Duloxetine for the management of pain in older adults with knee osteoarthritis: randomised placebo-controlled trial

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Abstract

Background: pain is the leading symptom of osteoarthritis (OA) and is often chronic in nature, leading to significant morbidity and decreased quality of life. Duloxetine, a selective serotonin norepinephrine reuptake inhibitor has been
Duloxetine for the management of pain

demonstrated to have a centrally acting analgesic effect.

Objectives: the aim of the present study was to investigate the efficacy of duloxetine in reducing pain in older adults with knee OA.

Methods: totally, 288 patients aged 65 years and above with primary knee OA were enrolled in this study. Patients were randomised 1:1. Totally, 144 received 60 mg/day of duloxetine HCL and 144 received placebo for 16 weeks. Outcome measures included pain reduction and improvement in physical functioning scores. Pain was assessed using the visual analogue pain scale (VAS; 0–100 mm). The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores were used to assess function.

Results: two-hundred and seventy four of the 288 patients completed the study. There was a statistically significant reduction in pain and a significant improvement in WOMAC scores at 16 weeks in the duloxetine group versus the placebo group. No serious side effects were reported.

Conclusions: the findings of the present study provide evidence for the efficacy and tolerability of duloxetine in reducing pain and subsequently improving function in older adults with knee OA.

Trial Registration: NCT01425827.

Keywords: pain, knee osteoarthritis, duloxetine, older people

Introduction

Osteoarthritis (OA), a common disabling condition among older adults, is the commonest type of arthritis worldwide [1]. Knee OA is the fourth leading cause of disability in women [2]. Pain is the leading symptom and is often chronic in nature, leading to significant morbidity and decreased quality of life [3–5].

In terms of clinical management, pain reduction and functional improvement are of paramount importance in the treatment of knee OA. To manage chronic pain due to OA, current treatment guidelines recommend a combination of pharmacological and non-pharmacological therapies [6]. Current treatment options have had limited symptomatic effect and are associated with significant side effects [7]. One of the reasons why attempts to address the overriding problem of pain in OA patients have been largely ineffective is that mechanisms underlying the pain of OA are complex [8].

OA pain has generally been viewed as a peripherally mediated nociceptive pain; however, it has been shown that when inflammatory mediators are released intra-articularly from damaged tissue, they modulate both peripheral and central nociceptors [7, 8].

The majority of recommended treatments for OA pain target the peripheral nociceptive nervous system. However, it is postulated that the continuous pain in OA leads to central sensitisation, manifesting as hyperresponsiveness to nociceptive stimuli and lowering of the pain threshold [8].

The imbalance of serotonin and norepinephrine (NE) systems within central pain pathways has been implicated in the development and maintenance of central sensitisation and associated chronic pain states. Chronic pain associated with OA involves dysfunction of central pain pathways [7, 8].

Duloxetine, a selective serotonin NE reuptake inhibitor has been demonstrated to have, besides its antidepressant properties, a centrally acting analgesic effect [9]. In previous studies, duloxetine has shown efficacy in the treatment of three distinct chronic pain conditions: diabetic neuropathic pain, fibromyalgia and chronic low back pain [10–12]. Accordingly, the aim of the present study was to investigate the efficacy of duloxetine in reducing pain in older adults with knee OA.

Methods

Study design

The present study was a single-centre double-blind randomised controlled clinical trial conducted at the Main University Hospital of our institution, with the approval of our university’s institutional review board and in compliance with the Helsinki Declaration.

Patients

Two hundred and eighty-eight patients aged 65 years and above attending the outpatient clinic of our institution were enrolled in this study. Recruitment of participants from the community occurred over a 4-month period. Methods to identify eligible participants included contacting employees of the university, educational presentations to various groups of older adults and placement of advertisements in strategic locations. Eligible participants were invited for face-to-face baseline screening visits. Informed consent was obtained from all patients prior to the commencement of the study.

