

## SHOULD DULOXETINE BE ADDED TO EXERCISE TO TREAT SEDENTARY PATIENTS WITH PAINFUL KNEE OSTEOARTHRITIS? A PILOT STUDY<sup>a</sup>

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### ABSTRACT

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**Introduction:** In knee osteoarthritis patients that benefit from chronic pain management and physical activity, the additional impact of duloxetine over and above exercise is yet to be determined. Our goal was to study the effects of duloxetine on muscle mass, strength, physical performance, pain, stiffness and physical function in sedentary patients with painful knee osteoarthritis treated with a home-based exercise (HE) program.

**Methods:** Adults with painful knee osteoarthritis and lower physical performance were assigned to receive duloxetine (60mg/d) or placebo, in addition to HE therapy. The primary endpoint was the difference in short physical performance battery (SPPB) between groups at week 12. Secondary endpoints included 12-week changes in muscle mass by dual-energy X-ray absorptiometry (appendicular skeletal muscle mass index – ASMI), strength by handgrip (HG) and knee extension (KE) maximal isometric voluntary contraction, pain by visual analog scale (VAS) and pain, stiffness and physical function by Western Ontario McMaster Universities (WOMAC) questionnaire.

**Results:** Twenty-four participants were included. After 12 weeks, HE+duloxetine showed no benefit in SPPB when compared to HE+placebo ( $p=0.456$ ) and both groups significantly improved SPPB when compared to baseline [HE+duloxetine: 1.52 (95%CI 0.53 to 2.51); HE+placebo: 2.00 (95%CI 1.23 to 2.77)]. Both groups significantly improved WOMAC, with no differences between them ( $p=0.389$ ). Only HE+duloxetine group improved pain VAS [-2.26cm (95%CI -4.08 to -0.44)], while only HE+placebo group improved ASMI [0.4Kg/m<sup>2</sup> (95%CI 0.0 to 0.9)] and KE strength [11.8Kg (95%CI 4.3 to 19.2)]. HE+duloxetine group performed less minutes of exercise than HE+placebo group (310 vs. 692,  $p=0.015$ ). Adverse events rates were similar between groups.

**Conclusions:** Duloxetine did not additionally improve physical performance, pain, stiffness and physical function of patients with lower physical performance and painful KOA treated with exercise. Muscle mass and muscle strength gains were only observed in the placebo group perhaps due to greater exercise adherence, but larger studies are needed to address this hypothesis.

**Keywords:** Osteoarthritis; Pain; Sarcopenia

<sup>a</sup> The study protocol was retrospectively registered at Registro Brasileiro de Ensaios Clínicos (ReBEC) under the identifier RBR-9c72hyz Effects of Duloxetine on muscle loss associated with knee arthrosis (<https://ensaiosclinicos.gov.br/rg/RBR-9c72hyz>) and universal trial number (UTN code): U1111-1259-3956. The ReBEC registration submission date was 20/02/2017 (before first participant enrollment) and final approval was on 01/04/2021.

## INTRODUCTION

Osteoarthritis is the most common chronic joint disease, and pain is the most dominant symptom and the major drive of clinical decision making<sup>1,2</sup>. As the disease progresses, joint nociception, marked by structural changes, synovitis, nerve growth and neovascularization, gives rise to peripheral and central sensitization<sup>1,3</sup>.

Due to its major role in chronic refractory pain, central sensitization has been considered a potential osteoarthritis treatment target<sup>4,5</sup>. Approved for painful conditions associated with central sensitization, duloxetine, a selective serotonin and norepinephrine reuptake inhibitor, is also recommended for chronic pain management in osteoarthritis patients<sup>6</sup>.

Pain in osteoarthritis has also been associated with sarcopenia, a condition frequently caused or aggravated by osteoarthritis<sup>7-9</sup>. Defined as a progressive and generalized skeletal muscle disorder associated with greater risk of falls, fractures, physical disability and mortality<sup>8</sup>, sarcopenia shares several pathophysiological mechanisms with osteoarthritis<sup>9</sup>. Mainly, osteoarthritis and sarcopenia are associated with inflammaging, a phenomenon characterized by excess secretion of proinflammatory cytokines, increase of oxidative stress, decrease in autophagy capacity and DNA damage response<sup>10</sup>.

