

Days which were not covered by a script were not included in the denominator of the MPR. It was believed that this approach provides a more accurate assessment of adherence compared to methods used elsewhere which appear to assume that 100% of days were covered by a prescription and so calculate MPR using a fixed 360 or 365 days in the denominator (95). In the case where a physician neglects to write a script, such an assumption would result in an artificially depressed value for adherence. A minority of patients filled their prescriptions outside the VA system, had no CPRS data for these fills and were excluded from this part of the analysis.

A cutoff of 80% by pharmacy data is widely used in the literature to define adequate medication adherence for a number of diseases. In the study of antihypertensive regimes, this threshold has been associated with a level of drug consumption below which adequate control of blood pressure was less likely to be achieved across a number of drug classes (17, 96-100). While this threshold has been criticized by authors as arbitrary and overbroad in its application - substantial numbers of non-compliant patients by this metric have controlled blood pressures (21) - its use is nevertheless widespread in adherence literature and will be employed for this analysis.

All followup, script and fill data were recorded by the co-investigator on a deidentified Excel spreadsheet stored on a secure VACT server.

Feasibility

A second protocol was written and approved for July 15, 2011 to August 15, 2011 during which a VACT Clinic doctor and a nurse specializing in care of hypertensive patients used the intervention to educate their patients on their disease process. The intervention employed during these sessions differed from the RCT in several important ways: the clinicians were free to use the script as they saw fit, explaining the intervention in their own words if they found that less disruptive to the rhythm of the clinic visit; the device employed during these sessions was substantially modified from that originally used in order to facilitate a faster intervention; and, because no followup comparisons were contemplated for these subjects, no baseline questionnaires were employed.

Structured interviews of both practitioners were performed via email in order to assess the practicality and utility of the device in everyday clinical use. The results of these interviews were used to inform questions regarding the feasibility of a larger study and overall clinical utility.

The questions used for the interviews were as follows:

How easy was it to find patients for the intervention?
Was it easy to get people to agree to participate?
Did patients seem interested in the intervention?
How easy was it to operate the device?
How long did a typical intervention take you?
How much of this time was paperwork vs the actual demonstration?
Do you think this intervention could be incorporated into your clinical practice?
Would you use this intervention if the device was available to you?
Do you think incorporating this intervention would be useful to your patients?
Do you think this intervention will encourage your patients to change their adherence behavior?
Do you think this intervention is particularly well or poorly suited for particular patients?

Outcome measures

The primary outcome of interest is subject adherence to regime of prescribed medication as determined by MMAS at index session and at 90-day followup. Patient self-reporting is direct, simple and inexpensive (101). Although self-report alone may lead to overestimates of adherence, many studies have compared self-report and other assessment methods with favorable results and correlate improved levels of self-reported adherence with better blood pressure control (102-107). While a metaanalysis of 86 studies comparing self-report with nonself-report measures found that only 17% of self-report measures were highly concordant with electronic measures, questionnaires presented the highest concordance (58%) of the self-report methodologies (108).

Adherence to an antihypertension regime includes an array of actions beyond timely consumption of one or more medicines. A number of different behaviors are also prescribed: losing and maintaining weight, reducing sodium intake, quitting smoking, reducing consumption of alcohol, initiating exercise and returning regularly for checkups to name a few. The sheer diversity of these behaviors suggests that a patient's adherence may vary across categories of prescribed activity. The variable and interacting contribution of each behavior to the ultimate goal of lowered blood pressure means that simply counting the number of pills the patient takes home from the pharmacy or miles logged on a treadmill is unlikely to result in an accurate assessment of adherence. Change in blood pressure would seem to be a sufficient measure of adherence, however there is often not a straightforward link between this outcome and medical adherence (43). The patient may be obtaining lower blood pressure because of weight loss, exercise or even reassurance from the physician or family. Conversely, a failure to achieve a lower blood pressure may be due to poor physiological response to a rigorously followed drug plan. Thus, a focus on blood pressure alone may lead to an incorrect evaluation of regimen adherence.

Because no single metric has proven optimal in accurately gauging medical adherence (30, 109) four additional metrics were employed to validate and assess the clinical significance of the results of any changes in the MMAS: a 7-point Likert scale gauging the subject's sense of any change in adherence motivation administered immediately

following the session, electronic prescription fill data, changes in motivation as measured by the TSRQ and changes in blood pressure.

Finally, the question of feasibility of a larger study was addressed through structured interviews with a primary care doctor and nurse who used the device and intervention in their own clinical practices.

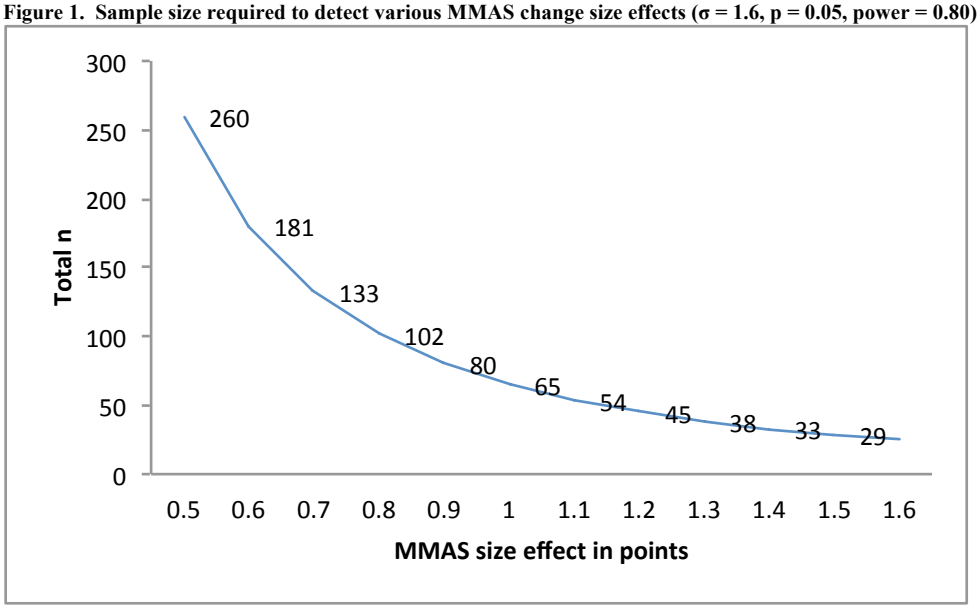
Pilot study sample size

The anticipated sample size for a full study of this intervention is 120 patients. This number is rounded upwards to account for anticipated losses to followup from 102 which was the sample size indicated by a standard statistical method for such approximation of difference of proportions (Figure 1). The equation was bounded by the following targets/assumptions regarding the primary outcome (change in MMAS): a target p-value of 0.05, statistical power of 0.80, standard deviation of 1.6 and a clinically important difference between Groups (size effect) of 0.8 on the 8-point scale in keeping with prior studies using the same questionnaire (110). This sample size also agrees with a widely employed rule-of-thumb which suggests a minimum of 60 participants per Group for single intervention group adherence RCTs (111).

In accord with the recommendations of the Medical Research Council, it was decided that a pilot study of 30 subjects was required before embarking on the larger inquiry given the novelty of this intervention. In addition, enrolling 120 subjects would require staffing and funding beyond what was feasible with available resources. While there is no

standard in the literature to guide sample size determination for interventional pilot studies (112), 30 subjects corresponds to a MMAS size effect of 1.5 points (all other assumptions unchanged) which was believed to provide a reasonable balance between a realistic target and a workable recruitment goal.

Figure 1. Sample size required to detect various MMAS change size effects (σ = 1.6, p = 0.05, power = 0.80)



Statistical analyses

Statistical analyses of continuous data included descriptive statistics, Pearson's and pairwise correlations, OLS regression and t-test comparisons. Categorical adherence measures were analyzed for correspondence and intergroup differences using chi-squared analysis and Fisher's exact tests. All computations were performed using Excel for Mac v. 14.2.0 (Microsoft Corporation, Redmond, WA) and Stata v. 10.1 (StataCorp, College Station, TX). Results were considered statistically significant at the 5% level ($p < 0.050$).

Results

Demographics

Thirty subjects were enrolled from June 15 to August 15, 2010 resulting in Intervention and Control Groups of 15 patients each. All were male veterans with no statistically significant differences in demographics or baseline clinical data between Groups (Table 1).

The mean age of subjects was 69.7 years (95% CI: 65.3, 74.1) with a range of 44 to 88 years. The majority, 21 (15.8, 26.2) were Caucasian with the remainder of subjects identifying as African American. There were 14 (8.3, 19.7) married subjects evenly distributed between Groups. The remaining subjects were either divorced (6 subjects), separated (1 subject), widowed (4 subjects) or single (5 subjects). The average duration of hypertension diagnosis at index session was 8.1 years (6.2, 9.9). Subjects in the sample had an average of 11.4 (9.1, 13.6) comorbidities (including hypertension) at index. The average subject took 8.0 (6.2, 9.7) different prescribed medications at the time of index session, including 2.9 (2.1, 3.7) hypertension medications. The average number of antihypertensive scripts increased by 0.6 ($p = 0.025$) during the index visit without significant differences between Groups ($p = 0.866$).

Baseline blood pressures

Index session SBP, DBP and MAP had no statistically significant differences between Control and Intervention Groups (Table 1). The mean SBP for the sample was 155.7mmHg (150.2, 161.2), mean DBP 81.9mmHg (76.3, 87.6) and mean MAP of 106.5mmHg (101.8, 111.2). Only 9 of 30 subjects were hypertensive by both systolic

(≥140mmHg) and diastolic (≥90mmHg) measures, the majority being hypertensive by systolic blood pressure only.

Index SBP was negatively correlated with index medical adherence as measured by both MPR and MMAS. Those categorized with low, medium and high MMAS had mean SBP of 164.5mmHg (152.8, 176.2), 150.0mmHg (143.7, 156.3) and 153.3mmHg (141.4, 164.6) respectively. Between Group differences in index SBP were noted by ANOVA for these categories with borderline significance ($p = 0.058$). However, no significant difference in baseline blood pressure was found between those categorized as adherent by MPR compared to nonadherent, with mean SBP of 157.8mmHg (139.3, 176.3) and 156.3mmHg (149.3, 163.2) respectively. Blood pressure had no other significant correlations with demographic or other index visit variables (Table 5).

Baseline motivation

Baseline adherence motivation was statistically indistinguishable between Intervention and Control Groups. Mean index session TSRQ was 52.9 (48.7, 57.1) out of a possible 84 points with roughly two-thirds of the contribution from autonomous motivation (Table 1). Mean baseline TSRQ was slightly lower in the Intervention Group for both controlled and autonomous subtypes. Index adherence motivation was negatively correlated with duration of disease, number of comorbidities and number of medications (Table 5).

Baseline adherence

There were no significant differences between Intervention and Control Groups in baseline adherence both in groupwide mean measurements and when the data were analyzed categorically (Table 1). Self-reported adherence for the sample as a whole, as measured by mean MMAS was 6.0 (5.2, 6.8) out of a possible 8, which is categorized as a "medium" level of adherence according to questionnaire validation studies (85). However, the baseline mean 360-day MPR was 54.6% (42.6, 66.8), well below the commonly employed 80% adequacy threshold.

As reported elsewhere and consistent with a relatively low specificity of 53% (85), mean self-reported scores appeared to overstate adherence levels when compared to pharmacy fill data (16, 17, 113). The majority, 66.7% (52.6%, 87.4%) of subjects self-reported medium or high levels of adherence by MMAS. In contrast to MMAS, less than one quarter of subjects, 23.1% (5.7%, 40.4%) were classified as adherent by medication possession. Index MPR was lower in the Intervention Group but the difference was not statistically significant.

The two metrics for index medical adherence were positively correlated with a significant slope coefficient indicating an 8.6% (4.3, 12.9) increase in fill rates for every 1 point increase in self-reported adherence ($R^2 = 0.418$) (Figure 2, left). Chi-squared measure of association between the categories of adherent/nonadherent for MPR and low/medium/high for MMAS was suggestive of good concordance but of borderline significance ($\chi^2 = 4.178$, $p = 0.124$). Fisher's Exact test resulted in similar significance ($p = 0.157$). Of the 6 subjects who were adherent by MPR, none were "low" adherers by

MMAS, 3 were classified as “medium” and 3 were “high”; of the 20 subjects classified as nonadherent by MPR, 9 were “low” adherers by MMAS, 6 were “medium” and 5 were “high” (Figure 2, left).

The inverse relationship between MMAS and baseline blood pressure noted above is consistent with the results of prior studies (85). For the study sample, each 1 point increase in MMAS was associated with a 3.1mmHg (-0.7, -5.5) decrease in index SBP ($R^2 = 0.202$) (Figure 2, right). The average SBP for medium and high adherers by MMAS was 151.8mmHg and 165.7mmHg for low adherers. As with MMAS, higher levels of MPR appeared to predict lower index blood pressure (-16.7mmHg SBP per 10% increase in MPR). However, the sample size was insufficient to establish the significance of this relationship.

In addition to lower index blood pressure values, better results for both adherence metrics were associated with lower scores for controlled motivation, higher scores for autonomous motivation, longer duration of disease and Caucasian race. The strength and significance of these associations was typically higher for medication possession ratio than for self-reported adherence (Table 5).

Immediate motivational impact

Subjects’ sense of their immediate motivational response to the index session as measured by their answers to a 7-point Likert-type question was positive and significant in the Intervention Group but not in the Control Group ($p < 0.001$) (Table 1).

A response of 4 indicated no change in motivation. The mean response for the question in the sample as a whole was 5.3 (4.8, 5.8) indicating a moderately positive impact on motivation from the session. Higher numbered responses were significantly correlated with shorter history of hypertension and larger improvements in self-reported adherence at 90 days (Table 5).

