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Clinical experience with duloxetine in the management of chronic musculoskeletal pain. A focus on osteoarthritis of the knee

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Abstract: Duloxetine is a serotonin and norepinephrine reuptake inhibitor (SNRI) with central nervous system activity. Its analgesic efficacy in central pain is putatively related to its influence on descending inhibitory pain pathways. The analgesic efficacy of duloxetine has been demonstrated in four distinct chronic pain conditions. These include neuropathic pain associated with diabetic peripheral neuropathy, fibromyalgia, chronic low back pain, and osteoarthritis knee pain (OAKP). The purpose of this review is to examine the clinical efficacy and safety of duloxetine in the management of chronic OAKP. Three separate randomized, double-blind placebo-controlled trials have demonstrated that (1) a clinically meaningful decrease in pain severity occurs at about 4 weeks relative to placebo, (2) patients receiving duloxetine report better improvements in physical functioning relative to placebo, (3) duloxetine is safe and effective when used adjunctively with nonsteroidal anti-inflammatory drugs, and (4) that there are no new safety signals beyond what has been observed in other indications.

Keywords: Chronic pain management, drug interactions, duloxetine, osteoarthritis

Introduction

Osteoarthritis (OA) is recognized as one of the most prevalent chronic musculoskeletal diseases worldwide [World Health Organization, 2002]. The joints typically affected are located in the hands, knees, hips, and spine with varying degrees of joint deformity and swelling [Sarzi-Puttini *et al.* 2005]. Usually beginning when adults are in their 40s, it is estimated that 9.6% of men and 18% of women >60 years of age are affected with symptomatic OA. Since age is a significant risk factor in its development, it is predicted that OA will be the fourth leading cause of disability by 2020 [Sarzi-Puttini *et al.* 2005; Woolf and Pfleger, 2003]. In fact, the prevalence of knee OA has been reported to be 44% in those who are 80 years old or greater [Felson *et al.* 1987].

The yearly global economic burden of OA measured by direct and indirect costs is in the tens of billions of dollars annually [Chen *et al.* 2012].

Pain is recognized as one of the hallmark symptoms in knee OA and is the primary reason why patients seek medical attention [Creamer, 2000]. It is a significant determinant of functional impairment and disability, even more so than radiographic findings [Jinks *et al.* 2002; McAlindon *et al.* 1993]. Therefore, it is necessary to consider other factors which may be involved in the maintenance of pain when it cannot solely be explained by peripheral nociceptive factors. As such, alterations in the central nervous system (CNS) may be implicated and understanding the role of central sensitization in pain modulation is important in conditions such as chronic knee OA since its treatment requires an approach that differs from the treatment of pain in a peripheral context [Mease *et al.* 2011; Phillips and Clauw, 2013].

Osteoarthritis of the knee: pathophysiology and diagnosis

Knee OA has been characterized as an insidious disease related to structural changes in the joint over many years and decades. Progressive and irreversible articular damage results in a loss of the extracellular matrix of cartilage in addition to

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changes in subchondral bone. These degenerative changes result in cartilage loss, synovitis, subchondral cysts, bone marrow lesions, and osteophyte formation. It is also characterized by an attempt of the joint to regenerate tissue such as fibrocartilage [Iannone and Lapadula, 2003].

A clinical diagnosis may be made on the basis of three symptoms (persistent knee pain, short-lived morning stiffness, and reduced function) and identification of three signs on examination (crepitus, restricted movement, and bony enlargement) without an absolute requirement for imaging. The estimated probability of having radiographic knee OA increases with increasing number of positive features, to 99% when all six are present [Zhang *et al.* 2010].

Osteoarthritis knee pain

It was thought that pain was caused by cartilage damage; however, this view has since evolved given that cartilage is both an avascular and aneural tissue and therefore not capable of generating pain [Sofat *et al.* 2011]. In the earlier stages of the disease, patients typically report pain that is deep and aching which may worsen with joint use and improve with rest. In the later stages of the disease, patients may experience pain after minimal motion, and pain at rest can be severe enough to awaken the patient. Morning stiffness, lasting usually <30 minutes, is a common complaint. Stiffness of an affected joint is often described when the patient mobilizes after a period of rest. This phenomenon is referred to as articular gelling which resolves after several flexation and extension cycles [Sarzi-Puttini *et al.* 2005].

Radiographic studies have demonstrated that the amount of joint deformity does not reliably predict the amount of pain a patient may experience [Cubukcu *et al.* 2012]. Therefore, the experience of pain may involve the CNS and become more centralized [Sofat *et al.* 2011]. Through quantitative sensory testing, Finan and colleagues [Finan *et al.* 2013] elegantly demonstrated that patients with high levels of pain and an absence of moderate to severe radiographic findings show more centrally mediated pain processing.

Pharmacological treatment of osteoarthritis knee pain

Since 2000, numerous professional societies have published recommendations for the management of knee OA, including those developed by the European League Against Rheumatism (EULAR) [Jordan *et al.* 2003], the Osteoarthritis Research Society International (OARSI) [Zhang *et al.* 2008], the American Academy of Orthopaedic Surgeons (AAOS) [American Academy of Orthopaedic Surgeons, 2008], and the American College of Rheumatology (ACR) [Hochberg *et al.* 2012a].