While in osteoarthritis patients greater pain intensity has been associated with lower muscle strength and mass<sup>7,11-14</sup>, and duloxetine and exercise are expected to improve pain and physical function<sup>6,15</sup>, the potential benefits of central sensitization drug therapy over and above exercise still need clarification. Therefore, our goal was to investigate the additional effects of duloxetine on physical performance, muscle mass, muscle strength, pain, stiffness and physical function of sedentary patients with painful knee osteoarthritis (KOA) treated with a home-based exercise (HE) program.

## METHODS

### *Design, participants and settings*

We conducted a double-blind parallel-group placebo controlled 12-week randomized clinical trial at a public tertiary care university teaching hospital from 2017 through 2020. The present work is being reported according to the CONSORT guidelines<sup>16</sup>.

Participants from a tertiary university hospital's outpatient clinics and community-dwelling adults were invited to participate. Those considered eligible was randomized on a 1:1 ratio, in blocks of 4, to receive HE and duloxetine or HE and placebo. Inclusion criteria were age between 40 and 75 years old, diagnosis of KOA according to the American College of Rheumatology classification criteria<sup>17</sup>,

low/moderate physical performance defined as a short physical performance battery (SPPB) less than or equal to 9, history of knee pain for at least 3 months, moderate/high knee pain in the last week measured by a visual analog scale (VAS) greater than or equal to 40 out of 100 and sedentary lifestyle defined as less than 20 minutes of physical activity per week. Exclusion criteria were widespread pain, depressive symptoms (geriatric depression scale greater than or equal to 6), conditions other than osteoarthritis that impaired muscle function, body mass index (BMI) less than or equal to 22 Kg/m<sup>2</sup>, use of systemic corticosteroids, nonsteroidal anti-inflammatory drugs, immunosuppressants, antidepressants, glucosamine, chondroitin, diacerein, doxycycline, avocado soybean unsaponifiables, *Harpagophytum procumbens*, capsaicin topical, new bisphosphonate in the last 6 months, any joint injection or surgery in the last 6 months, any knee prosthesis, any malignancy in the last 5 years, current or previous smoking, any cardiovascular condition except for controlled systemic arterial hypertension, liver cirrhosis or elevation of aspartate or alanine aminotransferase above three times the upper limit of normal, endogenous creatinine clearance or glomerular filtration rate less than or equal to 30ml/min, unable to adhere to study interventions or to sign written informed consent.

### *Interventions*

Participants were randomized to receive either duloxetine 60mg orally once a day (preferably in the morning with a glass of water independent of meals, according to label instructions) or placebo, plus resistance and flexibility exercise program to be performed for at least 30 minutes three times a week at home by both groups. This HE program was a compilation of previous studies protocols aiming at improving elderly physical performance and lower limbs muscle strength<sup>18-21</sup>. Basically, there were 19 exercises to be performed as 10-15 repetitions (chair stand with hands support; leg raise lying on back; leg raise lying aside; knee flexion lying ventrally; feet dorsiflexion while sitting; chair stand without hands support; knee extension while sitting; knee elevation while sitting; knee flexion while standing with hands on the wall; lateral leg rise while standing with hands on the wall; trunk flexion while lying on the back; squatting; hip extension while lying on the back with flexed knees; leg and arm rise with hands and knees on the floor; rise trunk while lying ventrally with elbows and feet on the floor; staying on toes while standing; staying on the toes of one foot while standing with hands on the wall; staying on heels while standing without hands support; staying on the toes of one foot while standing without hands on the wall) and 10 exercises to be executed during 20-30 seconds (standing on side-by-side feet without support;

heel-to-toe walk with support; walk sideways with support; standing on one leg with support; heel-to-toe walk without support; walk backwards with support; walk sideways without support; standing on one leg without support; walk over short obstacles; walk backwards without support).