Eligibility criteria

Patients with American College of Rheumatology clinical and radiographic criteria of primary knee OA [13] with knee pain, [>40 on the 24-h average pain severity scale (0–100) using mean of daily ratings from week preceding randomisation] for >14 days/month during three consecutive
months preceding enrolment were eligible. Radiographic criteria included Kellgren–Lawrence grade I–III tibiofemoral or patellofemoral OA found on weight-bearing anteroposterior and sunrise view radiographs [14].

Exclusion criteria
Potential participants were excluded if they had morbid obesity (BMI greater than 32 kg/m²), joint inflammatory diseases and or crystal-induced arthropathies, or any other concomitant disease (such as neuropsychiatric disease including cognitive impairment, Alzheimer’s disease, Parkinson’s disease, cerebrovascular disease, cardiovascular disease, liver and renal disease) or were taking any other antidepressants that could interfere with the evaluation of the intervention. Comorbidity was ascertained using a validated self-administered comorbidity questionnaire (SCQ). The original SCQ lists 13 common medical conditions and provides space to specify three optional health conditions in lay terms. The patient indicates if each condition is present, being treated and/or imposes functional limitation. ‘Yes’ responses are scored 1 point for a maximum score of 45 [15].

Treatment
At the screening visit, the patients were assessed by a blinded physician for fulfilment of criteria of entry, baseline demographic characteristics and medical history. Pre-intervention assessment was done by one of the physicians and a second physician was responsible for post-intervention assessments. Both physicians were blinded to treatment allocation. Patients meeting the eligibility criteria were randomised in a 1:1 ratio—144 received 60 mg/day of duloxetine HCL and 144 received identical placebo tablets for 16 weeks. A single clinical pharmacist randomised the patients to either the duloxetine group or the placebo group, using a computerised random number list and sealed envelopes. Concomitant rescue medication use by the patients, including paracetamol up to 4 g/day and non-steroidal anti-inflammatory drugs (NSAIDs) was allowed to continue, provided they did not increase the dose. All patients received a chart to record the amount of analgesics taken daily, and the use of rescue treatment during the previous weeks was recorded at each study visit. All patients underwent a physical examination and were questioned about the number of flares, pain and analgesic use.

Outcome measures
The primary outcome measure was the percentage of patients with a clinical response according to the Osteoarthritis Research Society International (OARSI) 2004 criteria [16] at the end of 16 weeks. Patients were classified as responders if the pain or physical function score decreased by 20% or more and at least 20 mm on the visual analogue pain scale (VAS). Secondary outcome measures included improvements in function using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores and use of OA rescue medication (paracetamol and NSAIDs) [17].

Pain assessment
Pain was assessed using the VAS (0–100 mm) and the WOMAC pain subscale [17]. The WOMAC pain subscale consists of five items and the total score ranges from 0 to 20, with a higher score indicating greater dysfunction.

Functional assessment
Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). Functional assessment was done using the self-reported physical function as measured with the WOMAC. The WOMAC uses 17 questions concerning the degree of difficulty performing activities of daily living function and to assess physical function. The individual scores for the 17 items are added to generate a summary score that ranges from 0 to 68, with higher scores indicating poorer function. WOMAC subscales: WOMAC pain (range 0–20) and WOMAC stiffness (range 0–8) scores were also assessed [17]. Higher scores on the WOMAC indicate worse pain, stiffness and functional limitations.

Geriatric depression scale. Patients were also screened for depression using the geriatric depression scale (GDS)—a 15-item questionnaire (range 0–15), with a score of ≥5 suggesting depression and with higher scores indicating greater depression [19]. The GDS is a 15-item yes/no questionnaire devised specifically to detect depression in elderly subjects. It has been extensively validated in hospital samples.

Alterations in dosage of analgesics [non-steroidal anti-inflammatory (NSAID) drugs and/or paracetamol] used were recorded.

Safety evaluation
Safety and tolerability to treatment were assessed based on the incidence and type of adverse events. Treatment-related adverse events reported by patients were collected at each
visit and evaluated. A treatment-related event was any event first occurring or worsening in severity during treatment, compared with baseline period. All staff involved in data collection was blinded to the treatment assignment groups.

