Contemporary Clinical Trials 50 (2016) 5–15

Contents lists available at ScienceDirect

Contemporary Clinical Trials

journal homepage: www.elsevier.com/locate/conclintrial

Open-label randomized trial of titrated disease management for patients with hypertension: Study design and baseline sample characteristics

George L. Jackson [a,b,*], Morris Weinberger [a,c], Miriam A. Kirshner [a], Karen M. Stechuchak [a], Stephanie D. Melnyk [a], Hayden B. Bosworth [a,b], Cynthia J. Coffman [a,d], Brian Neelon [e], Courtney Van Houtven [a,b], Pamela W. Gentry [a,b], Isis J. Morris [a], Cynthia M. Rose [a,b], Jennifer P. Taylor [a], Carrie L. May [a], Byungjoo Han [a], Christi Wainwright [a], Aviel Alkon [a,b], Lesa Powell [a], David Edelman [a,b]

[a] Center for Health Services Research in Primary Care, Durham Veterans Affairs Medical Center, Durham, NC 27705, USA
[b] Department of Medicine, Division of General Internal Medicine, Duke University, Durham, NC 27710, USA
[c] Department of Health Policy and Management, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599, USA
[d] Department of Biostatistics & Bioinformatics, Duke University, Durham, NC 27710, USA
[e] Department of Public Health Sciences, Medical University of South Carolina, Charleston, SC 29425, USA

ARTICLE INFO

Article history:
Received 24 May 2016
Received in revised form 6 July 2016
Accepted 10 July 2016
Available online 12 July 2016

Keywords:
Hypertension
Randomized controlled trial
Veterans

ABSTRACT

Despite the availability of efficacious treatments, only half of patients with hypertension achieve adequate blood pressure (BP) control. This paper describes the protocol and baseline subject characteristics of a 2-arm, 18-month randomized clinical trial of titrated disease management (TDM) for patients with pharmaceutically-treated hypertension for whom systolic blood pressure (SBP) is not controlled (≥140 mm Hg for non-diabetic or ≥130 mm Hg for diabetic patients). The trial is being conducted among patients of four clinic locations associated with a Veterans Affairs Medical Center. An intervention arm has a TDM strategy in which patients' hypertension control at baseline, 6, and 12 months determines the resource intensity of disease management. Intensity levels include: a low-intensity strategy utilizing a licensed practical nurse to provide bi-monthly, non-tailored behavioral support calls to patients whose SBP comes under control; medium-intensity strategy utilizing a registered nurse to provide monthly tailored behavioral support telephone calls plus home BP monitoring; and high-intensity strategy utilizing a pharmacist to provide monthly tailored behavioral support telephone calls, home BP monitoring, and pharmacist-directed medication management. Control arm patients receive the low-intensity strategy regardless of BP control. The primary outcome is SBP. There are 385 randomized (192 intervention; 193 control) veterans that are predominately older (mean age 63.5 years) men (92.5%). 61.8% are African American, and the mean baseline SBP for all subjects is 143.6 mm Hg. This trial will determine if a disease management program that is titrated by matching the intensity of resources to patients' BP control leads to superior outcomes compared to a low-intensity management strategy.

Published by Elsevier Inc.

1. Introduction

Despite its prevalence, associated morbidity and mortality, presence of evidence-based guidelines, and availability of >100 anti-hypertensive medications [1], only approximately half of American adults with hypertension (HTN) have achieved adequate blood pressure (BP) control [2,3]. Clinical trial results indicate that self-management support is critical to successful management of HTN and other chronic conditions [4–8]. Results from randomized trials would typically lead decision-makers to implement effective strategies per protocol. However, one size may not fit all. Instead, analogous to titrating medications when BP is above clinical targets [9], patients might reasonably require differing intensity of disease management depending on whether they have achieved these clinical targets. We are conducting a pragmatic clinical trial to evaluate the effectiveness of titrated disease management in which the intensity of disease management is adjusted based on an individual's systolic blood pressure (SBP).

1.1. Defining titrated disease management (TDM)

We view the process of TDM as analogous to the common process of titrating medication dosage in clinical care. For example, clinical guidelines often recommend adjusting the dosage and/or number of anti-hypertensive agents based on clinical parameters. This is often in the form of stepped care, where patient's initial medication dose is low to minimize risks of treatment (such as side effects) [10]. If patients are not responsive

* Corresponding author at: Durham VA Medical Center, HSR&D Service, (152), 508 Fulton St., Durham, NC 27705, USA.
E-mail address: george.l.jackson@duke.edu (G.L. Jackson).

http://dx.doi.org/10.1016/j.cct.2016.07.009
1551-7144/Published by Elsevier Inc.

to initial treatments, their medication regimen is intensified until clinical goals are met. Absent some change in the underlying pathophysiology of disease (e.g., weight loss) or side effects, patients do not have their treatment reduced once clinical goals are reached; it is assumed that any reduction in intensity would diminish level of control [11–13].