### **Study Procedures and Follow-up**

After randomization (baseline), participants were seen every 4 weeks through week 12. Study appointments were confirmed by phone calls and, whenever a participant could not be reached or did not show up, another phone call was made to reschedule the visit. At each study visit, participants were evaluated for every outcome measure and received a new drug bottle and a new 30-minute set of exercises. Each set of exercises comprised a group of 5 to 10 exercises with an individualized level of complexity according to each participant's abilities. During each visit, participants were engaged in exercise simulation and an illustrated handout was given containing written recommendations for each exercise, including training description and repetitions. In the same handout, there was an exercise log, where participants had to take notes of the days they performed exercises and the time spent during each training session. Besides the registration of frequency and duration of each training session, all participants received a phone call between visits to help with eventual difficulties and assure exercise adherence. Exercise intensity should be perceived at most as "somewhat hard"<sup>22</sup> and it should be stopped in the presence of unbearable pain. Throughout the study, exercise difficulty was increased according to each participant's tolerability.

### **Outcomes and measurements**

The primary study's outcome was to evaluate the effect of duloxetine on physical performance, measured by SPPB, at week 12. SPPB includes three physical performance domains: balance, walking speed and five-time sit-to-stand test<sup>23,24</sup>. SPPB score ranges from 0 through 12 and smaller values mean worse physical performance.

Additionally, the secondary outcomes were to investigate the effects of duloxetine on muscle mass measured by dual-energy X-ray absorptiometry (DXA), muscle strength measured by handgrip and knee extension strength tests, knee pain by VAS, knee pain, stiffness and physical function by Western Ontario McMaster Universities (WOMAC) questionnaire<sup>8,25,26</sup>. WOMAC score ranges from 0 through 68 and greater values mean worse osteoarthritis symptoms.

Muscle mass was evaluated by DXA (Lunar Prodigy Primo, GE Medical Systems). Appendicular skeletal muscle mass index (ASMI) was determined by the sum of arm muscles and leg muscles divided by height squared<sup>8,25</sup>.

Handgrip strength was measured using a handheld dynamometer (Jamar Hydraulic Hand Dynamometer, Preston, USA). The participant was instructed to squeeze the handle as hard as possible for 5 seconds, 3 times with 60-second rest intervals among them, and the maximal isometric voluntary contraction (MIVC) of each hand was thus quantified. The measurement was repeated after a recovery period of 60 seconds, and the mean value of the highest score from each side was used in the analysis<sup>25</sup>. Knee extension strength was assessed by MIVC using a knee extension chair with a portable digital dynamometer (SKDD-100, Central Brasil Instrumentos, São Paulo, Brazil). After sitting on a knee extension chair and resting the affected limb at a knee flexion angle of 60 degrees, the participant was instructed to perform 3 times a 5-second maximal quadriceps contraction with a 3-minute resting interval among them. The mean value of the greatest score from each side was used in the analysis<sup>27</sup>.

### **Ethics approval and consent to participate**

The study protocol was approved in 2015 by the institutional review board of the authors' affiliated hospital. All participants were above 16 years of age and signed written informed consent before entering the study. All of the procedures were in accordance with the The Code of Ethics of the World Medical Association (Declaration of Helsinki).

### **Sample size and statistical analysis**

Considering a clinically significant mean difference for SPPB of 0.8 (standard deviation of 0.7), 12 participants per group ( $n = 24$ ) would be necessary to reject the null hypothesis with a power of 80% and an alpha of 0.05 (bicaudal)<sup>21,28</sup>. Sample size calculation was performed using the software WinPepi v.11.46. Considering the lack of similar studies in the literature and the relatively small sample size the present calculation yielded, a pilot study designation was deemed more suitable.

Quantitative variables were described as means and standard deviations/errors or 95% confidence intervals (95%CI) and categorical variables were described as absolute and relative frequencies. Sample distribution was assessed by Shapiro-Wilk's test. For mean comparisons, Student's *t* test was used, and for proportions comparisons, Pearson's chi-squared or Fisher's exact test was used. For concomitant time and group effects analysis, generalized estimating equations (GEE) were used complemented by least significant difference (LSD) test. For variables with symmetrical distributions, linear model was applied, and, in case of asymmetry, gamma model was used. All tests were 2-sided and a *p* value of less than 0.05 was considered significant. All statistical analyses were performed in SPSS (IBM), v. 21.0, as intention to treat.