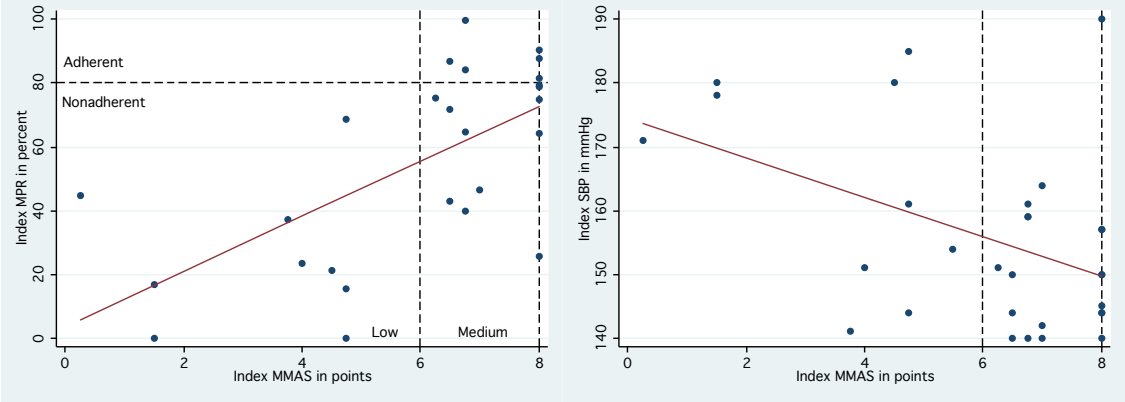
Table 1. Index visit and baseline data

	Control		Intervention		
	Mean	**95% CI**	**Mean**	**95% CI**	**p**
Demographics					
n	15		15		
Male	15		15		1.000
Caucasian	11	(10.8, 11.2)	10	(9.8, 10.2)	0.703
Married	7	(6.7, 7.3)	7	(6.7, 7.3)	1.000
Age in years	72.5	(66.0, 79.1)	66.9	(60.5, 73.2)	0.193
Dx in years	8.1	(5.8, 10.3)	8.1	(5.2, 11)	0.968
Comorbidities	10.7	(7.6, 13.9)	12.0	(9.2, 14.8)	0.563
Medications	7.7	(5.7, 9.6)	8.9	(6, 11.7)	0.490
HTN medications	2.3	(1.7, 2.9)	3.5	(2.2, 4.7)	0.135
Blood pressure					
n	15		15		
Systolic	153.3	(145.8, 160.8)	158.1	(150.7, 165.6)	0.382
Diastolic	81.5	(75.2, 87.8)	82.4	(73.3, 91.5)	0.869
Mean arterial pressure	105.4	(100.1, 110.7)	107.6	(100.2, 115.1)	0.636

* X^2, p-value for MMAS 0.602, 0.740; for MPR 1.321, 0.250

	Control		Intervention		
	Mean	**95% CI**	**Mean**	**95% CI**	**p**
Motivation (TSRQ)					
n	15		15		
Autonomous	38.2	(36.1, 40.3)	37.7	(35.1, 40.3)	0.756
Controlled	15.8	(10.6, 21)	14.2	(8.6, 19.8)	0.684
Total	54.0	(47.8, 60.2)	51.9	(46.5, 57.2)	0.613
Adherence					
Self-report (MMAS)	6.3	(5.4, 7.3)	5.7	(4.5, 6.9)	0.451
n (%)	15 (100%)		15 (100%)		
Low (<6)	4 (27%)		6 (40%)		*
Medium (6 to <8)	6 (40%)		5 (33%)		*
High (8)	5 (33%)		4 (27%)		*
Pharmacy data (MPR)	63.3%	(0.47, 0.79)	47.4%	(0.31, 0.63)	0.185
n (%)	12 (100%)		14 (100%)		
Nonadherent (<80%)	8 (67%)		12 (86%)		*
Adherent (>=80%)	4 (33%)		2 (14%)		*
Immed. motivation impact					
7-point Likert scale	4.3	(3.9, 4.6)	6.3	(5.7, 6.8)	0.000

Figure 2. Relationship between index self-reported adherence and medication possession (left), index blood pressure (right)



Changes in blood pressure

Both Groups exhibited decreases in mean SBP and MAP relative to index levels for every followup period (Table 2). Blood pressure decreases were apparent at 90 days and

persisted with little additional change through 360-day followup. The mean decline in SBP was 16.9mmHg (6.3, 27.4) at 90 days and 15.7mmHg (7.2, 24.1) at 360 days. Significance for 180-day and 270-day data suffered from outsized losses to followup as discussed below.

In general, the magnitude, duration and statistical significance of the declines in blood pressure were greater for the Intervention Group, however between Group differences were not statistically significant. The strength of the relationship of the intervention with these improvements was low by Pearson correlation, with $r = 0.057$ between the intervention binary variable and 90-day change in SBP. At 90-day followup, the Intervention Group exhibited a mean decline in MAP of 10.3mmHg ($p = 0.031$) whereas the Control Group had a mean decline of 7.6mmHg ($p = 0.275$). Blood pressure changes persisted through the end of the followup period with mean MAP declines of 12.2mmHg ($p = 0.008$) and 6.0mmHg ($p = 0.164$) for the Intervention and Control Groups respectively at 360 days.

Higher index MAP was associated with larger declines following the index session. A 1mmHg elevation in baseline MAP was associated with a subsequent decline of 0.862mmHg (0.436, 1.290) at 90-day followup ($R^2 = 0.485$). This effect was consistent in direction for both Intervention and Control Groups but was greater and more significant in the Intervention than the Control which underwent percentage declines in MAP of 8.6% (1.5%, 15.8%) and 5.6% (-7.6%, 18.8%) respectively.

Table 2. Changes in blood pressure, index visit vs 90-, 180-, 270- and 360-day followup

	Control		Intervention			Control			Intervention		
	Mean	95%CI	Mean	95%CI	p	Δ v index	95%CI	p	Δ v index	95%CI	p
SBP											
Index	153.3	(145.8, 160.8)	158.1	(150.7, 165.6)	0.382	-	-		-	-	-
90 days	139.8	(128.1, 151.5)	139.5	(129.8, 149.1)	0.965	-18.2	(-36.4, 0)	0.081	-15.6	(-25.9, -5.4)	0.014
180 days	140.4	(128.3, 152.6)	144.5	(128.8, 160.2)	0.691	-14.3	(-28.4, -0.2)	0.095	-11.2	(-25.4, 3)	0.184
270 days	137.2	(129.7, 144.6)	148.8	(134.8, 162.7)	0.141	-16.4	(-24.5, -8.2)	0.003	-7.9	(-21.2, 5.5)	0.286
360 days	141.2	(132.1, 150.3)	141.5	(134.4, 148.6)	0.953	-14.3	(-29, 0.4)	0.090	-16.9	(-24.6, -9.2)	0.002
DBP											
Index	81.5	(75.2, 87.8)	82.4	(73.3, 91.5)	0.869	-	-		-	-	-
90 days	81.1	(72.7, 89.5)	74.0	(67.7, 80.3)	0.195	-2.3	(-13.2, 8.6)	0.687	-7.6	(-17.4, 2.1)	0.155
180 days	79.1	(71.2, 87.1)	75.7	(65.2, 86.1)	0.608	1.1	(-10, 12.3)	0.848	-6.3	(-14, 1.3)	0.164
270 days	80.4	(74.5, 86.2)	78.4	(71.4, 85.4)	0.674	-3.8	(-10.3, 2.7)	0.279	-10.5	(-19, -2)	0.047
360 days	76.1	(71.9, 80.3)	71.5	(64.3, 78.6)	0.296	-1.8	(-8.1, 4.5)	0.588	-9.9	(-17.7, -2.1)	0.032
MAP											
Index	105.4	(100.1, 110.7)	107.6	(100.2, 115.1)	0.636	-	-		-	-	-
90 days	100.7	(92.1, 109.2)	95.8	(89.3, 102.3)	0.380	-7.6	(-20.4, 5.2)	0.275	-10.3	(-18.4, -2.3)	0.031
180 days	99.6	(91.7, 107.4)	98.6	(88.3, 108.9)	0.884	-4.0	(-14.3, 6.3)	0.476	-7.9	(-15.7, -0.2)	0.099
270 days	99.3	(93.7, 104.9)	101.8	(94.4, 109.2)	0.594	-8.0	(-13.9, -2.1)	0.024	-9.6	(-18.6, -0.6)	0.075
360 days	97.8	(93.6, 102)	94.8	(89.4, 100.2)	0.409	-6.0	(-13.7, 1.8)	0.164	-12.2	(-19.5, -5)	0.008