Statistical analyses
Analyses were conducted using SAS version 9.1 (SAS Institute, Inc., NC, USA). Data were analysed on an intention-to-treat basis, with the dropouts included. The trial was designed to randomise 300 individuals to achieve 250 evaluable individuals at the end of 4 months. A total sample size of 250 was predicted to provide a power of 90% to detect a difference of at least 25% of patients responding to treatment compared with placebo, with a two-sided significance level of less than 5%. Change from baseline to endpoint was analysed using analysis of covariance. For categorical outcomes, Fisher’s exact test was used. Estimates of intervention effects were obtained at each follow-up observation. The term ‘significant’ used throughout this manuscript denotes statistical significance. All tests of hypotheses and reported P-values are two-sided.

Results
A total of 411 individuals were screened during a 6-month recruitment period for eligibility (Figure 1). Of these, 123 (30%) were screening failures. Totally, 288 patients were eligible and enrolled in the study. Eighty-eight per cent (254) completed the study. Data were analysed on an intention-to-treat basis, with the dropouts included. More patients in the treatment group dropped out due to adverse events than in the placebo group; however, this did not reach statistical significance, P = 0.11. Significantly more patients in the duloxetine group dropped out due to lack of efficacy, P = 0.007. The demographic and clinical variables were similar between the two groups of the study population at baseline (Table 1). Overall, most of the patients (84%) were women, the mean age was 68.5 years, with a mean BMI of 26.5, a mean disease duration of 5.6 years, 77% had comorbid illness and 89% used NSAIDs and 97% used paracetamol.

The responder rates at 16 weeks were 48% and 9% in the duloxetine group and placebo group, respectively (P < 0.05). A significant reduction in pain on the VAS was found in the duloxetine group compared with the placebo group at 16 weeks, P < 0.001. There was a
There was a significant improvement in self-reported pain, WOMAC pain score, \( P < 0.05 \) (Table 2). WOMAC function scores showed significant improvement at 16 weeks in the duloxetine group when compared with the placebo group, \( P < 0.01 \) (Table 2). WOMAC stiffness scores at 16 weeks were also different between the two groups, but did not reach statistical significance, \( P = 0.55 \) (Table 2). NSAID and paracetamol use was significantly less in the duloxetine group compared with the placebo group at 16 weeks, \( P < 0.001 \) and 0.005, respectively. There was a significant improvement in depression in the duloxetine-treated group [mean GDS score 5.2(1.7)] compared with the placebo-treated group [mean GDS score 9.7(2.2)] after 16 weeks of intervention, \( P < 0.05 \). The assessment of safety and tolerability showed that there were no deaths or severe life-threatening events during the study. The main treatment-related adverse events recorded significantly more frequently in the duloxetine group were constipation, nausea, hyperhidrosis, cough, myalgia, arthralgia and palpitations.

**Discussion**

Pain in OA remains an undertreated problem and the inability to adequately treat OA pain may lead to increased morbidity, but may also, as evidence shows, significantly increase mortality [20]. Pain is the main cause discouraging OA patients from physical activity thus preventing adequate non-medical management of significant comorbid conditions such as diabetes mellitus, obesity and cardiovascular disease [20, 21].

In the present study, we sought to primarily determine the efficacy of duloxetine to reduce pain and to improve function in older adults with knee OA. Evidence from this study showed that older adults with knee OA treated for 16 weeks with duloxetine versus those treated with placebo had significantly greater pain reduction. This was observed by the significant improvement in pain assessment scores at 16 weeks in the duloxetine group compared with the placebo group. A significant reduction in pain on the VAS in the drug-treated group compared with the placebo-treated group was evident at all time points measured during the 16-week period. Furthermore, there was a significant improvement in self-reported pain (WOMAC) at 16 weeks in the duloxetine group compared with the placebo group. These observations are consistent with the previously reported association of duloxetine with pain reduction in chronic pain due to chronic back pain and fibromyalgia [13, 22]. The alleviation of pain in the duloxetine group is consistent with the role of 5-hydroxytryptamine (5-HT) and NE as modulators of descending pain pathways in the brain and spinal cord [8, 9].

