Osteoarthritis and Cartilage

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Brief report

Responsiveness of the Intermittent and Constant Osteoarthritis Pain (ICOAP) scale in a trial of duloxetine for treatment of osteoarthritis knee pain

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SUMMARY

Objective: To assess the change in the Intermittent and Constant Osteoarthritis Pain (ICOAP)-scale scores in patients taking duloxetine or placebo and to characterize the responsiveness of the ICOAP by comparing the effect size associated with its scales to effect sizes seen with other pain scales used in this study.

Methods: This was a secondary analysis of data from a 10-week, double-blind, randomized, flexible-dose, placebo-controlled trial that enrolled patients who had persistent moderate pain due to osteoarthritis (OA) of the knee, despite having received nonsteroidal anti-inflammatory drug (NSAID) therapy. The pain measures used in this study (focusing on the drug-placebo difference at week 8) were patient-rated pain severity, the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), the Brief Pain Inventory (BPI), and the ICOAP.

Results: The mean difference between duloxetine and placebo at week 8 for patient-rated pain severity, the BPI average pain, WOMAC pain, and each ICOAP scale was statistically significant ($P < 0.001$ for each). The ICOAP total showed a moderate effect size of 0.53, whereas the constant and intermittent scores showed effect sizes of 0.47 and 0.49, respectively. The patient-rated pain severity and the BPI average pain showed similar moderate effect sizes of 0.59 and 0.53, respectively.

Conclusion: The study demonstrated efficacy of duloxetine compared with placebo when using the ICOAP scale in a placebo-controlled trial. The observed treatment effect size for the ICOAP scores was similar to that for other reliable, valid and responsive pain assessments.

Clinical trials registration: ClinicalTrial.gov Identifier: NCT01018680

Introduction

Pain is the most commonly reported symptom in patients with osteoarthritis (OA) of the knee[1]. This pain may initially be associated with activity; however, as the disease progresses, it may become more constant and is eventually associated with intermittent episodes of greater pain. With the endorsement by the Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) and the Osteoarthritis Research Society International (OARSI), the Intermittent and Constant Osteoarthritis Pain (ICOAP)[2,3] questionnaire was recently developed as a pain assessment tool for knee or hip OA. Various studies describe the utility of the ICOAP including how to evaluate the measurement properties and examine the pain experience of patients with OA[2,3]. Additional studies have reported the responsiveness of the ICOAP following knee and hip replacement[4], after 4 weeks of physical therapy for knee OA[5], and after 6 months in a randomized, double-blind (nonplacebo-controlled) trial of various nonsteroidal anti-inflammatory drug (NSAID) therapies in patients with knee or hip OA[6]. Recently, Frakes et al.[7] showed that duloxetine was superior to placebo when added to NSAID therapy in the treatment of OA knee pain over 8 weeks. The purpose of the present work is two-fold. First, we provide results concerning the change in ICOAP-measured pain in patients taking duloxetine or placebo. Second, as this is the first known placebo-controlled study to include the ICOAP, we further characterize the responsiveness of the ICOAP by comparing the effect size associated with its scales to the effect size seen with other pain scales implemented in the study.

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Methods, results, and discussion

Methods

Study population

In this double-blind, randomized, placebo-controlled, 10-week, flexible-dose study of male and female patients greater than 40 years of age who met American College of Rheumatology (ACR) clinical and radiographic criteria for OA of the knee[8], patients were required to have knee pain for ≥14 days/month in the 3 months preceding study entry and report use of NSAIDs for treatment of knee pain on most days during that period. The enrolled patients had persistent moderate pain (≥4 on a 0-to-10 numerical rating scale) due to OA of the knee, despite having received optimized NSAID therapy (specific drug, dose, and frequency at investigator discretion to reflect patient-physician decisions around efficacy, tolerability, and cost). Additional patient inclusion and exclusion criteria for this study, as well as full study design details are provided in the previously published article associated with this clinical trial[7]. The study protocol was approved by appropriate institutional review boards (IRBs), and informed consent was obtained from all patients prior to study entry in accordance with the Declaration of Helsinki.

Study design

During the 2-week screening phase of the study, investigators were asked to optimize the patient's current NSAID treatment to reflect patient-physician decisions around efficacy, tolerability, and cost. Patients who had at least a 70% compliance rate with the telephone-based diary system and who had an average weekly pain severity rating of ≥4 during the previous week were randomly allocated to receive either 10 weeks of duloxetine (Cymbalta®, Eli Lilly and Company) treatment or placebo added to the optimized NSAID therapy. Patients allocated to duloxetine were given 30 mg/day for 1 week, followed by 60 mg/day for 2 weeks. At week 3 of active treatment, patients who had a mean average pain severity rating of ≥4 during the previous week had a blinded dose escalation to 120 mg/day. Week 8 was considered to be the efficacy end point of this 10-week study.