### Randomization and blinding

Each participant was randomly assigned to one of two groups: HE + duloxetine or HE + placebo. Randomization was performed in blocks of 4 participants to minimize the potential seasonal impact of the cold weather on exercise adherence. A research assistant who was not a member of the study team was responsible for randomization and drug bottles labeling. Firstly, a random sequence of twenty-four three-digit codes was generated at [www.randomization.com](http://www.randomization.com). Each code was sealed inside an opaque envelope and the envelopes were sequentially numbered from 1 through 24 according to the original series. The three-digit codes were the participants' codes. Afterwards, another sequence of group allocation (group 1 for HE + duloxetine and group 2 for HE + placebo) was generated at the same website in six blocks of four (two codes for each group in a single block), as an example: Block 1: 1-1-2-2; Block 2: 1-2-2-1; etc. The two lists were, then, matched so that the first three-digit participant code corresponded to the first group code and so forth up to the twenty-fourth code. Finally, the blinded research assistant labeled drug bottles with the three-digit codes according to the group allocation obtained from the sequence match. Accordingly, each

participant had a set of three drug bottles with 30 capsules of duloxetine 60 mg or placebo per bottle. Randomization and labeling were performed at the beginning of the study and drug bottles were stored in a specific locked research cabinet. When a new participant was included, a member of the study team opened the next envelope, picked up the respective labelled drug bottle from the research cabinet and handed it over to the participant. All participants and members of the research team were blinded to group allocation throughout the study.

### RESULTS

Between March 2017 and January 2020, 24 subjects were randomly assigned to receive either HE+duloxetine or HE+placebo, and 14 complete the study (overall dropout rate: 41.7%) (Figure 1). Participants mean age was 64.4 years old and predominantly white (79.2%), women (77.2%) with moderate/severe radiographic KOA (86.4%) (Table 1). There were 4 participants (2 per group) that withdrew the study due to adverse events (18.2%) and 6 participants were lost to follow-up (2 from HE + duloxetine group and 4 from HE + placebo group: 16.7% vs. 33.3%, respectively;  $p = 0.640$ ).

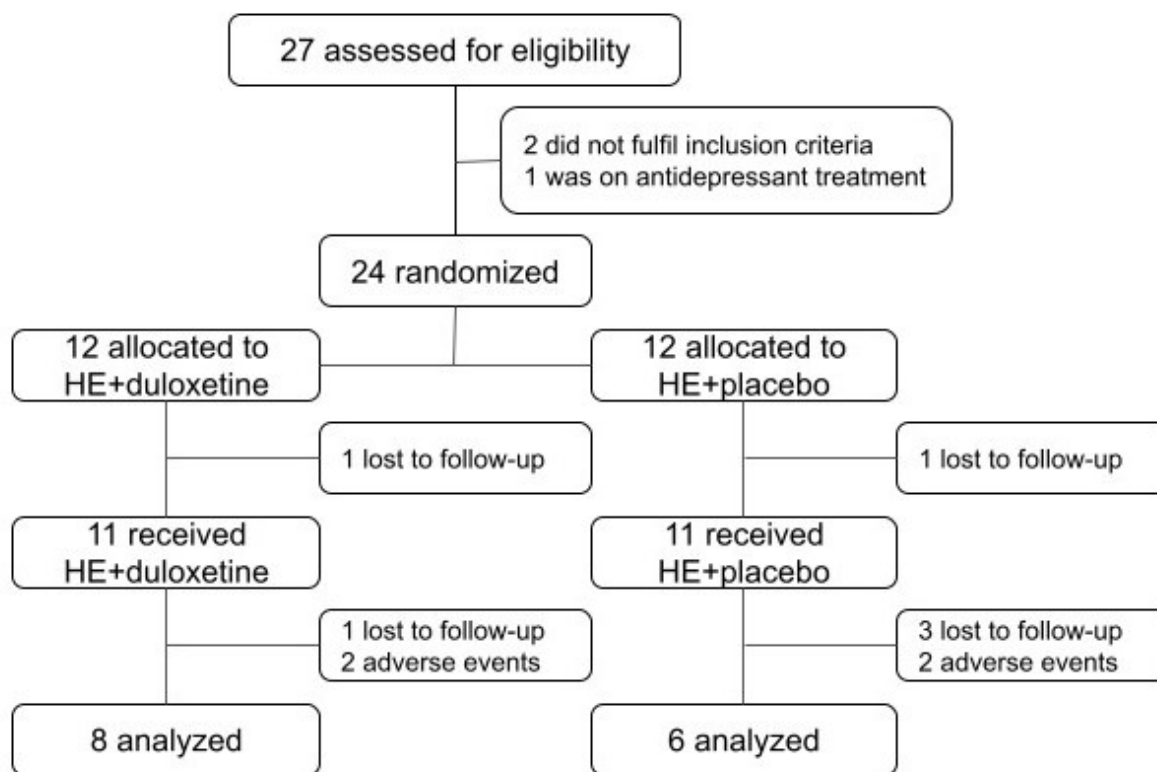


Figure 1: Participants' flowchart.