Changes in motivation

The mean TSRQ response at 90-day followup was suggestive of increased levels of motivation for both Groups, with a mean response of 55.8 (50.4, 61.1) corresponding to an increase of 2.7 points (-1.4, 6.8) compared to baseline, however significance of this relatively small change was limited by sample size (Table 3) and between Group differences were not statistically significant. Almost all of this effect was due to an increase of 4.5 points in controlled motivation in the Intervention Group (r = 0.119). Autonomous motivation was little changed for the sample as a whole with an increase of 0.1 (-2.0, 2.3).

The increase in controlled TSRQ for the Intervention Group was countered by a slight decline in autonomous motivation. The slight increase in motivation for the Control Group was evenly distributed between autonomous and controlled motivation.

Table 3. Changes in motivation as measured by TSRQ, index visit vs 90-day followup

	Control		Intervention			Control			Intervention		
	Mean	95%CI	Mean	95%CI	p	Δ v index	95%CI	p	Δ v index	95%CI	p
Autonomous											
Index	38.2	(36.1, 40.3)	37.7	(35.1, 40.3)	0.756	-	-	-	-	-	-
90 days	39.0	(36.8, 41.2)	36.5	(32.4, 40.6)	0.293	1.2	(-1, 3.3)	0.311	-1.0	(-4.5, 2.5)	0.590
Controlled											
Index	15.8	(10.6, 21)	14.2	(8.6, 19.8)	0.684	-	-	-	-	-	-
90 days	16.5	(11.9, 21.1)	19.5	(12.4, 26.6)	0.493	0.8	(-2, 3.7)	0.569	4.5	(-1.6, 10.6)	0.174
Total TSRQ											
Index	54.0	(47.8, 60.2)	51.9	(46.5, 57.2)	0.613	-	-	-	-	-	-
90 days	55.5	(49.5, 61.6)	56.0	(47.4, 64.6)	0.931	2.0	(-2.3, 6.3)	0.318	3.5	(-3.3, 10.3)	0.335

Changes in adherence

Mean adherence improved for the Intervention Group and was close to unchanged for the Control Group as measured by MMAS and MPR with statistical significance varying by measure (Table 4). Pearson correlation coefficients between the intervention and outcome measures were 0.210 and 0.271 for point change in MMAS and percent change in MPR respectively. Between Group differences were not statistically significant (MMAS p = 0.349, MPR p = 0.181).

The combined sample underwent almost no change in self-reported adherence at 90 days with a change of -0.2 (-0.8, 0.4) points on the 8-point MMAS. The Intervention Group had a mean improvement of 0.5 (-0.5, 1.5) points, however the result was not significant.

The sample as a whole exhibited an increase in mean 360-day medication possession ratio of 6.3% (0.0%, 14.5%) improving from 54.7% (42.6%, 66.8%) to 60.9% (53.8%, 68.0%) but remaining below the 80% threshold for adequate adherence. The majority of this change was due to improvement in the Intervention Group where the average MPR

increased 11.3% (0.0%, 23.3%, p = 0.088) while the Control Group improved by 0.7% (-8.8%, 9.6%).

Two of the subjects in the Intervention Group had baseline 360-day MPR of zero and started filling their scripts (with variable consistency) following the index session. This resulted in a low baseline MPR for the Intervention Group and contributed to its relatively large increase in mean adherence. Removing these patients from the calculation results in a mean increase in MPR of 5.0% (p = 0.255) for the Intervention Group. There were no similar patients in the Control Group.

Improvement in MMAS was positively correlated with index SBP, controlled and aggregate motivation (TSRQ) at index visit and scores indicating higher immediate motivational impact from the session. Improvement in MPR was likewise positively correlated with baseline motivation (controlled and total TSRQ) (Table 5). Lower levels of improvement and even negative changes in adherence were associated with longer disease burdens and higher baseline adherence. These relationships were consistent across both MMAS and MPR. The association between length of diagnosis and adherence intervention efficacy has been noted in prior studies (22, 66).

Table 4. Changes in adherence as measured by MMAS and MPR, index visit vs 90-day followup

	Control		Intervention			Control			Intervention		
	Mean	95%CI	Mean	95%CI	p	Δ v index	95%CI	p	Δ v index	95%CI	p
MMAS											
Index	6.3	(5.4, 7.3)	5.7	(4.5, 6.9)	0.451	-	-	-	-	-	-
90 days	6.1	(5.4, 6.8)	6.6	(5.9, 7.3)	0.330	-0.1	(-0.7, 0.5)	0.798	0.5	(-0.5, 1.5)	0.372
MPR											
Pre-index	63.3%	(0.47, 0.79)	47.4%	(0.31, 0.63)	0.185	-	-	-	-	-	-
Post-index	64.1%	(0.55, 0.74)	58.7%	(0.49, 0.68)	0.487	0.7%	(-0.1, 0.1)	0.934	11.3%	(0, 0.2)	0.088

Table 5. Pairwise correlation coefficients

		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
1	Age	-																		
2	Caucasian	**0.33**																		
3	Married	0.13	0.18																	
4	HTN years	0.26	0.11	0.12																
5	Comorbidities	-0.01	-0.25	0.08	**0.46**															
6	Medications	**-0.38**	-0.21	-0.15	0.27	**0.59**														
7	HTN medications	-0.26	-0.20	-0.19	**0.42**	**0.45**	**0.62**													
8	Index SBP	0.08	-0.07	-0.09	-0.04	0.08	-0.11	0.08												
9	TSRQ Autonomous	-0.23	**-0.32**	-0.16	0.12	0.00	-0.04	-0.16	0.12											
10	TSRQ Controlled	0.08	-0.11	0.19	-0.12	**-0.32**	**-0.36**	-0.24	-0.06	**-0.45**										
11	TSRQ Total	-0.02	-0.23	0.11	-0.06	**-0.30**	**-0.36**	-0.30	-0.01	**0.36**	**0.91**									
12	MMAS	0.25	0.29	0.16	**0.37**	0.02	0.10	0.10	**-0.45**	0.07	**-0.65**	**-0.57**								
13	MPR	0.04	0.24	0.30	**0.50**	-0.07	0.24	-0.01	**-0.33**	0.44	**-0.57**	**-0.42**	**0.65**							
14	Δ immed. motivation	-0.04	0.08	0.01	**-0.67**	-0.02	0.00	0.12	**0.40**	-0.07	0.01	-0.02	-0.15	**-0.34**						
15	90d Δ SBP	-0.26	-0.06	-0.07	-0.15	0.31	0.34	0.03	**-0.68**	-0.06	-0.24	-0.25	0.30	0.18	-0.09					
16	90d Δ TSRQ Auton.	-0.16	0.02	0.17	-0.18	0.02	**0.38**	0.18	-0.17	**-0.33**	0.19	0.04	-0.01	0.26	-0.01	0.19				
17	90d Δ TSRQ Control.	-0.22	-0.20	-0.09	-0.23	0.21	0.34	0.19	0.12	0.09	**-0.44**	**-0.38**	0.07	0.11	0.18	**0.45**	0.02			
18	90d Δ TSRQ Total	-0.27	-0.16	0.01	-0.29	0.19	**0.48**	0.25	0.01	-0.10	-0.27	-0.30	0.05	0.23	0.14	**0.46**	**0.54**	**0.85**		
19	90d Δ MMAS	-0.23	-0.27	0.14	**-0.45**	-0.14	-0.06	-0.19	0.57	-0.01	**0.61**	**0.55**	**-0.82**	**-0.36**	**0.36**	-0.29	0.21	-0.06	0.05	
20	Δ MPR	-0.16	-0.20	-0.27	**-0.46**	0.03	-0.19	0.08	0.15	-0.14	**0.53**	**0.47**	**-0.57**	**-0.82**	0.16	-0.07	-0.29	0.00	-0.14	0.28

