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Discontinuing a non-steroidal anti-inflammatory drug (NSAID) in patients with knee osteoarthritis: Design and protocol of a placebo-controlled, noninferiority, randomized withdrawal trial

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ABSTRACT

Background: Knee osteoarthritis (OA) is the most common cause of knee pain in older adults. Despite the limited data supporting their use, non-steroidal anti-inflammatory drugs (NSAID) are among the most commonly prescribed medications for knee OA. The use of NSAIDs for knee pain warrants careful examination because of toxicity associated with this class of medications.

Methods: We describe the design of a placebo-controlled, noninferiority, randomized withdrawal trial to examine discontinuation of an NSAID in patients with painful knee OA. Participants will be veterans enrolled in the VA Healthcare System with knee OA pain despite NSAID use and/or relatively higher risk of NSAID toxicity. After a two-week run-in period where eligible subjects will replace their current NSAID with the study NSAID (meloxicam), those remaining eligible (target N = 544) will be randomized to receive four weeks of either placebo or continued meloxicam. The primary outcome is knee pain (Western Ontario and McMaster Universities Osteoarthritis Index pain subscale, range 0—20) at four weeks post-randomization. The primary hypothesis is that placebo will be noninferior to (that is, not much worse than) meloxicam within a noninferiority margin of 1. Secondary outcomes include lower extremity disability, global impression of change, adherence to study medication and use of co-therapies.

Discussion: This study is the first clinical trial to date examining the effects of withdrawing an NSAID for OA knee pain. If successful, this trial will provide evidence against the continued use of NSAIDs in patients with OA knee pain.

Trial registration: ClinicalTrials.gov: NCT01799213. Registered February 22, 2013.

1. Background

Osteoarthritis (OA) is a common cause of knee pain and lower extremity disability in older adults [1]. Persons with knee OA have significantly lower quality of life in all domains compared to age-matched controls [2]. Veterans have higher prevalence of OA compared to non-Veterans [3] and over half report daily activity limitations because of joint symptoms [4]. Moreover, because of injuries incurred during training and active duty, veterans develop OA at a younger age than civilians [5]. Developing safe approaches to managing pain in this younger population is particularly important given the chronicity of OA.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly prescribed for OA [6], with over 50% of people with OA reporting regular use [7]. While short-term studies have demonstrated that NSAIDs are more effective than placebo and acetaminophen, there are limited long-term data supporting their use [6,8]. Moreover, the decrease in pain conferred by NSAIDs does not meet patient-defined

Abbreviations: ASA, acetylsalicylic acid; AUC, area under the curve; CBT, cognitive behavioral therapy; ITT, intention-to-treat; LME, linear mixed effects; MAR, missing at random; MNAR, missing not at random; NSAID, non-steroidal anti-inflammatory drug; OA, osteoarthritis; PP, per-protocol; RCT, randomized controlled trial; RWT, randomized withdrawal trial; VA, Veterans Affairs; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index

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thresholds indicating clinically significant improvement [9]. Given these data and the substantial morbidity associated with long-term NSAID use [10,11], discontinuation trials to determine whether there is a clinically significant incremental benefit of NSAIDs over and above placebo are warranted.

We describe the design and rationale of a randomized, placebo-controlled, noninferiority, withdrawal trial to examine discontinuation of an NSAID for painful knee OA. Eligible subjects will be those for whom a trial of NSAID discontinuation is most important: those who continue to have OA symptoms despite regular NSAID use and/or those at increased risk for NSAID-related toxicity. In the primary four-week phase of the trial, we will seek to determine whether placebo is non-inferior to the study NSAID. In a subsequent secondary phase, we will switch subjects allocated to placebo to cognitive behavioral therapy (CBT), while continuing NSAID in the NSAID group, and test whether the strategy of placebo followed by CBT is noninferior to NSAID.

2. Choice of study design

Since the primary question is to determine whether placebo is *not much worse* than continued NSAID (equivalently, NSAID *not much better* than placebo), a superiority trial is not well-suited. Although superiority trials that fail to reject the null hypothesis are frequently interpreted as showing no difference between groups, they should be interpreted as indeterminate [12]. A noninferiority trial is appropriate because the new strategy under investigation is safer than the long-term NSAID use [13].