These professional societies recommended the following steps in the pharmacological management of knee OA pain. If the healthcare provider chooses to initiate acetaminophen in the full dosage up to 4000 mg/day, the patient should be counseled to avoid all other products that contain acetaminophen, including over-the-counter cold remedies as well as combination products with opioid analgesics. If the patient does not have a satisfactory clinical response to full-dose acetaminophen, it is strongly recommended to use oral or topical nonsteroidal anti-inflammatory drugs (NSAIDs) or intra-articular corticosteroid injections. If they are ineffective or contraindicated, then it is conditionally recommended that tramadol, duloxetine, or intra-articular hyaluronan injections be used.

Pain processing, modulation and central sensitization

Both ascending nociceptive [Iyengar *et al.* 2004] and descending modulatory [Woolf, 2004] pathways are involved in pain perception (Figure 1). Ascending nociceptive pathways carry pain signals from the periphery to the brain [Scholz and Woolf, 2002]. More specifically, transduction occurs with the activation of peripheral nociceptors (C and Aδ-fibers) through stimulation of peripheral nerve endings which creates an electrical signal, a potential pain impulse, that is conducted to the spinal cord. The signal is then transmitted to central nerves in the spinal dorsal horn where peripheral nociceptors synapse with dorsal horn neurons. This is the first stage at which a pain signal can be modulated: either amplified or inhibited. Modulation of the signal is accomplished by neuronal, glial, and endocrine factors in the dorsal horn. Inhibition of the pain signal is referred to as gate control theory [Melzack and Wall, 1965]. This theory has been updated to reflect the notion that pain in itself is a multidimensional experience involving a distributed neural network, or 'neuromatrix' [Finan *et al.* 2013; Melzack, 1999]. Various neurotransmitters and neuromodulators are

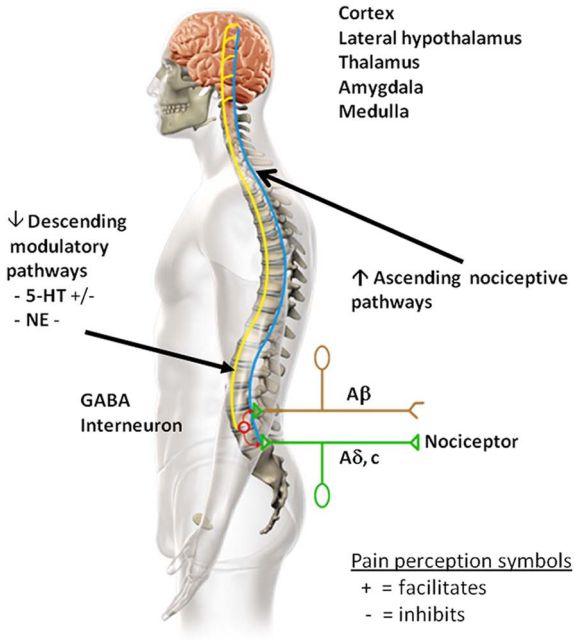

Figure 1. Ascending nociceptive pathways transmit/conduct noxious stimuli from the peripheral regions of the body to the brain. Descending modulatory pain pathways alter the processing of pain signals. Chronic pain, like that associated with knee osteoarthritis (OA), results in changes in the central nervous system, which likely reflect alterations in supraspinal modulation of nociception, and include increases in excitatory and decreases in inhibitory modulation pathways. In the descending modulatory pain system, the neurotransmitters 5-hydroxytryptamine (5-HT) and norepinephrine (NE) modulate pain signals. 5-HT both inhibits and facilitates the perception of pain. 5-HT inhibits pain via the descending inhibitory arm of the descending modulatory pathway and facilitates the perception of pain via the descending facilitatory arm of the descending modulatory pathway. NE inhibits the perception of pain via the descending inhibitory arm of the descending modulatory pathway. NE does not seem to be involved in the facilitatory aspect of pain perception in the descending modulatory pathway.

involved in the gating process. Both substance P and glutamate are involved in the amplification of pain signals whereas gamma aminobutyric acid (GABA), glycine, endocannabinoids, endorphins, monoamines, and neurosteroids are linked to the inhibition of pain signals. Through ascending pathways, the signal is then conducted further until it reaches the brain [Bolay and Moskowitz, 2002; Marchand, 2012].

A painful sensory input is not perceived as painful until it reaches the brain. This is the stage at which the signal is processed by various cortical and subcortical regions responsible for the overall experience and interpretation of pain for an individual. The brain is not only implicated in the interpretation and experience of pain, but it can also modulate pain signals [Apkarian *et al.* 2005; Schweinhardt and Bushnell, 2010].

Pain signals are also modulated via descending pathways [Woolf, 2004]. These pathways travel down from the brain to subcortical nuclei within the mid-brain until they reach the dorsal horn of the spinal cord and can either amplify or attenuate pain signals. Two essential neurotransmitters involved in the attenuation of pain signals are serotonin (5-HT) and norepinephrine (NE). While 5-HT can both amplify and attenuate pain signals, NE only has an attenuation effect. In addition to 5-HT and NE, opioids and GABA are involved in the inhibition of pain signals whereas glutamate and aspartate are involved in their amplification [Benn and Woolf, 2004; Fields *et al.* 1991; Richardson, 1990]. Chronic pain, similar to pain associated with knee OA, results in changes in the CNS, which likely reflect alterations in supraspinal modulation of nociception, and include increases in excitatory and decreases in inhibitory modulation pathways [DeSantana and Sluka, 2008; Staud, 2011].