Index demographics and clinical data

Index motivation metrics

Index adherence metrics

Followup data

Bolded correlations are significant at the 10% level.

Pearson correlation coefficients between the intervention Boolean variable and outcome measures were 0.76, 0.21, 0.27, 0.12 and 0.06 for immediate change in motivation, point change in MMAS, percent change in MPR, point change in TSRQ and mmHg change in SBP respectively.

Losses to followup

Losses to followup varied by dataset. Blood pressure followup window periods sometimes did not coincide with clinic visits and thus no blood pressure data were available in CPRS for some patients for some periods (Table 6). Losses to followup for both Control and Intervention Groups for the 90-day and 360-day samples were 33% and 27% respectively. The 180-day and 270-day blood pressure datasets had even larger losses. Baseline blood pressure characteristics for those lost to followup at 90 days were asymmetric between Groups. The Control Group lost 5 subjects with average index blood pressures below the Group's mean. Conversely, the Intervention Group lost 4 subjects with relatively high index blood pressures.

Loss to followup for the questionnaire data was of lower magnitude than that for blood pressure measurements. Subjects were considered lost if the co-investigator was unsuccessful in contacting them despite three attempts via phone. However, OLS regression indicates a very weak positive relationship between index TSRQ and change in TSRQ with a slope not significantly different from zero. Thus, while the Control Group lost subjects with relatively high index motivation and the Intervention Group lost relatively low motivation subjects, this asymmetry seems unlikely to have caused significant bias in their subsequent changes in TSRQ. Both Groups lost patients with lower index adherence as measured by MMAS.

One subject died of an unrelated illness during the year following the index visit. The subject had already undergone his followup questionnaires but analysis of his script fill behavior was limited to 180 days before and following the index visit.

Table 6. Analysis of losses to followup for blood pressure, motivation and self-reported adherence data

	Control			Intervention		
	n	Mean at index	Loss to followup	n	Mean at index	Loss to followup
SBP						
Index	15	153.3	0%	15	158.1	0%
90 days	10	158.0	33%	11	155.1	27%
180 days	7	154.7	53%	6	155.7	60%
270 days	11	153.5	27%	8	156.6	47%
360 days	10	155.5	33%	11	158.5	27%

	Control			Intervention		
	n	Mean at index	Loss to followup	n	Mean at index	Loss to followup
TSRQ						
Index	15	54.0	0%	15	51.9	0%
90 days	13	53.5	13%	12	52.5	20%
MMAS						
Index	15	6.3	0%	15	5.7	0%
90 days	13	5.4	13%	12	4.9	20%

Feasibility

An additional seven subjects were enrolled from June 15 to August 15, 2011 (the year following the RCT) as part of the feasibility component of this pilot study. These

subjects were introduced to the intervention by a doctor (n = 4) in the course of a regular Clinic appointment or a nurse (n = 3) specializing in the instruction of patients in the use of home blood pressure monitoring systems. An identical script was used for the intervention but was not required to be read by the clinician. The aim was to assess the viability of the use of the device and intervention in everyday clinical practice. No data on these patients were collected beyond demographics and no subjects served as controls.

The physician reported positive reception from his patients and favorable opinion of the intervention, describing it as "incredibly easy" to use and "a very impressive tool" for patient education. His assessment of patient experience was that they were typically "very eager" to participate when asked. Patients were interested in the intervention and smiled, showing positive body language while using the device. He estimated that a typical intervention took 5 minutes of which the majority was usually occupied by the consent process. He believed that the intervention was suitable for most people regardless of educational level, and that "a large segment of [his] patients" would find the intervention useful. However, he was unsure whether the intervention would actually change adherence behavior and noted that "it certainly can't hurt". He felt that the intervention was a novel tool for use in addition to the traditional printed, web-based and verbal vectors.

The physician believed that he would likely make use of the device and intervention in clinical practice but that it might be best employed by a healthcare extender such as a nurse or health technician. He noted that it was sometimes hard to find time to employ

the intervention given all that is required of a primary care visit and that use of the device requires no specialized knowledge or skillset which would preclude use by a non-physician.

The nurse also reported very positive reception from her patients. It was easy to find suitable patients and they were generally eager to participate and interested in the device once it was explained to them. She felt that the device was easy to operate but that the pressure seemed to leak out over time. She estimated that a typical intervention took 15 minutes including explanation of the balls' use and the meaning of the pressure differences. She estimated that only 5 minutes of this time was used for the actual intervention, the remainder dedicated to the consent process.

She felt that the device could easily be incorporated into her clinical practice and would "definitely" use the device were it available. She noted that "this intervention may motivate them and encourage them to be more serious about taking their medication... I definitely feel that this intervention would help. I always think that visual aids and hands-on always helps a patient learn... will definitely improve patient adherence behavior". She concluded, "this is a fairly simple intervention and would be well suited for several types of patients. I also do group visits with diabetes and hypertension [where] I would like to use this intervention, if available, as a teaching tool."

There was no formal assessment of patient satisfaction or opinion of the intervention. There were no withdrawals, complaints or adverse events associated with the study.

Discussion

Poor adherence to prescribed antihypertensive medication has been characterized by the National Council on Patient Information and Education as "America's other drug problem" (114). More than sixty-five million Americans and one billion people worldwide have blood pressure high enough to warrant treatment. Studies in the United States consistently report adherence to antihypertensive regimes of 30%-60%, well below the 80% threshold commonly associated with consistent blood pressure control. The sequelae of untreated hypertension are serious and their burden to the patient and economic cost to society are substantial. Prior inquiries have established that patients are less apt to adhere to prescribed treatments for asymptomatic diseases (14). Thus, it seems worthwhile to investigate the effect of providing a conscious, subjective awareness (i.e., a symptom) to the usually asymptomatic pathology of hypertension. The aim of this pilot randomized controlled study was to determine the utility of a somatosensory educational intervention to improve adherence to prescribed antihypertensive regimes and the feasibility of a full-scale trial. The results of the inquiry suggest that the intervention shows promise in promoting adherent behavior and may encourage clinically useful improvements in blood pressure. The results of recruitment efforts and the comments from practitioners suggest that a larger scale study is feasible in the clinical setting. The intervention presents feedback directly calibrated to the individual patient's level of disease in the moment, it is inexpensive, simple, noninvasive, easily understood and appears feasibly integrated into the rhythm of the typical clinic visit. A larger study is required to confirm these results and establish their statistical significance.