HE: home-based exercise

Table 1: Baseline participants' characteristics.

|                           | HE+duloxetine<br>(n=11) | HE+placebo<br>(n=11) | p     |
|---------------------------|-------------------------|----------------------|-------|
| Age (years)               | 64.8 ± 6.4              | 63.9 ± 7.3           | 0.760 |
| Skin color                |                         |                      | 0.035 |
| White                     | 11 (100)                | 6 (54.5)             |       |
| Sex                       |                         |                      | 1.000 |
| Women                     | 9 (81.8)                | 8 (72.7)             |       |
| Affected side of KOA      |                         |                      | 0.305 |
| Right                     | 5 (45.5)                | 2 (18.2)             |       |
| Left                      | 1 (9.0)                 | 3 (27.3)             |       |
| Bilateral                 | 5 (45.5)                | 6 (54.5)             |       |
| Kellgren & Lawrence scale |                         |                      | 0.420 |
| I                         | 0 (0.0)                 | 0 (0.0)              |       |
| II                        | 2 (18.2)                | 1 (9.1)              |       |
| III                       | 3 (27.3)                | 6 (54.5)             |       |
| IV                        | 6 (54.5)                | 4 (36.4)             |       |
| BMI (kg/m <sup>2</sup> )  | 31.4 ± 6.8              | 29.9 ± 4.4           | 0.548 |
| Vitamin D, serum (ng/mL)  | 22.5 ± 10.1             | 24.7 ± 7.7           | 0.574 |
| Pain VAS (0 to 10)        | 7.1 ± 1.2               | 6.3 ± 2.2            | 0.328 |
| WOMAC total               | 50.3 ± 19.2             | 53.8 ± 9.6           | 0.593 |

Values as mean ± SD or n(%).

HE: home-based exercise; KOA: knee osteoarthritis; BMI: body mass index; VAS: visual analog scale; WOMAC: Western Ontario McMaster Universities questionnaire

After 12 weeks, HE + duloxetine group showed no benefit in SPPB when compared to HE + placebo group ( $p = 0.456$ ) and both groups significantly improved

SPPB when compared to baseline [HE + duloxetine: 1.52 (95%CI 0.53 to 2.51); HE + placebo: 2.00 (95%CI 1.23 to 2.77)] (Table 2).

Table 2: Comparisons of SPPB score along the study according to group.