Duloxetine as an analgesic

Duloxetine is a serotonin norepinephrine reuptake inhibitor (SNRI) and it is hypothesized that potentiation of 5-HT and NE activity in the CNS results in pain inhibition [Woolf, 2004]. The analgesic properties of duloxetine have been demonstrated in several chronic pain conditions. These include neuropathic pain associated with diabetic peripheral neuropathy [Goldstein *et al.* 2005; Raskin *et al.* 2005; Wernicke *et al.* 2006], fibromyalgia [Arnold *et al.* 2004, 2005; Chappell *et al.* 2009a; Russell *et al.* 2008], and chronic low back pain [Skljarevski *et al.* 2009, 2010a, 2010b].

Duloxetine has also been evaluated in three separate double-blind, randomized, placebo-controlled trials in chronic osteoarthritis knee pain (OAKP). These trials will herein be referred to as OA-1 [Chappell *et al.* 2009c], OA-2 [Chappell *et al.* 2011], and OA-3 [Frakes *et al.* 2011]. The recommended dose for OAKP is 60 mg once daily. Some patients may benefit from dosages above the recommended 60 mg once daily up to a maximum dose of 120 mg per day, although

the higher dose has been associated with a higher rate of adverse reactions. A lower starting dose of 30 mg may be considered for tolerability reasons in some patients, with a target dose of 60 mg/day within 1–2 weeks [Eli Lilly Canada Inc., 2012].

Duloxetine in OAKP

A concerted effort is underway to ensure that clinical trial research in pain is conducted according to the best available standards. The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) aims to systematically address the challenges related to pain research and has proposed recommendations related to clinical trial methodology and design [Dworkin *et al.* 2010], the inclusion of appropriate core outcome measures and domains [Dworkin *et al.* 2005; Turk *et al.* 2003], and the clinical interpretation of statistical results [Dworkin *et al.* 2008, 2009].

With the purpose of drawing clinically relevant information, a review of duloxetine's analgesic efficacy in OAKP will be presented within the context of IMMPACT recommendations.

Trial methodology

OA-1 [Chappell *et al.* 2009c] was a 13-week, randomized, double-blind, placebo-controlled trial. The trial design was divided into three study periods. Study period I was a 1-week screening phase in order to determine patient eligibility. In study period II, the 13-week treatment phase, eligible patients were randomly assigned 1:1 to receive either duloxetine 60 mg/day or placebo. During this period, patients started duloxetine at 30 mg/day during the first week and were then titrated to 60 mg/day. At week 7, patients receiving duloxetine were randomly re-assigned at a 1:1 ratio to receive either 60 mg/day or 120 mg/day for the remainder of the trial. At the end of the treatment period, week 13, patients underwent a 2-week taper phase.

The design for OA-2 [Chappell *et al.* 2011] is almost identical to that for OA-1 [Chappell *et al.* 2009c]. The primary difference is related to the dose escalation of patients at week 7. Here, patients had their dose increased to 120 mg/day based on their response. Response was defined as having less than a 30% pain reduction from baseline using the Brief Pain Inventory (BPI) average pain score [Cleeland and Ryan, 1994].

The aim of OA-3 [Frakes *et al.* 2011] was to evaluate duloxetine's efficacy in OAKP when added to patients already optimized on NSAID therapy. Patients were optimized on NSAIDs over a 2-week period. Those still experiencing at least a 4/10 on average weekly pain severity during the previous week were included into the study and were randomly assigned to 10 weeks of duloxetine or placebo treatment. However, the primary efficacy end point was at week 8. Efficacy ratings may be influenced by the impending end to a study; therefore both patients and investigators were unaware of the sham end point at week 10.

Similar to the other two studies, patients were started on duloxetine 30 mg/day for the first week of blinded therapy and were then titrated to 60 mg/day. To reflect what may occur in clinical practice, patients were re-evaluated at week 3 to determine response to treatment. Patients with a mean average pain severity score of at least 4/10 had their dose augmented to 120 mg/day of blinded treatment for the remainder of the trial.

Study patients

IMMPACT has identified several important characteristics which should be considered in subject selection. These include information on demographic and related characteristics, diagnosis, disease and pain duration, pain intensity, medical and psychiatric comorbidities, concomitant and rescue medications, and response to previous medications [Dworkin *et al.* 2010].

At a minimum, trials should report key demographic variables which include age, sex, and race/ethnicity. All three trials examining the effect of duloxetine on OAKP included age, sex and race [Chappell *et al.* 2009c, 2011; Frakes *et al.* 2011] (Table 1). IMMPACT has recommended that pain trials utilize already-existing validated diagnostic criteria in patient selection such as those from the ACR. ACR clinical and radiographic criteria for knee OA were used as the diagnostic inclusionary criteria for the three studies [Altman *et al.* 1986].

The duration of the disease as well as the duration of the pain can also influence the outcome of a trial. Patients must be in a chronic phase of their illness; however, they should not necessarily be in a treatment refractory stage either. Pain which has persisted at least 3 months can be considered as chronic [Dworkin *et al.* 2010]. Inclusion criteria

Table 1. Baseline patient characteristics.