Several metrics of adherence were investigated as well as motivation and blood pressure before and after the intervention in order to gain a preliminary assessment of clinical utility. Generally speaking, the mean changes in measures of interest were encouraging for the intervention but significance and generalizability were seriously limited by sample size and homogeneity. Cohen's Rule of Thumb classifies the effect size of the Intervention on immediate motivational impact as "high" with a correlation of 0.76. Higher levels of immediate motivational impact, in turn, were significantly associated with greater subsequent improvement in self-reported adherence. Effect sizes on the outcome measures of point change in MMAS, percent change in MPR, point change in TSRQ and mmHg change in SBP were classified as "small" (0.10 to 0.25) to "medium" (0.25 to 0.50) (115). However, modest effect size does not preclude clinical relevance particularly in the case of low cost, high prevalence interventions (116).

These size effects are consistent with those found by Roter and colleagues whose meta-analysis of efforts to improve antihypertensive adherence noted larger intervention effect sizes on indirect measures such as MPR and small effects on subjective measures such as MMAS and health outcomes such as SBP (71). This discrepancy may be explained by a possible ceiling effect in index visit MMAS reducing room for post-intervention improvement as compared to changes in MPR and blood pressure which are not limited by the same ex ante inflation.

Scientists have identified many factors associated with poor adherence in the treatment of hypertension. Demographic, economic, disease- and treatment-specific variables all play a role. The disease is largely insensible and many of the medications are associated with serious side effects including sexual dysfunction, cough, dizziness, nausea, headache and other effects of autonomic dysregulation. Furthermore, unlike treatments for other illnesses, antihypertensives do not generally provide negative reinforcement in the form of relief from consciously experienced symptoms. For a patient considering taking his/her antihypertensives, the drawbacks of adherence are quite clear: side effects, inconvenience and money. The benefits are usually nebulous - "long life", "cardiovascular health", "improved quality of life" - and the risks of nonadherence are equally abstract, distant and uncertain. The pathology itself is detected by an occult and unexplained process, measured and discussed using a ratio of two undefined numbers presented in the unhelpful units of "millimeters of Mercury". In one survey of 587 patients under treatment for hypertension, fully 80% reported reservations about taking their antihypertensive medicine and 66% preferred to lower their blood pressure without medication (117).

There is a substantial body of inquiry seeking to identify successful interventions to improve antihypertensive adherence and clinical outcomes. Categories of intervention include education, dose simplification, motivational approaches and combinations of these efforts. Modalities include lecture, interactive sessions, improved access, self-monitoring, reminders and rewards among many others. Although not amounting to a consensus among researchers, several reviews cite advantages to multi-approach, patient-

specific interventions (51, 69, 71, 72, 74). Unfortunately, such approaches are typically complex, expensive and difficult to implement. Thus, there is interest in simple, patient-specific interventions capable of producing clinically relevant improvements with the possibility of realistic administration during the office visit (45). This individually tailored intervention addresses the problems of expense and complexity in that it is unimodal, easily administered by one caretaker, requires no followup reinforcement and employs a device fabricated from widely available, inexpensive components.

Data on the benefits of educational sessions are mixed at least in part due to widely varying modalities, venues, frequencies of teaching sessions and outcome measures. In the largest, best-designed and most often-cited interventions, education-only efforts fare poorly. Of the six educational RCTs sufficiently rigorous to be included in the latest Cochrane Review of interventions to improve antihypertensive adherence (51), only one relatively small trial (n = 110) of group education sessions by Marquez-Contreras et al demonstrated improved adherence but evinced no effect on clinical outcomes (118). Pierce and colleagues, in a study of 115 patients, found that a set of four office-based educational sessions had a larger impact on blood pressure control and adherence by pill-count than daily pressure monitoring (54). In contrast, an earlier landmark study by Sackett et al found that mastery by 230 steelworkers of facts regarding hypertension and its sequelae provided and reinforced at work elicited no improvement in adherence (57). Kirscht et al, in a study of 400 almost entirely Caucasian patients identified no improvement in adherence from an educational session employing written material as part of four sequential multi-approach interventions. Similarly, Webb and colleagues

noted no improvement in either adherence or blood pressure in 123 low-income African-American patients who received additional education and psychosocial counseling when compared to those receiving regular family physician care (55). Finally, Kerr and colleagues identified significant improvements in pill-count adherence from combinations of self-monitoring and education, but no such improvements when education was utilized alone (52). Were the results of the present inquiry supported in a larger study, this intervention may add a standalone educational initiative capable of encouraging improvements in medication possession and blood pressure management to the armamentarium of clinicians and researchers.

Self-reported medical adherence, the primary outcome as measured by mean MMAS, was improved in the Intervention Group and slightly decreased in the Control. Greater levels of improvement in MMAS were associated with responses indicating greater immediate motivational impact from the intervention. Encouragingly, this latter metric evidenced a "high" size effect from the intervention according to Cohen's Rule of Thumb. As with prior studies, self-report in the sample appeared to overstate adherence levels both at baseline and followup when compared to more objective measures.

Intervention Group MMAS responses demonstrated a mean increase of 0.5 points out of 8 ($p = 0.372$) moving from a "low" level of adherence (<6 points) to "medium" (6 to <8 points). The study was powered to detect a difference of 1.5 points and thus could not establish the significance of this result. However, were this difference to persist upon further investigation, such an improvement would likely accompany clinically relevant

blood pressure improvements on average. Crossing this threshold has been shown to have clinical significance. In a study of 1367 patients, Morisky et al found that 67.2% of "low" adherers by MMAS had uncontrolled hypertension compared to 55.2% of "medium" adherers (85). Krousel-Wood et al, in a study of 116 patients, found that the odds-ratio for non-persistence (<80% adherence by MPR) decreased from 8.2 to 2.3 for the same change in MMAS category (87).

In order to validate and explore the clinical significance of the primary outcome, three secondary outcomes were examined. The results of these analyses also suggest a positive impact from the intervention on medication possession ratios, motivation for adherence and clinically relevant improvements in blood pressure.

Medical adherence as measured by 360-day MPR increased 11.3% ($p = 0.088$) in the Intervention Group and 0.7% ($p = 0.934$) in the Control. However, the study was not sufficiently powered to detect a between-Group difference. Of all the outcome variables, the estimate of size effect by Pearson correlation was highest between the intervention and MPR. Unfortunately, the average post-intervention MPR of 58.7% is still well below the threshold of 80% commonly used to define adequate adherence for antihypertensives. This persistence is perhaps unsurprising given that the study sample included only patients with uncontrolled hypertension despite treatment. This result emphasizes the multifactorial approach of successful interventions; on average, use of this device alone is unlikely to transform a nonadherent hypertensive into an adherent one as measured by MPR.

Self-Determination Theory proposes that autonomous motivation is an essential component of durable changes in health behaviors (46). Subjects' response to the question of immediate change in motivation substantially and significantly favored the Intervention ($p < 0.001$) and more positive responses to this question were significantly associated with greater improvements in MMAS. This question was intended to gauge patients' "gut" response to the intervention outside of any changes that it may or may not precipitate in their motivation or behavior. It was also conceived as a safeguard against poor questionnaire followup. Because the question was not vetted for content validity, predictive validity or reliability, the importance of this result is unclear. Nevertheless, this result and the clinicians' feedback are encouraging for a larger study as they suggest that patients find the intervention interesting and useful as a heuristic device.

