Onset of Response with Duloxetine Treatment in Patients with Osteoarthritis Knee Pain and Chronic Low Back Pain: A Post Hoc Analysis of Placebo-Controlled Trials

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ABSTRACT

Background: Knowing when to change pain-medication strategy is not well researched and remains a gap in treating chronic pain.

Objective: Our aim was to determine how long to treat osteoarthritis (OA) knee pain and chronic low back pain (CLBP) with duloxetine before considering a change in medication strategy.

Methods: We employed a post hoc analysis of changes in pain-severity data from placebo-controlled studies of duloxetine treatment in nondepressed patients with OA knee pain and CLBP. The studies were selected for inclusion in the analyses based on similarity of study design. Pain severity was recorded daily in patient diaries using an ordinal 11-point numerical rating scale (0 = no pain to 10 = most severe pain). The weekly means of the daily 24-hour average pain severity ratings from these diaries were pooled within disease states. Moderate response was defined as at least a 30% reduction from baseline in pain severity, and minimal improvement was defined as <10% reduction from baseline. The probability of achieving at least moderate pain reduction during 3 months treatment with duloxetine was estimated by Kaplan-Meier methods in patients with no or minimal improvement after 2, 4, and 6 weeks of treatment, as well as in all patients who had not yet achieved a moderate response (<30% reduction in pain severity).

Results: There were 239 OA patients and 541 CLBP patients who were randomly assigned to treatment with duloxetine 60/120 mg/d. OA and CLBP patients with minimal improvement at 2 weeks of treatment had <40% probability of achieving a moderate response, and at 4 weeks of treatment their chances were reduced to <30% in OA patients and <25% in CLBP patients. In patients showing <30% improvement at week 2 of treatment, OA patients had a 62% probability of achieving a moderate response, and CLBP patients had a 52% probability for a moderate response, and at 4 weeks of treatment, their chances were reduced to <50% in OA patients and <40% in CLBP patients.

Conclusions: Patients taking duloxetine for OA or CLBP who have <10% reduction in pain after 4 weeks of treatment have limited possibility for eventually achieving even moderate pain reduction by the end of 12 weeks. ClinicalTrials.gov identifier: NCT00433290, NCT00408421, NCT00424593, NCT00408876, NCT00767806. (*Clin Ther.* 2014;▮:▮▮▮–▮▮▮)

Key words: back, chronic pain, duloxetine, minimal response, osteoarthritis.

INTRODUCTION

Low back pain and osteoarthritis (OA) knee pain are common musculoskeletal disorders, with estimated population prevalence rates in the United States ranging from 14% to 37% for knee OA to >65%

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of the adult population for low back pain.[1] When these painful conditions persist, they can become quite disabling and cause an enormous economic burden to the individual, as well as to society.[2,3] Consequences of chronic pain extend beyond just the pain itself, and often negatively affect sleep, mood, and energy, which contribute to the global suffering of the individual.[4]

Chronic musculoskeletal pain is associated with a dysregulation of the descending inhibitory pathways in the modulation of pain.[5] Analgesics that might provide relief are those that inhibit the afferent pain pathways or stimulate the efferent (descending) pain-modulating pathways. The major neurotransmitters in the descending pathways are serotonin and norepinephrine. Agents that potentiate serotonergic and noradrenergic activity in the synapses within the central nervous system act as analgesics and inhibit pain perception.[6]

Duloxetine (a selective serotonin and norepinephrine reuptake inhibitor) is a nonopioid medication that has demonstrated efficacy in clinical studies in chronic pain conditions, such as diabetic peripheral neuropathic pain,[7,8] fibromyalgia,[9,10] musculoskeletal pain associated with OA knee pain,[11,12] and chronic low back pain (CLBP).[13–15] Duloxetine has been approved by the US Food and Drug Administration for use in managing each of these types of pain. Because duloxetine does not work immediately, clinicians initiating treatment frequently ask for guidance on setting patient expectations about onset of improvement, as well as how long to keep patients on a trial of this medication. To determine how long to treat with duloxetine before considering a change in medication strategy, we conducted a post hoc analysis of response data from 2 OA knee-pain studies and 3 CLBP studies. Knowing when to change treatment due to inadequate pain response, whether that change is a switch to or addition of another agent, would be of clinical interest.[4]

METHODS

Study Design

This was a post hoc analysis of 3-month data from placebo-controlled studies of duloxetine treatment in nondepressed patients with OA knee pain and CLBP that were sponsored by Eli Lilly and Company. All 3 of the CLBP studies[13–15] in the duloxetine database were included in the analysis, but only 2 of the 3 OA knee pain studies were included (**Table I**).[11,12] The rationale for not including the third OA study[16] was that the entry criteria required all patients to have failed a trial of optimized treatment with NSAIDs and still have clinically significant knee pain, and dosage escalation was at 3 weeks instead of 7 weeks, as in the other 2 studies.

Details pertaining to trial design, as well as study population, conduct, and results have been published previously.[11–15] The OA studies were conducted from December 2006 through May 2008 and the CLBP studies were conducted from November 2006 through July 2009. All study protocols were developed in accordance with the ethical standard of Good Clinical Practice and the Declaration of Helsinki. Before studies began, all patients provided written informed consent and each clinical study site's Institutional Review Board approved the protocol.

Across all 5 studies, 24-hour mean pain severity was recorded daily in patient diaries using an ordinal 11-point numerical rating scale (0 = no pain to 10 = most severe pain). Efficacy assessments were the weekly means of the daily 24-hour mean pain severity ratings from these patient diaries. All study participants were adult (18 years of age or older) outpatients who had mean pain severity rating ≥ 4 on daily pain diary ratings during the screening and baseline periods. With the exception of one CLBP study,[15] all patients were allowed to continue with concomitant stable doses of acetaminophen or NSAIDs (including aspirin). None of the patients had a diagnosis of major depressive disorder, as defined by criteria of the *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition).[17]

For inclusion in the OA studies, patients were also required to have knee pain for ≥ 14 days of each month for 3 months before study entry. All patients randomly assigned to duloxetine treatment were started on 30 mg/d for 1 week, and then escalated to 60 mg/d. At week 7, patients were escalated to duloxetine 120 mg either by re-randomization without regard to change in pain severity[11] or their dosage was increased to 120 mg/d if they had $<30\%$ reduction from baseline in pain severity.[12]

For inclusion in each of the CLBP studies, patients had to have a clinical diagnosis of CLBP, with pain restricted to the lower back (class 1) or associated with radiation to the proximal portion of the lower limb only (class 2), according to the Quebec Task Force on Spinal Disorders,[18] and pain present on most days for ≥ 6