Characteristics	OA-1 [Chappell *et al.* 2009]		OA-2 [Chappell *et al.* 2011]		OA-3 [Frakes *et al.* 2011]	
	Duloxetine 60–120 mg/day (*N* = 111)	Placebo (*N* = 120)	Duloxetine 60–120 mg/day (*N* = 128)	Placebo (*N* = 128)	Duloxetine 60–120 mg/day (*N* = 264)	Placebo (*N* = 260)
Age, mean (SD), years	62.1 (9.6)	62.5 (9.3)	63.2 (8.8)	61.9 (9.2)	61.6 (9.2)	60.3 (9.2)
Ethnicity, *n* (%) Caucasian	94 (84.7)	100 (83.3)	126 (98.4)	124 (96.9)	218 (82.6)	206 (79.5)
Female gender, *n* (%)	70 (63.1)	81 (67.5)	89 (69.5)	107 (83.6)*	152 (57.6)	147 (56.5)
Duration of osteoarthritis since diagnosis, mean (SD), years	6.9 (8.4)	7.1 (7.2)	6.2 (5.9)	5.6 (6.2)	9.8 (8.9)‡	9.2 (8.9) ‡
Mean duration of pain, mean (SD), years	9.0 (8.7)	9.3 (8.3)	8.1 (7.6)	6.7 (6.6)	9.8 (8.9)	9.2 (8.9)
Weekly average pain severity score, mean (SD)	6.1 (1.3)	6.2 (1.3)	6.0 (1.2)	6.1 (1.3)	6.27 (1.41)	6.36 (1.41)
NSAID use, yes, *n* (%)	58 (52.3)	59 (49.2)	47 (36.7)	53 (41.4)	100	100

*Significantly different from placebo ($p = 0.012$).
SD, standard deviation; NSAID, nonsteroidal anti-inflammatory drug.
‡Duration of osteoarthritis pain, years mean.

for the three duloxetine trials required that patients be at least 40 years of age and have OAKP for a minimum of 14 days of each month for 3 months. The duration of pain ranged from 6.7 to 9.8 years across all three trials [Chappell *et al.* 2009c, 2011; Frakes *et al.* 2011] (Table 1) indicating that patients included in the duloxetine trials were well within the chronic phase of their illness.

Homogeneity of pain intensity at baseline is a very important variable. To minimize floor effects (patients with very little pain at baseline), IMMPACT has stated that randomized controlled trials (RCTs) include patients who have a moderate pain severity of least 4 on a 0–10 numeric rating scale [Dworkin *et al.* 2010]. This cutoff was used in the three RCTs investigating duloxetine, and the range in pain severity at baseline was remarkably consistent across groups and trials and ranged from 6.0/10 to 6.4/10 [Chappell *et al.* 2009c, 2011; Frakes *et al.* 2011] (Table 1).

Overall, patients participating in these three trials were fairly consistent across trials and representative of patients suffering from chronic OA pain.

Other medical and psychiatric comorbidities may influence the outcome and interpretation of efficacy and safety results in RCTs, and IMMPACT recommends that these be exclusionary criteria [Dworkin *et al.* 2010]. All three duloxetine trials excluded patients with potentially confounding painful conditions and psychiatric illnesses [Chappell *et al.* 2009c, 2011; Frakes *et al.* 2011]. Patients with major depressive disorder (MDD), a previous diagnosis of psychosis, bipolar disorder, or schizoaffective disorder were also excluded from studies OA-1 and OA-2 [Chappell *et al.* 2009c, 2011; Frakes *et al.* 2011].

Patients receiving concomitant analgesic medications prior to study entry is a noteworthy potentially confounding variable [Dworkin *et al.* 2010]. Therefore, RCTs must adjust for this reality in their design. In trials which permit the use of concomitant analgesics, IMMPACT recommends that these patients remain on stable doses of the medication(s) and that rescue medication be available for pain unrelated to the condition under investigation (e.g. pain related to a dental procedure) and that it only be used temporarily

[Dworkin *et al.* 2010]. NSAIDs were allowed to be continued in all three duloxetine trials. In OA-1 [Chappell *et al.* 2009c] and OA-2 [Chappell *et al.* 2011], patients entering the trial were permitted to continue taking their NSAID/acetaminophen if they were taking therapeutic doses for at least 14 days per month for more than 3 months and were not permitted to increase their dose during the study. In order to ensure that groups were balanced for NSAID/acetaminophen use, patients were stratified at randomization. The third trial, OA-3, required that all patients be optimized on NSAIDs over the course of 2 weeks prior to study entry [Frakes *et al.* 2011].

Results from OA-1 [Chappell *et al.* 2009c] revealed that both the placebo (49.2%) and duloxetine (52.3%) groups were balanced at baseline for NSAID/acetaminophen use. However, a treatment-by-subgroup analysis between NSAID users and nonusers revealed that the nonuser group appeared to have a better response to both placebo and duloxetine relative to the user group. The authors posit that NSAID users may represent a subset of patients who may be more difficult to treat. This finding was not observed in OA-2 [Chappell *et al.* 2011]. Here, 41.4% of patients in the placebo group and 36.7% of patients in the duloxetine group were receiving NSAIDs at trial entry [Chappell *et al.* 2011].