Although patients' endorsement of the immediate impact of the intervention on motivation was encouraging, the question did not distinguish between forms of motivation and the followup data are much more ambiguous. None of the changes in motivation were significant at 90 days and mean changes indicated an increase in the controlled motivation subcategory. In fact, there is no reason to believe that one session of the intervention should have a durable impact on feelings of competence or encourage autonomous forms of motivation. On the contrary, it is possible that the intervention was viewed by subjects as an attempt to elicit feelings of guilt or shame which are examples of controlled influences and are usually counterproductive.

Higher levels of controlled motivation are often (but not always (95)) associated with poorer adherence and health outcomes. However, SDT also proposes that behavioral change involves the internalization of initially external influences (47) and that motivation is a dynamic concept in which a patient experiencing a controlled motivation type can eventually internalize this influence (46). It is plausible that an initially controlled influence from the intervention could ultimately become integrated into more self-derived sources of motivation and enhance the patient's sense of self-efficacy in the longer run.

Both the Control and Intervention Groups appeared to experience durable, clinically useful, statistically significant mean improvements in SBP and MAP. Mean improvements were greater in magnitude, duration and statistical significance in the Intervention Group. In a landmark recommendation, The National High Blood Pressure Education Program emphasized that a sustained reduction of even 5mmHg in SBP was shown to reduce mortality from cardiovascular disease by 7% per year (119). Thus, were a larger study to affirm these reductions in blood pressure, such changes would have clinical relevance.

Any effect from the session on blood pressure was heavily confounded by index visit changes in number of antihypertensives. The average subject increased their number of antihypertensive scripts by 0.6 ($p = 0.025$) during the index visit. This change was seen equally in both Groups. New antihypertensives given at index visit would provide explanation for the symmetry of blood pressure improvements between Groups and the

poor estimate of the intervention effect size on change in 90-day SBP despite a significant improvement in MPR. Interestingly, regression of blood pressure changes on number of new scripts did not result in significant slope coefficients or measures of association. In addition, new medications were evenly distributed between Groups and so would not explain the greater apparent durability of improvements in the Intervention Group.

A number of different behaviors are prescribed and proscribed with the ultimate goal of blood pressure control. Thus, it is possible that the index visit (both Control and Intervention sessions) encouraged pressure reductions through behavioral changes not captured by the adherence and motivation outcome measures utilized for this study. Indeed, several trials of educational interventions have noted similar reductions in blood pressure in control Groups exposed to regular care, particularly for studies which focus on patients with poor medical adherence (49, 59). Studies of biases have found that rates of adherence in clinical trials are typically high due to attention effect (120). However, while both Groups received the informational talk on the benefits of antihypertensive adherence, it seems unlikely and is inconsistent with prior studies (14) to believe that such a brief and unexceptional lecture precipitated the improvements noted in the present study. It may be more plausible to assert that hypertensive patients under care of primary care physicians will, on average, achieve a fall in their blood pressure through various avenues including addition of new drugs - an effect which the intervention may have augmented.

Baseline blood pressure characteristics for those lost to followup at 90 days were asymmetric between Groups. The Control Group lost 5 subjects with average index blood pressures below the Group's mean. Conversely, the Intervention Group lost 4 subjects with relatively high index blood pressures. As discussed above, 90-day change in blood pressure was inversely and significantly related to index SBP with a slope of roughly -1. Thus, the magnitude of the Control Group's reduction in BP at 90 days may have been biased upwards (by roughly 5mmHg) and that of the Intervention Group may have been biased downwards (by roughly 3mmHg). The combination of these influences could have led to a low estimate for impact on blood pressure from the intervention.

Correlations between demographic data, baseline adherence and changes in adherence metrics were largely in line with prior inquiries and common sense. Baseline blood pressures were negatively and significantly correlated with better adherence as measured by both self-report and prescription data. Index motivation was negatively correlated with duration of disease, number of comorbidities and number of medications. The two metrics for index medical adherence (MMAS and MPR) were positively correlated. In addition to lower index blood pressure, higher baseline values for both adherence metrics were associated with lower scores for *controlled* motivation, higher scores for *autonomous* motivation, longer length of diagnosis and Caucasian race.

Improvement in MMAS was positively correlated with index SBP, controlled and aggregate motivation (TSRQ) at index visit and a higher immediate motivational impact from the session. Improvement in MPR was likewise positively correlated with baseline

motivation (controlled and total TSRQ). Longer disease burdens were associated with higher baseline adherence, reduced immediate motivational impact as well as lower levels of improvement and even negative changes in adherence by MMAS and MPR.

Feasibility of a larger study

The feasibility of a larger study was evaluated through implementation of a small number of interventions on a randomized convenience sample of patients at a busy primary care clinic, followed by structured interviews with clinicians who instituted the intervention in their everyday practice. These results suggest that a larger scale study wherein the intervention is administered by working care extenders such as RNs, PAs and/or research assistants in the primary care setting is feasible and would not be unacceptably disruptive to the everyday flow of clinical practice.

Patients typically expressed curiosity regarding the device and appeared pleasantly surprised at the novelty of the concept. There were no complaints or withdrawals from the study and patients typically responded with interest and curiosity when the intervention was described and during the demonstration. The physician who employed the intervention in his practice felt that it was simple, fast, useful and very well-received by his patients. However, as time is extremely limited in the primary care visit, he recommended involvement of care-extenders to facilitate enrollment. The nurse reported very positive reception from her patients and she felt that the device was easy to operate and useful as a motivational tool. She felt that the intervention could easily be incorporated into her clinical practice and would "definitely" use the device for her

individual patient visits as well as group education sessions, were it commercially available.

The consent and questionnaire processes represent at least half of the 10-15 minutes required for the intervention. The physician reported that these steps made it difficult to incorporate the study into his clinical schedule. Thus, while the device may represent a useful and viable intervention by itself, it does not appear feasible to ask busy primary care doctors to bear the burden of the paperwork associated with a larger study. Administration of the intervention by care-extenders may provide benefits outside of any derived from the heuristic itself; one study of 457 participants found that patients who received supplementary care from specially trained nurses had better blood pressure control and medical adherence behavior when compared to those who received standard primary care (56).

Mechanistically, implementation of a larger study appears feasible. In 2009, the VACT Primary Care Clinic treated 47,044 patients of which 25,474 (70 people per workday) were hypertensive by ICD-9 code. An estimated 50 to 70% of such patients could be expected to have SBP greater than 140mmHg despite treatment (11, 56). One person working for one month was able to enroll 30 subjects. This suggests that the target of 120 patients could be reached in a reasonable amount of time with one or two additional personnel trained to perform the intervention and associated informed consent. Beyond simply increasing the number of people enrolling subjects in the same manner as in the pilot study, a number of additional points of contact may be explored.

Administration of the intervention in additional venues may allow for increased enrollment and could validate the use of the intervention by a wider group of professionals. Triage or check-in areas, counseling, group sessions (for diabetics, hypertensives and other patients with chronic diseases), and blood drives all present such opportunities and typically are less time-restricted than the primary care office visit. The pharmacy is another point of contact in which the patient is thinking about his/her health and may be amenable to participation. Pharmacies offer the added advantages of trainable health professionals, less rigid scheduling than the clinic and, oftentimes, automated blood pressure machines for customer use.