| SPPB                          | HE+ Duloxetine |                           | HE+Placebo |                           | p value |
|-------------------------------|----------------|---------------------------|------------|---------------------------|---------|
|                               | n              | Mean ± SE                 | n          | Mean ± SE                 |         |
| Balance component (0-4)       |                |                           |            |                           |         |
| Baseline                      | 11             | 3.73 ± 0.13 <sup>a</sup>  | 11         | 3.45 ± 0.15 <sup>a</sup>  | 0.176   |
| W4                            | 10             | 3.70 ± 0.20 <sup>ab</sup> | 10         | 4.00 ± 0.00 <sup>b</sup>  | 0.138   |
| W8                            | 9              | 3.67 ± 0.16 <sup>a</sup>  | 7          | 3.71 ± 0.17 <sup>ab</sup> | 0.837   |
| W12                           | 8              | 4.00 ± 0.00 <sup>b</sup>  | 6          | 3.83 ± 0.15 <sup>ab</sup> | 0.273   |
| Variation (12w-Baseline)      |                | 0.27 (0.01 to 0.54)       |            | 0.38 (-0.10 to 0.86)      | 0.706   |
| p value                       |                | 0.042                     |            | 0.125                     |         |
| Walking speed component (0-4) |                |                           |            |                           |         |
| Baseline                      | 11             | 2.91 ± 0.35 <sup>a</sup>  | 11         | 3.27 ± 0.26 <sup>a</sup>  | 0.405   |
| W4                            | 10             | 3.10 ± 0.33 <sup>a</sup>  | 10         | 3.50 ± 0.21 <sup>a</sup>  | 0.308   |
| W8                            | 9              | 3.11 ± 0.25 <sup>a</sup>  | 7          | 3.71 ± 0.17 <sup>a</sup>  | 0.044   |
| W12                           | 8              | 3.13 ± 0.28 <sup>a</sup>  | 6          | 3.67 ± 0.19 <sup>a</sup>  | 0.107   |
| Variation (W12-Baseline)      |                | 0.22 (-0.49 to 0.92)      |            | 0.39 (-0.14 to 0.93)      | 0.693   |
| p value                       |                | 0.547                     |            | 0.149                     |         |
| FTSTST component (0-4)        |                |                           |            |                           |         |
| Baseline                      | 11             | 1.09 ± 0.16 <sup>a</sup>  | 11         | 1.27 ± 0.19 <sup>a</sup>  | 0.453   |
| W4                            | 10             | 1.90 ± 0.26 <sup>b</sup>  | 10         | 1.60 ± 0.21 <sup>b</sup>  | 0.372   |
| W8                            | 9              | 2.00 ± 0.27 <sup>b</sup>  | 7          | 2.00 ± 0.35 <sup>bc</sup> | 1.000   |
| W12                           | 8              | 2.13 ± 0.28 <sup>b</sup>  | 6          | 2.50 ± 0.31 <sup>c</sup>  | 0.368   |
| Variation (W12-Baseline)      |                | 1.03 (0.33 to 1.74)       |            | 1.23 (0.44 to 2.02)       | 0.720   |
| p value                       |                | 0.004                     |            | 0.002                     |         |
| Total (0-12)                  |                |                           |            |                           |         |
| Baseline (n=11)               | 11             | 7.73 ± 0.45 <sup>a</sup>  | 11         | 8.00 ± 0.22 <sup>a</sup>  | 0.585   |
| W4 (n=10)                     | 10             | 8.70 ± 0.68 <sup>bc</sup> | 10         | 9.10 ± 0.30 <sup>b</sup>  | 0.590   |

Continues...

Table 2: Continuation.

| SPPB                            | HE+ Duloxetine |                              | HE+Placebo |                              | p value |
|---------------------------------|----------------|------------------------------|------------|------------------------------|---------|
|                                 | n              | Mean $\pm$ SE                | n          | Mean $\pm$ SE                |         |
| W8 (n=9)                        | 9              | 8.78 $\pm$ 0.52 <sup>b</sup> | 7          | 9.43 $\pm$ 0.45 <sup>b</sup> | 0.340   |
| W12 (n=8)                       | 8              | 9.25 $\pm$ 0.42 <sup>c</sup> | 6          | 10.0 $\pm$ 0.41 <sup>c</sup> | 0.203   |
| Variation W12-Baseline (CI 95%) |                | 1.52 (0.53 to 2.51)          |            | 2.00 (1.23 to 2.77)          | 0.456   |
| p value                         |                | 0.003                        |            | <0.001                       |         |

<sup>a,b,c,d</sup> Same letters do not differ according to Least Significant Difference (LSD) test at 5% of significance level

SPPB: short physical performance battery; HE: home-based exercise; SE: standard error; FTSTST: five-time sit-to-stand test

HE + duloxetine group performed less minutes of exercise than HE+placebo group [310 (IQR 333) vs. 692 (IQR 820),  $p = 0.015$ ]. Both groups significantly improved WOMAC, with no differences between them ( $p = 0.389$ ) (Table 3).

Only HE + duloxetine group improved pain VAS [- 2.26 cm (95%CI - 4.08 to - 0.44)] and the balance component of SPPB [0.27 (95%CI 0.01 to 0.54)], while only HE+placebo group improved ASMI [0.4 Kg/m<sup>2</sup> (95%CI 0.0 to 0.9)] and knee extension strength [11.8 Kg (95%CI 4.3 to 19.2)] (Tables 2, 3 and 4). Handgrip

strength did not change significantly throughout the study in either group (Table 4). Overall, intra-group significant differences were not complemented by inter-group statistical significance.