Overall, the three trials examining the efficacy of duloxetine in OAKP [Chappell *et al.* 2009c, 2011; Frakes *et al.* 2011] adhered to key IMMPACT recommendations for clinical trial designs related to pain studies [Dworkin *et al.* 2010].

Core outcome measure and domains

In addition to pain intensity, IMMPACT has recommended five other core domains which should be considered in clinical trials of analgesia efficacy. These include (1) physical functioning, (2) emotional functioning, (3) participant ratings of improvement and satisfaction with treatment, (4) symptoms and adverse events, and (5) participant disposition (e.g. adherence to the treatment regimen and reasons for premature withdrawal from the trial) [Dworkin *et al.* 2005; Turk *et al.* 2003]. IMMPACT has also proposed reliable and validated measures which address these core domains [Dworkin *et al.* 2005] and recommendations regarding the translation of statistical results into clinically relevant terms [Dworkin *et al.* 2008, 2009]. The following section on the efficacy and safety of duloxetine will be presented within the context of these IMMPACT recommendations.

Effect of duloxetine on pain intensity

The majority of RCTs evaluating analgesic efficacy utilize reductions in pain intensity as their primary outcome measure. Visual analog scales, numerical rating scales, as well as verbal rating scales have all been demonstrated as being valid and reliable measures of pain [Dworkin *et al.* 2005].

All three duloxetine trials utilized changes in pain intensity as their primary efficacy outcome variable. OA-1 [Chappell *et al.* 2009c] and OA-3 [Frakes *et al.* 2011] measured changes in pain intensity by the weekly mean of the 24-h average pain scores. This numerical rating scale is based on an 11-point Likert scale (an ordinal scale with 0 = 'no pain' and 10 = 'worst pain imaginable'). OA-2 [Chappell *et al.* 2011] utilized the average pain score item from the BPI [Cleeland and Ryan, 1994]. The BPI is a validated self-reported tool which assesses pain severity (BPI-S) in addition to its interference on daily functions (BPI-I). The BPI-S subscale is composed of four questions which ask the subject to rate their pain on a 0 to 10 Likert scale (with 0 = no pain to 10 = pain as bad as you can imagine). They are asked about their (1) worst pain in the past 24 h, (2) least pain in the last 24 h, (3) their average pain in the past 24 h, and (4) their pain right now [Cleeland and Ryan, 1994].

Results from OA-1 [Chappell *et al.* 2009c] revealed that the duloxetine 60/120 mg/day group had statistically significant reductions in average pain scores relative to placebo beginning at week 1 and at each weekly time point thereafter. The mean change from baseline to end-point in the 24-h average pain score also showed a statistically significant difference in favor of duloxetine 60/120 mg/day (duloxetine = −2.92; placebo = −2.08). A similar finding was observed in OA-2 [Chappell *et al.* 2011]. Reductions in BPI average pain severity at each time point (weeks 4, 7, and 13) were statistically significantly different in favor of duloxetine 60/120 mg/day *versus* placebo. The mean change from baseline to end point at week 13 was −2.72 for duloxetine 60/120 mg/day and −1.88 for placebo. A similar pattern emerges in OA-3 where duloxetine or placebo is added to patients optimized on NSAID therapy [Frakes *et al.* 2011]. Here, there is a statistically significant

separation between groups beginning at week 1 which is continued through to week 8. The mean change from baseline to end point on the average pain rating was −2.46 for duloxetine 60/120 mg/day and −1.55 for placebo.

From a clinical stand point, what do these magnitudes of change on an ordinal scale that ranges from 0 to 10 mean? IMMPACT recommends that a decrease of two points from baseline to end point is clinically meaningful for patients and represents a important decrease in chronic pain intensity [Dworkin *et al.* 2008]. Although statistical significance separated duloxetine from placebo as early as week 1 (OA-1 and OA-3), a statistical significance does not necessarily equate to clinical significance. These results across the three trials suggest that the impact of duloxetine on a clinically meaningful reduction in pain occurs at about 4 weeks and is maintained for the remainder of the trial periods. Placebo also achieved a clinically meaningful change in OA-1 [Chappell *et al.* 2009c].

According to IMMPACT recommendations on the interpretation of group differences, it is suggested that responder analyses be used to elucidate the question of whether or not the magnitude of differences between groups is clinically meaningful despite statistical significance [Dworkin *et al.* 2008]. IMMPACT provisionally suggests that a 30% change from baseline to end point on the primary outcome variable is considered to be a moderate improvement in pain severity whereas a 50% improvement is reflective of a substantial improvement. A comparison of responder rates between an active medication and placebo provides clinically meaningful information regarding the magnitude of improvement between groups.

Responder analyses were conducted in all three duloxetine trials. OA-1 [Chappell *et al.* 2009c] reported a statistically significant 30% improvement in 59% of duloxetine patients and 45% of placebo patients. A similar statistically significant pattern emerged for the 50% response rate; 47% for duloxetine patients and 29% for placebo. These results suggest that there was a clinically meaningful difference in the reduction of pain severity for patients treated with duloxetine relative to placebo in OA-1.