We are conducting a pragmatic trial to examine the effectiveness of titrated (not stepped) care when applied to disease management. Specifically, we are adjusting (titrating) the resource intensity (and expense) of a disease management strategy based upon the patient's clinical status. Depending on the individual's BP, resources are either intensified or reduced to achieve or maintain BP control. This resource intensity differs by: 1) who delivers disease management; 2) the complexity of the treatment (i.e., whether there is medication intensification); and 3) frequency of patient contacts. The assumption of this novel approach is that patients will be titrated to different initial resource levels and will be evaluated over time to determine if they will: 1) remain at the same level of resource intensity; 2) increase to a higher intensity level; or 3) decrease to a lower resource intensity level. This type of titration addresses a criticism about stepped care where there is no plan to reduce level of drug or other resource use for patients with improving illness severity [14].

2. Materials and methods

2.1. Study sponsorship and IRB approval

This trial is funded by the United States Department of Veterans Affairs (VA) Health Services Research and Development Service (grant # IIR 10-383; clinicaltrials.gov registration # NCT01390272). It is being conducted under the approval of the Intuitional Review Board (IRB) of the Durham VA Medical Center.

2.2. Specific aims of the pragmatic trial

The primary question of the pragmatic trial is: will the TDM intervention reduce systolic blood pressure (SBP) over 18 months compared to licensed practical nurse (LPN)-delivered behavioral support calls occurring every two months [control arm]? The primary hypothesis is that veterans randomized to TDM will have greater improvement in mean SBP over the 18 months of follow-up than veterans in the control arm. Secondary outcomes include HTN control (dichotomous), cost-effectiveness (if successful), and adherence to hypertension medications.

2.3. Setting

The study is being conducted among patients receiving primary care at clinics in four separate locations affiliated with the Durham VA Medical Center. One location is the main VA hospital, one satellite clinic is located approximately 1.5 driving miles to the north, a second clinic is located approximately 45 driving miles to the east, and a final clinic is located approximately 110 driving miles east of the hospital. In 2015, these sites had approximately 46 primary care provider (PCP) full-time equivalents for delivery of care to approximately 44,000 unique patients.

2.4. Summary of the intervention

This is a two-arm 18-month pragmatic randomized clinical trial for veterans with pharmaceutically-treated hypertension and uncontrolled SBP (defined as ≥140 mm Hg for non-diabetic or ≥130 mm Hg for diabetic patients). The intervention arm includes three levels of resource intensity targeted to improve patients' SBP (Table 1).

- Low resource intensity: An **LPN** provides non-tailored behavioral support telephone calls every two months to patients whose SBP comes under control. The low resource intensity also serves as the control arm (described below).
- Medium resource intensity: A **registered nurse (RN)** provides monthly tailored behavioral support telephone calls **plus** home BP monitoring.
- High resource intensity: A **pharmacist** provides monthly tailored behavioral support telephone calls, home BP monitoring **and** pharmacist-directed medication management.

At the initial baseline visit patients who are randomized into the intervention arm are first titrated to either RN or pharmacist levels based on baseline blood pressure values. Subsequent titrations that include the LPN level happen at the 6 and 12 month study visits.

In the control arm (Table 1), a LPN provides behavioral support telephone calls every two months. This is identical to the low resource intensity component of the TDM intervention. This control arm differs from usual care in that patients receive additional regular contact that has been shown to enhance BP control among veterans [15] and medication adherence among North Carolina Medicaid beneficiaries [16].

2.5. Eligibility criteria

Eligible individuals included English speaking adults living in the community with access to a telephone who had been seen at a study clinic in the last year, had a VA PCP (Table 2). and had a history of pharmaceutically-treated HTN with uncontrolled SBP in the past year [17]. Specifically, based on the Seventh Report of the Joint National Commission on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC7), HTN is considered uncontrolled if SBP is ≥140 mm Hg for patients without diabetes or ≥130 mm Hg for patients with diabetes. While JNC 8 guidelines were issued during the trial [9],

Table 1
Summary of differences in intervention resource levels.

Attributes	Resource level		
	Low[a]	Medium	High
Delivered by Key clinician attributes	Licensed practical nurse (LPN) • Able to follow directions of higher level clinicians per protocol • May not do clinical assessments	Registered nurse (RN) • Can use clinical judgment to answer clinical questions and provide related assistance to patients • Can do clinical nursing assessments	Pharmacist • Can prescribe medication • Trained in medication management • Can provide clinical assessments of patients
Behavioral call frequency	Every two months	Monthly	Monthly
Modules activated by telephone calls will be tailored to patient	No	Yes	Yes
Clinician trained in motivational interviewing	No	Yes	Yes
Home BP monitoring	Not part of intervention	Yes	Yes
Pharmaceutical management	No	No	Yes

[a] The control arm for the study is delivery of the LPN/low intensity calls as described.