In total, 10 (45.5%) patients experienced any adverse event throughout the study: 6 (27.3%) mild/moderate and 4 (18.2%) severe adverse events (2 participants in each group). Numerically, more patients in HE + duloxetine group than in the HE + placebo group had mild/moderate adverse events without statistical significance [4 (36.4%) vs. 2 (18.2%),  $p=0.598$ ].

Table 3: Comparisons of pain visual analog scale and WOMAC score along the study according to group.

|                                  | HE+Duloxetine |                          | HE+Placebo |                           | p value |
|----------------------------------|---------------|--------------------------|------------|---------------------------|---------|
|                                  | n             | Mean ± SE                | n          | Mean ± SE                 |         |
| Pain VAS (0-10cm)                |               |                          |            |                           |         |
| Baseline                         | 11            | 7.08 ± 0.35 <sup>b</sup> | 11         | 6.32 ± 0.64 <sup>b</sup>  | 0.293   |
| W4                               | 10            | 3.84 ± 0.88 <sup>a</sup> | 9          | 4.78 ± 0.88 <sup>a</sup>  | 0.012   |
| W8                               | 9             | 4.42 ± 0.70 <sup>a</sup> | 6          | 4.72 ± 1.33 <sup>ab</sup> | 0.844   |
| W12                              | 8             | 4.68 ± 0.78 <sup>a</sup> | 6          | 4.35 ± 0.91 <sup>ab</sup> | 0.786   |
| Variation W12-Baseline (CI 95%)  |               | -2.41 (-3.82 to -0.99)   |            | -1.97 (-4.40 to 0.47)     | 0.760   |
| p value                          |               | 0.001                    |            | 0.113                     |         |
| WOMAC – Pain (0-20)              |               |                          |            |                           |         |
| Baseline                         | 11            | 10.6 ± 1.19 <sup>c</sup> | 11         | 10.6 ± 0.95 <sup>c</sup>  | 1.000   |
| W4                               | 11            | 6.18 ± 0.96 <sup>a</sup> | 10         | 9.40 ± 1.32 <sup>b</sup>  | 0.049   |
| W8                               | 9             | 8.56 ± 1.31 <sup>b</sup> | 6          | 7.67 ± 1.94 <sup>ab</sup> | 0.704   |
| W12                              | 8             | 8.38 ± 1.33 <sup>b</sup> | 6          | 6.50 ± 1.35 <sup>a</sup>  | 0.323   |
| Variation W12-Baseline (CI 95%)  |               | -2.26 (-4.08 to -0.44)   |            | -4.14 (-5.90 to -2.38)    | 0.147   |
| p value                          |               | 0.015                    |            | <0.001                    |         |
| WOMAC – Stiffness (0-8)          |               |                          |            |                           |         |
| Baseline                         | 11            | 3.82 ± 0.49 <sup>a</sup> | 11         | 4.36 ± 0.67 <sup>a</sup>  | 0.513   |
| W4                               | 11            | 3.27 ± 0.48 <sup>a</sup> | 10         | 2.90 ± 0.54 <sup>a</sup>  | 0.606   |
| W8                               | 9             | 3.67 ± 0.72 <sup>a</sup> | 6          | 3.50 ± 0.81 <sup>a</sup>  | 0.878   |
| W12                              | 8             | 3.38 ± 0.93 <sup>a</sup> | 6          | 3.50 ± 0.94               | 0.925   |
| Variation W12-Baseline (CI 95%)  |               | -0.44 (-1.50 to 0.61)    |            | -0.86 (-2.49 to 0.76)     | 0.671   |
| p value                          |               | 0.412                    |            | 0.298                     |         |
| WOMAC – Physical function (0-68) |               |                          |            |                           |         |
| Baseline                         | 11            | 35.8 ± 4.36 <sup>b</sup> | 11         | 38.8 ± 2.25 <sup>b</sup>  | 0.541   |
| W4                               | 11            | 24.0 ± 4.72 <sup>a</sup> | 10         | 34.3 ± 3.65 <sup>b</sup>  | 0.084   |
| W8                               | 9             | 25.1 ± 5.47 <sup>a</sup> | 6          | 20.8 ± 5.91 <sup>a</sup>  | 0.595   |
| W12                              | 8             | 25.9 ± 6.08 <sup>a</sup> | 6          | 25.3 ± 4.64 <sup>a</sup>  | 0.944   |
| Variation W12-Baseline (CI 95%)  |               | -9.94 (-17.5 to -2.44)   |            | -13.5 (-22.0 to -4.99)    | 0.540   |
| p value                          |               | 0.009                    |            | 0.002                     |         |

Continues...