Similar to OA-1, statistically significant differences in 30% responder rates for OA-2 were observed; 65% for duloxetine and 44% for placebo [Chappell *et al.* 2011]. However, differences in 50% responder rates failed to show a statistically significant difference; 44% for duloxetine and 32% for placebo. In OA-3, both 30% and 50% responder rates were statistically significant in favor of duloxetine. More specifically, 54% of patients in the duloxetine group and 34% in the placebo group achieved a 30% improvement. Furthermore, 36% of duloxetine patients and 16% of placebo patients achieved a 50% response [Frakes *et al.* 2011]. With the exception of 50% improvement in OA-2, these results suggest that patients receiving duloxetine 60/120 mg/day show moderate to substantial improvements in their pain severity.

Effect of duloxetine on physical functioning

The assessment of physical functioning in each of the three duloxetine trials used the BPI-I [Cleeland and Ryan, 1994] and the physical functioning subscale of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC-pf) [Bellamy *et al.* 1988].

As mentioned previously, the BPI is a validated self-reported tool which assesses pain severity (BPI-S) in addition to its interference on daily functions (BPI-I). The BPI-I subscale uses a 0 (does not interfere) to 10 (completely interferes) Likert scale and is composed of seven items. Patients are asked to rate the amount of interference their pain has had in the last 24 h on (1) general activity, (2) mood, (3) walking ability, (4) normal work, (5) relations with other people, (6) sleep, and (7) enjoyment of life [Cleeland, 1994].

The general activity item was the only item which was consistently statistically significantly different from placebo in each of the three trials. The mean change from baseline to end point for duloxetine ranged from −2.16 in OA-2 [Chappell *et al.* 2011] to −2.72 in OA-1 [Chappell *et al.* 2009c]. The mean change from baseline to end point for placebo ranged from −1.56 in OA-3 [Frakes *et al.* 2011] to −2.01 in OA-1 [Chappell *et al.* 2009c]. In considering each trial individually, patients treated with duloxetine in OA-3 had statistically significantly greater improvements in each of the seven items from the BPI-I compared to placebo [Frakes *et al.* 2011]. Duloxetine patients in OA-1 [Chappell *et al.* 2009c] had significant improvements relative to placebo on four of the seven items. In addition to general activity, these included walking ability, sleep, and enjoyment of

life. Finally, the only two items to show a statistically significant difference between duloxetine and placebo in OA-2 were general activity and normal work [Chappell *et al.* 2011].

The WOMAC 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 using a 5-point scale ranging from 0 (none) to 4 (extreme) [Bellamy *et al.* 1988]. A composite score of these 17 items is then calculated (range 0–68) and lower scores reflect better functioning. Statistically significant differences between duloxetine patients and placebo were observed in all three OA trials [Chappell *et al.* 2009c, 2011; Frakes *et al.* 2011]. Decreases in WOMAC-pf change scores from baseline to end point ranged from −12.69 [Chappell *et al.* 2011] to −21.10 [Frakes *et al.* 2011] for duloxetine and from −9.43 [Chappell *et al.* 2011] to −13.81 [Frakes *et al.* 2011] for placebo.

In considering results from the BPI-I and the WOMAC-pf, duloxetine patients demonstrated greater improvements in physical functioning relative to placebo patients.

Effect of duloxetine on emotional functioning

IMMPACT recommends [Dworkin *et al.* 2005] that emotional symptoms be assessed with an instrument such as the Beck Depression Inventory-II (BDI-II) [Beck *et al.* 1988]. However, both OA-1 and OA-2 [Chappell *et al.* 2009c, 2011] excluded patients if they had current MDD or any other psychiatric diagnosis. For instance, patients in OA-1 had scores <6 on the BDI-II at baseline indicating minimal depressive symptoms well within the normal range at study entry [Chappell *et al.* 2009c]. This floor effect would preclude observing significant decreases in depressive symptoms over the course of the trials. Nevertheless, depressive as well as anxiety symptoms were evaluated using path analysis in both OA-1 [Chappell *et al.* 2009c] and OA-2 [Chappell *et al.* 2011] in order to determine the contribution of emotional symptoms (depression and anxiety) to the overall analgesic effect of duloxetine. This analysis revealed that changes from baseline to end point in depression and anxiety had very little influence on the analgesic effect of duloxetine on changes in pain severity [Chappell *et al.* 2009c, 2011].

Patient global impression of change

Other secondary measures including the Patient Global Impression of Improvement (PGI-I) [Guy, 1976] were included in all three studies. The PGI-I is a one-item, seven-point scale which evaluates a patient's impression of their overall change from randomization to the end of the trial. The scale ranges from 1 (very much better) to the midpoint of 4 (no change) to 7 (very much worse). While there was no significant improvement on the PGI-I between the duloxetine patients and the placebo group in OA-2 [Chappell *et al.* 2011], significant differences in both OA-1 and OA-3 were observed. The duloxetine patients in OA-1 reported that their improvement was 2.38 whereas the placebo group reported their improvement to be 2.91 (2 = much better and 3 = a little better) [Chappell *et al.* 2009c]. OA-3 reports that 53% of duloxetine patients reported feeling at least much better compared with 32% of placebo patients [Frakes *et al.* 2011]. Overall, duloxetine patients report better global improvements relative to placebo.