OA and the resulting functional disability place older adults at heightened risk of depression [23]. The results of this study demonstrate that there was a significant intervention effect on depression together with improved pain and functional outcomes in the duloxetine group. These findings of improved pain and function outcomes associated with decreased depression are in agreement with the wider literature demonstrating a substantial co-occurrence of pain and depression [22–24]. It is speculated that NE and 5-HT may facilitate a link between pain and depression [8, 9]. The pattern of simultaneous improvement in depression and pain supports the close

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**Table 1.** Demographic and clinical characteristics of the study population at baseline

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Duloxetine ( (n = 144) )</th>
<th>Placebo ( (n = 144) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>68.9 (6.2)</td>
<td>68.5 (5.8)</td>
</tr>
<tr>
<td>Sex (F/M)</td>
<td>121/23</td>
<td>120/24</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.6 (4.6)</td>
<td>27.5 (5.1)</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–1</td>
<td>93</td>
<td>91</td>
</tr>
<tr>
<td>≥2</td>
<td>20</td>
<td>18</td>
</tr>
<tr>
<td>Analgesic use, ( n (%)/\text{NSAID use} )</td>
<td>128 (89)</td>
<td>129 (90)</td>
</tr>
<tr>
<td>Paracetamol use ( (%) )</td>
<td>140 (97)</td>
<td>139 (96)</td>
</tr>
<tr>
<td>Disease duration (years)</td>
<td>5.7 (4.9)</td>
<td>5.6 (4.5)</td>
</tr>
<tr>
<td>Visual analogue pain scale</td>
<td>58.3 (11.7)</td>
<td>58.5 (11.8)</td>
</tr>
<tr>
<td>WOMAC pain score (0–100 mm), mean (SD)</td>
<td>9.1 (4.6)</td>
<td>8.9 (5.1)</td>
</tr>
<tr>
<td>WOMAC stiffness score (0–80)</td>
<td>6.4 (2.6)</td>
<td>6.3 (2.5)</td>
</tr>
<tr>
<td>WOMAC function score (0–68)</td>
<td>33.1 (7.5)</td>
<td>33.5 (7.1)</td>
</tr>
<tr>
<td>Kellgren–Lawrence grade, ( n (%) )</td>
<td>103 (72)</td>
<td>101 (70)</td>
</tr>
<tr>
<td>II</td>
<td>41 (28)</td>
<td>43 (30)</td>
</tr>
<tr>
<td>III</td>
<td>6 (4)</td>
<td>6 (4)</td>
</tr>
<tr>
<td>Geriatric depression scale</td>
<td>9.9 (2.7)</td>
<td>9.8 (2.5)</td>
</tr>
<tr>
<td>(range 0–15), mean (SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Activities of daily living (ADLs)</td>
<td>7.1 (2.3)</td>
<td>7.0 (2.5)</td>
</tr>
<tr>
<td>(range 0–10), mean (SD)</td>
<td></td>
<td></td>
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</tbody>
</table>

Values are given as mean (SD) or number (percentage).

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**Table 2.** WOMAC pain, function and stiffness scores at baseline and at 16 weeks

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Duloxetine ( (n = 144) )</th>
<th>Placebo ( (n = 144) )</th>
<th>( P )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>WOMAC pain score (0–20)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At baseline</td>
<td>9.1 (4.6)</td>
<td>8.9 (5.1)</td>
<td>0.44</td>
</tr>
<tr>
<td>At 16 weeks</td>
<td>6.0 (4.1)</td>
<td>8.4 (5.4)</td>
<td>0.05</td>
</tr>
<tr>
<td>WOMAC function score (0–80)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At baseline</td>
<td>33.1 (7.5)</td>
<td>33.5 (7.1)</td>
<td>0.61</td>
</tr>
<tr>
<td>At 16 weeks</td>
<td>24.6 (8.4)</td>
<td>30.3 (9.8)</td>
<td>0.01</td>
</tr>
<tr>
<td>WOMAC stiffness score (0–100 mm), mean (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At baseline</td>
<td>6.4 (2.6)</td>
<td>6.5 (2.5)</td>
<td>0.48</td>
</tr>
<tr>
<td>At 16 weeks</td>
<td>6.1 (3.1)</td>
<td>6.4 (2.5)</td>
<td>0.55</td>
</tr>
</tbody>
</table>