Measurements

Patient-rated pain severity was the primary measure of efficacy in this study. Patients used a telephone-based diary system to record daily average pain severity considering the previous 24 h. Daily pain ratings were based on a scale ranging from 0 (no pain) to 10 (pain as severe as you can imagine). For analysis, the daily ratings were composed into weekly means, and focussed on the drug-placebo difference at week 8 as the primary endpoint.

In addition, three measures of OA pain were obtained at each treatment visit: the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)[9], the Brief Pain Inventory (BPI)[10], and the ICOAP[2,3].

The WOMAC is designed to assess pain, stiffness, and physical function in patients with OA of the knee or hip. It consists of 24 questions: five on pain, two on stiffness, and 17 on physical function, each answered by using a 5-point scale ranging from 0 (none) to 4 (extreme). Each WOMAC multi-item subscale is normalized to values between 0 (best condition) and 100 (worst condition). In these analyses, the focus for the WOMAC is on the outcome assessing pain. The BPI is a self-reported scale that measures the severity of pain and the interference of pain on function. Severity of pain was assessed with four questions: patients assign scores to characterize their worst pain, least pain, average pain in the previous 24 h, and their current pain. Pain ratings range from 0 (no pain) to 10 (pain as bad as you can imagine). Use of the ICOAP in this study was based on an exploratory objective. The ICOAP consists of 11 items each rated on a 5-point (0 = not at all/no pain, 1 = mildly, 2 = moderately, 3 = severely, and

4 = extremely) anchored scale and assessed within the past week. A score is produced for the constant pain subscale (0-20), intermittent pain subscale (0-24), and total pain (0-44, calculated by summing the subscale scores). Each score is normalized to values between 0 (best condition) and 100 (worst condition). For both, the constant knee pain, and the knee pain that comes and goes [intermittent], the patient is asked to select a response that best describes how intense the pain has been during the past week, how much the pain affects sleep and overall quality of life, and how frustrated or annoyed, and, upset or worried the patient has been, due to the knee pain. In addition, the patient is also asked how frequently the intermittent knee pain occurred (0 = never/no knee pain that comes and goes, 1 = rarely, 2 = sometimes, 3 = often, and 4 = very often).

Statistical analyses

The analyses were done on the intent-to-treat efficacy population. Only patients with a baseline and at least one postbaseline measure were included in the analysis of each measure. Change in the patient-rated pain severity was analyzed using a mixed-model repeated measures (MMRM) approach which contained terms for treatment, week, site, baseline severity rating, and treatment-by-week and baseline-severity-rating-by-week interaction terms as fixed effects, and patient as a random effect. A similarly constructed MMRM model was used to analyze change in the BPI average pain score, the WOMAC pain subscale, and the ICOAP total, intermittent, and constant pain scores with visit replacing week for these measures taken at each visit. The week 8 comparison between the duloxetine and placebo group was used for the primary, secondary, and exploratory efficacy measures. Estimated [least squares (LS)] means by treatment at each week/visit were compared using Student's t-tests. The observed effect size was derived as the difference in estimated means at week 8 divided by the estimated within-patient standard deviation (SD) at week 8 as derived from the MMRM-based within-patient variance-covariance matrix. Confidence intervals (CIs) on the observed effect size associated with treatment differences for various measures of pain or function were computed using the properties of the noncentral t-distribution and the interval inversion principles described by Steiger and Fouladi[11].

Statistical tests were performed at the two-tailed 0.05 level of significance and 95% CIs were computed. All analyses were performed with SAS® software version 9.1 (Cary, NC, USA).

Results

A total of 524 patients were randomly assigned to treatment, 264 to duloxetine and 260 to placebo[7]. The average age of the patients was 61 years (age range: 40–92 years), 80.9% of patients were white, and 57.1% were women. Ibuprofen (45.6%) and naproxen (34.2%) were the most frequently used NSAIDs by patients overall, while meloxicam, celecoxib, and diclofenac accounted for a majority of the remaining NSAIDs that were used.

The mean changes and effect sizes for the ICOAP results are presented in Table I. The results for the other measures, while previously reported[7], are included here for comparison purposes. The mean difference between duloxetine and placebo at week 8 for the patient-rated pain severity, the BPI average pain score, WOMAC pain subscale, and ICOAP subscales was statistically significant (P < 0.001 for each) (Table I). Further, the ICOAP total pain score showed a moderate effect size[12] of 0.53, whereas the constant and intermittent scores showed effect sizes of 0.47 and 0.49, respectively (Table I). The patient-rated pain severity and the BPI average pain score showed similar moderate effect sizes of 0.59 and 0.53, respectively. The WOMAC pain subscale had the lowest effect size (0.43) of the pain measures used in the study (Table I).