Health outcomes

Health-related outcomes were assessed in OA-1 and OA-2 with the 36-Item Short-Form Health Status Survey (SF-36) [Ware *et al.* 1993] and the EuroQol: 5 Dimensions Questionnaire (EQ-5D) [Kind, 1996]. The SF-36 is composed of eight items which measure changes related to (1) bodily pain, (2) general health, (3) mental health, (4) physical functioning, (5) role: emotional, (6) role: physical, (7) social functioning, and (8) vitality. Results for the SF-36 in OA-1 revealed significant differences between the duloxetine and placebo groups on three of the eight items. These were bodily pain, mental health and vitality [Chappell *et al.* 2009c]. Results in OA-2 showed significant differences in bodily pain, physical functioning, and role: physical [Chappell *et al.* 2011]. Both the US and UK indices for the EQ-5D were significantly improved in favor of the duloxetine patients in OA-1 [Chappell *et al.* 2009c].

Safety

The safety of duloxetine has been well characterized in clinical trials in more than 32,000 patients across all indications. Since its first approval in 2004, over 53 million patients have been treated with duloxetine worldwide, accounting for over 19 million patient-years of therapy. Duloxetine has been shown to be generally safe and well

Table 2. Adverse events.

Characteristics	OA-1 [Chappell *et al.* 2009]		OA-2 [Chappell *et al.* 2011]		OA-3 [Frakes *et al.* 2011]	
	Duloxetine 60–120 mg/day (*N* = 111)	Placebo (*N* = 120)	Duloxetine 60–120 mg/day (*N* = 128)	Placebo (*N* = 128)	Duloxetine 60–120 mg/day (*N* = 264)	Placebo (*N* = 260)
	n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
Discontinuation due to adverse event	15(13.5)	7(5.8)	24(18.8)	7(5.5)	40 (15.2)	23 (8.8)
Nausea	7(6.3)	2(1.7)	13(10.2)*	3(2.3)	41(15.5)***	12(4.6)
Fatigue	7(6.3)*	1(0.8)	2(2.3)	1(0.8)	18(6.8)**	4(1.5)
Constipation	4(3.6)	0	10(7.8)*	2(1.6)	23(8.7)**	8(3.1)
Somnolence	5(4.5)	1(0.8)	5(3.9)	3(2.3)	14(5.3)	7(2.7)
Dizziness	4(3.6)	2(1.7)	6(4.7)	2(1.6)	17(6.4)	7(2.7)
Diarrhea	5(4.5)	3(2.5)	6(4.7)	3(2.3)	18(6.8)	10(3.8)
Abdominal pain	1(0.9)	2(1.7)	6(4.7)	1(0.8)	–	–
Insomnia	3(2.7)	1(0.8)	6(4.7)	3(2.3)	13(4.9)*	3(1.2)
Hyperhidrosis	1(0.9)	1(0.8)	7(5.5)*	0	10(3.8)*	1(0.4)
Dry mouth	2(1.8)	2(1.7)	6(4.7)	1(0.8)	25(9.5)*	7(2.7)
Decreased appetite	3(2.7)	1(0.8)	1(0.8)	0	15(5.7)***	1(0.4)
Headache	3(2.7)	1(0.8)	4(3.1)	5(3.9)	16(6.1)	10(3.8)
Decreased libido	4(3.6)	0	1(0.8)	0	–	–
Hypertension	4(3.6)	1(0.8)	0	1(0.8)	–	–
Vomiting	–	–	1(0.8)	0	11(4.2)	3(1.2)
Dysgeusia			4(3.1)	1(0.8)	–	–
Asthenia	2(1.8)	0	4(3.1)	0	–	–

Incidence of treatment-emergent adverse events that occurred in ≥3% of patients treated with duloxetine and with an incidence greater than placebo.
*$p \leq 0.05$.
**$p \leq 0.01$.
***$p \leq 0.001$.

tolerated with no new safety concerns identified in the OA population. An analysis of safety data from 52 completed RCTs of duloxetine identified that the proportion of patients experiencing treatment-emergent adverse events was lowest in studies of OAKP *versus* other indications [Brunton *et al.* 2010]. The incidence of adverse events occurring at a rate of ≥3% in the three OA trials is summarized in Table 2. The most commonly experienced adverse events in OA knee patients include nausea, constipation, dry mouth, diarrhea, fatigue, dizziness, somnolence and insomnia [Chappell *et al.* 2009c, 2011; Frakes *et al.* 2011]. Nausea is typically mild–moderate and usually resolves within 8 days [Brunton *et al.* 2010]. Two strategies can be utilized in order to mitigate nausea. Patients can start at 30 mg/day or they can take the 60 mg dose with food in order to improve tolerability [Whitmyer *et al.* 2007].

The prescribing information for duloxetine contains warnings about certain rare but potentially clinically important adverse events. Cases of elevated liver enzymes, hepatitis, jaundice, and hepatic failure have been reported. Duloxetine should not be prescribed to patients with hepatic impairment or to patients with substantial alcohol use. As part of class labeling for all serotonin reuptake inhibitors, the duloxetine label includes precautions related to potential increases in suicidality in adolescents and young adults, the possibility of increased risk of bone fracture and potential increase risk of bleeding events due to serotonergic effects on platelet aggregation [Eli Lilly Canada Inc., 2012].