Prior inquiries conclude that multiple points of contact increase the likelihood of success for a given adherence intervention (14, 34). A future study might examine whether serial applications of this intervention for an adherent patient provides a tangible sense of their progress in reaching their blood pressure goal. Deci et al, in their elucidation of the principles of SDT, note that positive feedback is associated with internalization of external motivations (46). There is evidence that repeated interventions and positive feedback encourage the process of motivational internalization and medical adherence (50). Johnson and colleagues evaluated different forms of feedback on antihypertensive adherence, finding that regular blood pressure monitoring had the single most significant influence, above that of information from the physician, family or the media (23). Such reinforcement may be associated with increased sense of accomplishment, competence and autonomous motivation. The present intervention may serve as a possible corollary

to routine blood pressure measurement, intended to give the patient a conscious, tangible manifestation of the numbers recorded in his/her chart and the progress that they represent.

One strength of this intervention is that the degree of feedback increases with the severity of disease. In informal testing, it takes several squeezes to notice a difference of 10-20mmHg but higher differences than this are quite easily detected. The higher a person's SBP, the greater the difference in pressure that they feel upon squeezing the two bladders and the faster their "hypertensive" arm gets tired. Presumably, the emotional weight and educational value of the intervention increases in proportion to the magnitude of the pressure difference experienced and thus with the severity of disease. It seems logical to believe that the psychological impact, motivational utility and degree of improvement in outcome variables would be more pronounced for higher pressures. The present study was insufficiently powered to explore this question and may provide an interesting avenue of exploration for a larger inquiry. Further investigations may benefit from a higher blood pressure cutoff value for screening purposes as well as targeting patients early in the course of their disease in hopes of maximizing changes in adherence.

Limitations

All subjects were male veterans which seriously limits the generalizability of the results of this pilot study. In addition, the sample size was often insufficient to establish statistical significance of the intra-Group outcomes and in cases where significant improvements in the Intervention Group were identified, significant inter-Group

differences with the Control were not always established. In order for the Intervention Group's mean outperformance in MMAS (the primary outcome) of 0.6 to have been significant the required sample size would have been 329 subjects after losses to followup, assuming the realized standard deviation of 1.8, power = 0.80 and p = 0.05. The modesty of this inquiry was necessitated by limited resources and the desire to minimize the disruption to the activities of the Clinic. The exclusion of subjects with history of advanced vascular compromise or atherosclerosis was intended to reduce the chance of adverse events associated with participation in the intervention. However, it is possible that this group of patients would benefit substantially from improved adherence to antihypertensive prescriptions and their exclusion from the study limits its relevance to clinical practice. As physical effort involved in participation is quite minimal, the risk to these patients is likely small and a larger study should consider their inclusion.

The study's design limited its utility as a pilot. More data on recruitment, uptake of intervention, patient satisfaction and acceptability should have been sought. Because a convenience sample was employed, very few people decided not to participate, however a larger study may approach sequential patients, likely resulting in higher rates of refusal. Physicians recommending their patients for the study may have selected for more agreeable personalities which could have introduced additional confounding to the adherence metrics. Nevertheless, the results of the immediate motivational impact question and clinician interviews suggest that patients were amenable and generally enthusiastic about participation, or at least did not find the intervention counterproductive or unpleasant.

For practical reasons, the process of randomization and Group allocation was known to the enrolling co-investigator. Due to their necessary participation in the intervention, subjects were also aware of their status in the study. The effect of the former may have led to selection or measurement biases while the latter may have encouraged attention bias.

The question gauging the immediate motivational impact of the session was developed by the investigators and had no external or predictive validation outside this study. The question used the term "motivation" but it did not define this word and it did not attempt to parse out autonomous and controlled components. As a result, comparability with 90-day TSRQ responses is limited.

As discussed above, index levels for self-reported adherence and medication possession were significantly correlated. However, changes in these metrics were positively but not significantly related. Any relationship between the two was likely weakened by the difference in timing between the administration of the MMAS at 90 days and the year-long scope of the MPR. It also appears that MMAS responses were subject to ceiling effect with significant overestimation of index adherence by self-report allowing little space for improvement ex post.

The measurement of medication possession ratio presented several challenges. The model was highly detailed and required manual input of several thousand datapoints.

Changes in medication classes or brands during the study period were not examined. It is possible that such a change may produce an impact on adherence that would be erroneously attributed to the session. While the model does include drug names, it does not consider whether medication adherence rates varied with drug class. A prior study found that averaging MPR data across antihypertensive classes did not mask any class-specific differences in adherence (87). Data regarding non-VA medications were inconsistent. In one Intervention and two Control subjects, such data was missing and these patients were not included in MPR calculations. It is plausible that patients who fill their meds outside the VA are wealthier or have better access to the healthcare system, both variables found to be associated with higher adherence. Finally, the VA pharmacy presents a semi-closed system in which data for most patients are readily available. A larger study outside the VA system would have the added challenge of gathering MPR data from a variety of sources.

Review of prescription records provides data on gross consumption patterns but not on more granular adherence phenomena: for example, if the subject is consistently missing his weekend doses, nighttime doses or if he misses doses sporadically. These questions could have been addressed by MEMS and allowed for a richer analysis of changes in adherence. Each visit is an opportunity for changes to medical plan of treatment and some patients have their medications changed or supplemented with new medications. As the index session occurred immediately following a routine primary care visit, new medications or new dosages were often introduced on the same day as the session. If the intervention had any effect, it seems plausible that this effect would be greatest at the

time of the session which, in this case, coincides with new scripts being written. This "white-coat adherence" would have the effect of augmenting any MPR changes than had the intervention occurred between medical visits (121) along with the confounding effects of new antihypertensives introduced at the time of the intervention.

Similarly, it is often difficult to distinguish between different types of nonadherent behavior. For example, two separate analyses may report 50% adherence but this can indicate that either 100% of patients stopped therapy halfway through the period or that 100% of patients took half their medicine for the entire period. A rough analysis of the pharmacy data indicate that the change in the number of days with no pills taken was inversely proportional to the change in MPR. This suggests that changes in adherence were more likely to include all hypertension scripts rather than piecemeal decisions by the patient to improve adherence to just one or two drugs. Furthermore, pairwise correlation and OLS regression analyses were limited to those subjects for whom complete MMAS followup was possible.

There were substantial losses to followup in the blood pressure data as those without appointments within 15 days of followup dates were excluded from these calculations which reduced sample size most substantially for the 180- and 270-day comparisons. This problem could have been ameliorated by taking averages of blood pressure data over wider windows rather than discrete, periodic readings. Lost subjects may have been more prone to poor adherence and their loss may have resulted in overestimation of post-intervention adherence in both Groups.

Conclusions

The results of this inquiry suggest that a brief educational intervention designed to provide a somatosensory manifestation of the patient's disease process shows promise in promoting adherent behavior and clinically useful reductions in blood pressure in poorly controlled hypertensives. A larger study appears feasible and is required to confirm and investigate the statistical significance of these results.

Should further studies prove encouraging, there may be potential use for this device in several healthcare-associated venues. It is simple, inexpensive, fast and noninvasive and thus potentially useful for primary care physicians, nurses, PAs, or pharmacists, particularly those working with high-prevalence populations.

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