Values are given as mean (SD).
interrelationship between pain and depression. Recent research in the biology of pain provides insight as to how improvement in depression may be related to pain reduction [24, 25]. Neurotransmitters such as serotonin and noradrenaline can dampen peripheral pain signals by mediating a bidirectional feedback between a central pain modulation system and a peripheral nociceptive stimulus such as OA pain [25, 26]. Depressed mood has been associated with alterations in central pain processing which renders patients more sensitive to particular pain stimuli [26].

Depression is prevalent among patients with chronic pain due to OA [23, 26–29]. In the present study, the mean GDS score at baseline was 9.8 (2.5). Similarly, other studies have reported a high GDS scores in OA patients [22–24, 29]. However, further studies are needed, with stratification of patients by the GDS level. Furthermore, even though it is expected that OA patients who are not depressed will also have improved pain outcomes, this cannot be confirmed.

Data from the present study showed that NSAID and paracetamol usage had decreased significantly at 16 weeks in the duloxetine-treated group compared with the placebo group. This is in accordance with the findings of Skljarevski et al. who reported that NSAID usage in patients with chronic back pain on duloxetine compared with those on placebo decreased significantly from baseline [12]. The findings of this and previous studies provide evidence for the efficacy of duloxetine in chronic pain, regardless of origin, at the central pain inhibitory level. There is an increasing recognition of the role of central non-neuropathic pain [8]. Studies suggest that approximately one-third of patients with knee OA have a component of central non-neuropathic pain [8, 9, 25].

Improvement in WOMAC scores which reflect function, were particularly noteworthy in patients on duloxetine compared with those receiving placebo. WOMAC scores measure physical function and an improvement in WOMAC scores indicate better functioning ability due to less pain, stiffness and/or less functional limitations.

When interpreting the results of physical function, one needs to keep in mind the progressive nature of OA. Thus, an improvement in WOMAC scores or even a stable physical represents a treatment success. This may in itself justify the use of duloxetine with its higher treatment cost as opposed to the cheaper standard therapy in OA patients.

Four double-blind, placebo-controlled studies have shown that duloxetine, compared with placebo, produced clinically significant improvement in pain and functional ability [11, 12, 25, 27].

Safety analysis confirmed that duloxetine was mostly well-tolerated with lack of severe or life-threatening events. However, the side effect profile including constipation, myalgias, arthralgias and palpitations is not insignificant and this is a point that has to be borne in mind when dealing with older OA adults.

The population characteristics of this study are on the whole similar to a number of other studies showing far more women than men to have OA and concurrent depression and with relatively high baseline GDS scores [22–24, 29]. However, the results of this study should be interpreted in light of several limitations. The patient population utilised in this study included far more women than men, the patients were relatively young (68 years) and with a mean BMI of 27.6, raising the concern about selection bias. This was also an acute treatment trial, based on a 16-week trial and consequently the results may not generalise to a longer duration of treatment. Yet another limitation is the lack of follow-up after 16 weeks and hence longer-term trials are required to fully assess the safety and efficacy of duloxetine in a time course that is more reflective of clinical practice.

Conclusions

The findings of the present study indicate that duloxetine, by targeting central neuronal pathways, has a dual beneficial effect of improving depression and pain symptoms, both of which improve function and quality of life in older adults with knee OA. Despite the limitations of the present study, our findings demonstrating the efficacy of duloxetine in reducing pain may well be applicable to the wider population of knee OA patients. Further large-scale longitudinal studies are needed to replicate these effects and explore the factors driving the pain-depression-function dynamic. This is necessary given the clinical implications of the findings of the present study.

Key points

- Pain reduction.
- Functional improvement.
- Efficacy and tolerability of duloxetine in older adults with knee OA.

Conflicts of interest

The authors acknowledge the support of the pharmaceutical industry, Eli Lilly, Egypt, for providing the medicines for the study. The industry had no role in approval or preparation of the published manuscript.

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