Table 3. Drug interactions.

Substrates of CYP2D6	Potential for increased concentrations of these agents or reduced efficacy of prodrugs that require conversion to their active metabolite, e.g. TCAs, tramadol (↑ tramadol concentration and ↓ conversion to M1), codeine (↓ conversion to morphine), tamoxifen(↓ conversion to endoxifen)
Potent inhibitors of CYP1A2	Potential for increased duloxetine concentrations, e.g. fluvoxamine (↓ clearance of approx. 77%), ciprofloxacin
Potent inhibitors of CYP2D6	Potential for higher concentrations of duloxetine, e.g. fluoxetine, paroxetine, bupropion
Seronergic agents	Potential for serotonin syndrome, e.g. MAOIs (absolute contraindication), caution is advised with triptans, serotonin reuptake inhibitors, tramadol, tapentadol, methadone, pentazocine or St. John's Wort
Drugs affecting platelet function or bleeding risk	Potential to potentiate the anticoagulant effects caused by serotonin reuptake inhibition of duloxetine, e.g. caution is advised with warfarin, NSAIDs, ASA, and other anticoagulants

ASA, acetylsalicylic acid; MAOI, monoamine oxidase inhibitor; NSAID, nonsteroidal anti-inflammatory drug; TCA, tricyclic antidepressant.

Drug interactions

Duloxetine is extensively metabolized, predominantly by CYP1A2 and also by CYP2D6, and its metabolites are not pharmacologically active. Duloxetine is also a moderate inhibitor of CYP2D6. Duloxetine should not be used concomitantly with potent inhibitors of CYP1A2 and with other drugs that are primarily metabolized by CYP2D6 (Table 3) [Eli Lilly Canada Inc., 2012].

Discussion

The importance of understanding pain mechanisms is crucial in the selection of appropriate analgesic treatments [Martel-Pelletier *et al.* 2012; Mease *et al.* 2011]. Duloxetine is an SNRI with CNS activity and its analgesic efficacy is putatively thought to involve its effect on descending inhibitory pain pathways [Woolf, 2004].

The efficacy of duloxetine as an analgesic for OAKP was evaluated in three randomized, double-blind, placebo-controlled trials. With respect to its effect on reducing pain intensity, IMMPACT recommends that a decrease of two points from baseline to end point is clinically meaningful for patients and represents an important decrease [Dworkin *et al.* 2008]. Results from the three trials suggest that impact of duloxetine on a clinically meaningful reduction in pain occurs at about 4 weeks and is maintained for the remainder of the trial periods [Chappell *et al.* 2009c, 2011; Frakes *et al.* 2011]. Furthermore, 30% and 50% responder analyses [Dworkin *et al.* 2008] suggest that a greater proportion of patients treated with duloxetine have moderate to substantial improvement in their pain intensity when compared with placebo [Chappell *et al.* 2009c, 2011; Frakes *et al.* 2011].

Similar results are reported in an independent 16-week trial evaluating duloxetine 60 mg/day and placebo in OAKP in older patients; ≥65 years [bou-Raya *et al.* 2012]. Here, OARSI 2004 clinical response criteria were used as the primary efficacy measure [Pham *et al.* 2004]. Response was defined as having at least a 50% reduction in pain scores or in physical function scores and had at least a 20 mm reduction on a visual analog pain scale (range 0–100 mm). The authors report that the duloxetine group had a significantly greater reduction in pain and physical function (WOMAC function scores) relative to placebo. They also report that the duloxetine group had a significantly greater reduction in paracetamol use at 16 weeks. Adverse events were also consistent with the three trials reported above. Duloxetine patients had significantly more constipation, nausea, hyperhidrosis, cough, myalgia, arthralgia, and palpitation.

A pooled analysis [Hochberg *et al.* 2012b] of OA-1 [Chappell *et al.* 2009c] and OA-2 [Chappell *et al.* 2011] revealed that duloxetine patients were 33% more likely to have a clinically meaningful response to treatment than placebo patients and that the number needed to treat (NNT) = 6. A clinically meaningful response is based on criteria developed by the Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) and the OARSI criteria [Pham *et al.* 2004]. Also, more duloxetine than placebo patients reported >30% improvement in pain from baseline to end point with an NNT = 5

and improvements >50% occurred more often in the duloxetine group with an NNT = 7. The authors conclude that duloxetine has a clinically meaningful effect on both pain and function. Also, duloxetine patients were more likely than placebo patients to experience a treatment-emergent adverse event and the NNH was 8 [Hochberg *et al.* 2012b].

A second recently published pooled analysis [Micca *et al.* 2013] of OA-1 [Chappell *et al.* 2009c] and OA-2 [Chappell *et al.* 2011] examining potential differences between older (≥65 years) and younger patients (40–65 years) revealed that there was no statistically significant difference between groups on OAKP when treated with duloxetine. Both groups did show statistically significant improvement over placebo. In addition, increasing the dose of duloxetine to 120 mg/day did not confer any additional benefit in either age category.

At the present time, there are no long-term studies evaluating duloxetine in OAKP. However, duloxetine has been evaluated in a 1-year extension trial of fibromyalgia [Chappell *et al.* 2009b]. Effectiveness was maintained over the course of the year and the safety of duloxetine was consistent with that observed in other indications.

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