While traditional randomized controlled trials (RCT) are the most commonly used to assess treatment efficacy, the large number of Veterans with knee OA using NSAIDs, the expected number of dropouts in a long-term study, the safety concerns related to initiating long-term use of NSAIDs in an experimental setting, and the expected increased use of co-therapies over time, warrant consideration of an alternative approach. The randomized withdrawal trial (RWT) randomizes subjects currently using the intervention to continued use or placebo [14]. This approach is particularly useful for examining the long-term efficacy of non-curative treatments when prolonged use of placebo and expected number of dropouts is likely to threaten the internal validity of the trial. The RWT is also a practical method of obtaining evidence to support/refute the continued use of medications which are already widely prescribed despite the lack of definitive evidence justifying their use. RWT is an efficient design requiring sample sizes of 20%–50% of those in classic RCTs due to the greater homogeneity in the study population [15] [16]. Carryover and withdrawal syndromes, important limitations of this approach, are not relevant for this study, as NSAIDs have relatively short half-lives and unlike opioids do not cause withdrawal symptoms (apart from recurrent pain) upon discontinuation.

3. Overview of study design

Eligible participants will partake in a two-week run-in period where all subjects will replace their current NSAID with the study NSAID (meloxicam). Those who remain eligible at the end of the run-in period will then participate in a four-week, double-blind, placebo-controlled, noninferiority RWT and will be randomized to continued meloxicam use versus placebo for four weeks (Fig. 1). After four weeks, subjects will enter the secondary phase of the trial, with those in the meloxicam arm continuing meloxicam and those in the placebo arm stopping the placebo and participating in a 12-week CBT program.

4. Study aims

The primary aim of the study is to determine whether placebo is noninferior to continued study NSAID (meloxicam) use in terms of knee pain intensity at 4 weeks post-randomization (primary endpoint) in patients with knee OA. A secondary aim is to determine whether placebo followed by CBT is noninferior to continued NSAID use in terms of knee pain intensity at 16 weeks post-randomization in patients with knee OA. We will also compare the two groups over time in terms lower extremity disability, global impression of change and use of co-therapies.

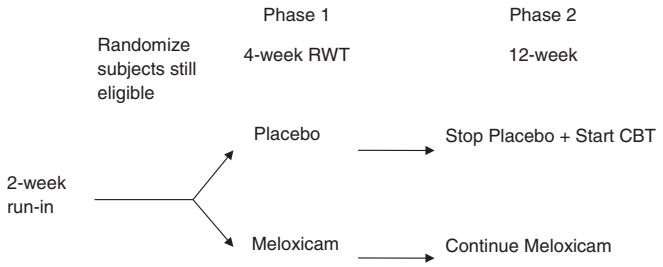

Fig. 1. Study design.

5. Study population

Participants will be drawn from Veterans with knee OA currently enrolled in the VA Connecticut Healthcare System (VACHS), Providence VA Medical Center, North Florida/South Georgia Veterans Health System or VA Boston Healthcare System. The study will include those for whom a discontinuation trial of NSAIDs is most appropriate: Veterans with knee pain despite NSAID use and/or at relatively higher risk of NSAID toxicity [17–21]. Subjects must meet all of the following criteria:

- be age 20 years or older. While the usual cutoff for knee OA is approximately 40 years, we chose to lower the age cutoff as younger Veterans have a higher than expected risk of OA.
- have radiographic evidence of knee OA;
- be using an NSAID (other than daily ASA) for knee pain on most days of the month for at least the past 3 months;
- be able to understand and speak English and have a telephone;
- be willing to engage in a CBT program, to discontinue (or replace) their NSAID, and to restrict co-therapies to acetaminophen for 16 weeks;
- be willing to start or continue taking a proton pump inhibitor (PPI) or misoprostol if found to have one or more risk factors for a NSAID-induced gastrointestinal toxicity. Subjects on anticoagulants are excluded.

In addition, subjects must meet one or more of the following four criteria:

- answer affirmatively to the question: “Do you have some knee pain on at least a few days out of every month?”;
- have one or more risk factors for NSAID-induced nephrotoxicity (age > 60 years, atherosclerotic cardiovascular disease, current diuretic use, chronic renal insufficiency, congestive heart failure (New York Heart Association Class I–II. Class III-IV are excluded);
- have one or more risk factors for NSAID-induced gastrointestinal toxicity (history of peptic ulcer disease, age > 65 years, concurrent use of daily acetylsalicylic acid (ASA) or corticosteroids);
- have one or more risk factors for NSAID-induced cardiovascular toxicity (prevalent cardiovascular disease, hypertension, hypercholesterolemia, diabetes, smoking, family history of early heart disease or age > 55 years for women).

Exclusion criteria are:

- Subjects desiring escalation of analgesics for their current level of knee pain as determined by endorsement of the following statement: