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Efficacy and safety of duloxetine in Chinese patients with chronic pain due to osteoarthritis: a randomized, double-blind, placebo-controlled study

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SUMMARY

Objective: We assessed the efficacy and safety of duloxetine (60 mg, once daily), compared with placebo, during a 13-week treatment period in Chinese patients with chronic pain due to osteoarthritis (OA).
Design: Patients were at least 40 years old (male or female) who met American College of Rheumatology clinical and radiographic criteria for the diagnosis of OA of the knee or hip. The primary efficacy measure in this phase 3, randomized, double-blind, placebo-controlled clinical trial was assessment of pain severity by the Brief Pain Inventory (BPI) 24-h Average Pain rating. The clinical trial was conducted at 17 study centers. Statistical approaches included mixed-effects model repeated measures and analysis of covariance. A Fisher exact test was applied to categorical variables.
Results: Of 407 patients randomized (duloxetine: $N = 205$; placebo: $N = 202$), 166 (81.0%) patients from the duloxetine group and 176 (87.1%) patients from the placebo group completed the 13-week treatment phase. The majority (76.4%) of patients was female; mean age was 60.5 years. Duloxetine-treated patients reported significant pain reduction, compared with placebo treatment, on the BPI 24-h Average Pain rating (least-squares mean (LS Mean) change from baseline to endpoint [95% confidence interval (CI)], duloxetine: −2.23; placebo: −1.73; difference = −0.50 [−0.80, −0.20]; $P = 0.001$). The incidence of discontinuations due to adverse events was 9.0% in duloxetine-treated patients and 4.5% in placebo-treated patients ($P = 0.109$).
Conclusions: This study demonstrated the efficacy of duloxetine in Chinese patients with chronic pain due to OA. The safety profile of duloxetine observed in this study was consistent with that in previous duloxetine trials.
This trial is registered with ClinicalTrials.gov (NCT01931475).

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Introduction

Osteoarthritis (OA) is a disease of the joints that results from breakdown of cartilage and underlying bone, most commonly in the knee, hip, and hand. The most common symptoms of OA are joint pain, loss of function, and stiffness[1]. The worldwide prevalence of OA is estimated to be 9.6% for men and 18.0% for women ≥60 years old[2]. OA is also common in China. A survey in Beijing found that OA of the knee affects 5.6% of men and 15% of women ≥60 years of age[3]. Another survey, in Guangzhou, found that OA of the knee affects 9.1% of men and 20.5% of women ≥40 years of age[4].

Analgesics commonly used to treat OA pain in China include acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), weak opioids (such as, oral codeine and tramadol), and topical capsaicin[5]. However, these drugs have limited efficacy and/or are associated with safety concerns[6]. Therefore, other treatment options are needed.

Recently, it has been shown that augmented central pain processing may play a role in peripheral or nociceptive pain conditions, such as OA[7]. Impaired activity of descending inhibitory pain pathways may contribute to certain chronic pain states[8–10]. Indeed, activation of descending pain pathways by aerobic exercise, for example, has proven benefits[11].

The neurotransmitters serotonin and norepinephrine are involved in these descending inhibitory pathways[12,13]. Duloxetine is a potent and selective inhibitor of serotonin and norepinephrine reuptake in the central nervous system *in vitro* and *in vivo*[14]. In addition, duloxetine has been approved for the treatment of diabetic peripheral neuropathic pain, fibromyalgia, and chronic musculoskeletal pain in the United States as well as in other countries. Given the similar pharmacokinetic profiles of duloxetine between Chinese and Caucasians[15,16], it is thought that duloxetine may also prove effective in the treatment of chronic pain in Chinese patients. Indeed, duloxetine has shown efficacy in treating diabetic peripheral neuropathic pain in Chinese patients[17].

The primary objective of this 13-week study was to assess the efficacy of duloxetine (60 mg, once daily [QD]), compared with placebo, in the reduction of OA-related knee or hip pain severity in Chinese patients, as measured by the Brief Pain Inventory (BPI) 24-h Average Pain rating. Secondary objectives included further assessments of the reduction of OA-related pain over the 13-week treatment period and the evaluation of the safety and of health outcomes in this population.

Methods

This was a multicenter, randomized, phase 3, double-blind, parallel clinical trial, comparing the efficacy and safety of duloxetine 60 mg QD with placebo in Chinese patients with OA knee or hip pain during a 13-week treatment period, followed by a 13-week open-label treatment period. This study was conducted from December 2012 to June 2015 at 17 study centers in China. This manuscript will only present the results of the 13-week double-blind treatment period.

Patients

This study included male and female outpatients of at least 40 years of age who met clinical and radiographic criteria for the diagnosis of OA of the knee or hip, had pain for ≥14 days of each month for 3 months prior to study entry, and had a rating ≥4 on the BPI 24-h Average Pain item (Question 3 of the BPI-modified short-form) during screening, prior to treatment.

Patients were excluded from the study if they had any diagnosis of psychosis, bipolar disorder, schizoaffective disorder, current major depressive disorder, anxiety disorders (excluding phobias), alcohol or eating disorders, or suicidal risk. Also excluded were patients who were taking any excluded medications (analgesic agents including but not limited to NSAIDs, acetaminophen/paracetamol, and opioids) that could not be discontinued at the first study visit and patients who were anticipated by the investigator to require use of excluded medications during the study. After the start of treatment, episodic use of short-acting analgesics was allowed for management of breakthrough OA knee/hip pain (rescue therapy) or unrelated acute conditions. “Episodic use” was defined as no more than 3 consecutive days, not exceeding 20 total days. No rescue medication was allowed during the 24 h prior to any study visit.

Disease diagnostic criteria

The American College of Rheumatology criteria for diagnosis of OA were used. For the knee, OA disease criteria included knee pain, osteophytes (with radiographic evidence), and at least 1 of the following 3 conditions: age >50, morning stiffness <30 min, or crepitus[18]. For the hip, OA disease criteria included hip pain and at least 2 of the following 3 conditions: erythrocyte sedimentation rate <20 mm/h, femoral or acetabular osteophytes (with radiographic evidence), or radiographic joint space narrowing (superior, axial and/or medial)[19].

The presence of osteophytes in the index knee or hip and the hip joint space narrowing were confirmed by historical record of imaging studies (any of the following: plain X-ray, computed tomography [CT], or magnetic resonance imaging [MRI] within the last 2 years). In cases with no history of relevant imaging studies, an X-ray of the index knee or hip taken during the screening period was used instead.

Study design

This multicenter, randomized, parallel, placebo-controlled clinical trial included 5 study periods: a 1-week screening phase (Study Period I), a 13-week double-blind treatment phase (Study Period II), a 1-week titration phase (Study Period III), a 12-week open-label treatment phase (Study Period IV), and a 1-week taper phase (Study Period V). Only results of the 13-week double-blind treatment phase are being presented in this communication. Patients who met enrollment criteria during Study Period I continued into Study Period II and were randomized in a 1:1 ratio to either duloxetine 60 mg or placebo. Assignment to treatment groups was determined by a computer-generated random sequence using an interactive web-response system (IWRS). The IWRS was used to assign investigational product packages to each patient throughout this study. To achieve between-group comparability for site factor, randomization was stratified by site with the block size of 4. Emergency codes, generated by a computer drug-labeling system, were available to the principal investigator.

Patients, investigators, and all other personnel involved in the conduct of the study were blinded to individual treatment assignments during the double-blind treatment phase. After all patients completed or discontinued from the double-blind treatment phase, a reporting database was validated and locked to analyze the data from this phase. At this point, each patient's treatment assignment during Study Period II was unblinded to the statisticians (patients' treatment assignment was kept blinded to patients, investigators, and physicians until the end of the study). All study drugs used were identical in color, shape, smell, and taste, and all patients took the same number of capsules regardless of their treatment group assignment.

Patients assigned to duloxetine were started on duloxetine 30 mg for 1 week and then titrated up to duloxetine 60 mg. Patients