Table 3: Continuation.

|                                 | HE+Duloxetine |                        | HE+Placebo |                        | p value |
|---------------------------------|---------------|------------------------|------------|------------------------|---------|
|                                 | n             | Mean $\pm$ SE          | n          | Mean $\pm$ SE          |         |
| WOMAC – Total (0-96)            |               |                        |            |                        |         |
| Baseline                        | 11            | 50.3 $\pm$ 5.52        | 11         | 53.8 $\pm$ 2.77        | 0.566   |
| W4                              | 11            | 33.5 $\pm$ 5.56        | 10         | 46.6 $\pm$ 4.93        | 0.077   |
| W8                              | 9             | 37.3 $\pm$ 7.12        | 6          | 32.0 $\pm$ 8.17        | 0.622   |
| W12                             | 8             | 37.6 $\pm$ 7.88        | 6          | 35.3 $\pm$ 6.57        | 0.823   |
| Variation W12-Baseline (CI 95%) |               | -12.7 (-21.3 to -3.99) |            | -18.5 (-28.6 to -8.41) | 0.389   |
| p value                         |               | 0.004                  |            | <0.001                 |         |

a,b,c,d Same letters do not differ according to *Least Significant Difference* (LSD) test at 5% of significance level

WOMAC: Western Ontario McMaster Universities; VAS: visual analog scale; HE: home-based exercise; SE: standard error

Table 4: Comparisons of appendicular skeletal muscle mass index and handgrip and knee extension strength along the study according to group.

|                                                              | HE+Duloxetine |                             | HE+Placebo |                              | p value |
|--------------------------------------------------------------|---------------|-----------------------------|------------|------------------------------|---------|
|                                                              | n             | Mean $\pm$ SE               | n          | Mean $\pm$ SE                |         |
| Appendicular skeletal muscle mass index (Kg/m <sup>2</sup> ) |               |                             |            |                              |         |
| Baseline                                                     | 11            | 7.1 $\pm$ 0.3               | 11         | 7.8 $\pm$ 0.4                | 0.170   |
| W12                                                          | 8             | 7.2 $\pm$ 0.3               | 6          | 8.2 $\pm$ 0.4                | 0.021   |
| Variation (W12-Baseline)                                     |               | 0.1 (-0.5 to 0.5)           |            | 0.4 (0.0 to 0.9)             | 0.204   |
| p value                                                      |               | 0.924                       |            | 0.044                        |         |
| Handgrip strength (Kg)                                       |               |                             |            |                              |         |
| Baseline                                                     | 11            | 21.8 $\pm$ 1.9 <sup>a</sup> | 11         | 27.1 $\pm$ 3.8 <sup>a</sup>  | 0.209   |
| W4                                                           | 11            | 23.8 $\pm$ 2.0 <sup>a</sup> | 10         | 27.8 $\pm$ 4.4 <sup>a</sup>  | 0.404   |
| W8                                                           | 10            | 23.8 $\pm$ 2.0 <sup>a</sup> | 8          | 32.1 $\pm$ 4.9 <sup>a</sup>  | 0.114   |
| W12                                                          | 8             | 22.6 $\pm$ 2.0 <sup>a</sup> | 6          | 32.7 $\pm$ 5.0 <sup>a</sup>  | 0.061   |
| Variation W12-Baseline (CI 95%)                              |               | 0.8 (-3.6 to 5.3)           |            | 5.6 (-1.3 to 12.6)           | 0.482   |
| p value                                                      |               | 0.723                       |            | 0.113                        |         |
| Knee extension strength (Kg)                                 |               |                             |            |                              |         |
| Baseline                                                     | 11            | 15.7 $\pm$ 2.8 <sup>a</sup> | 11         | 19.5 $\pm$ 3.4 <sup>a</sup>  | 0.384   |
| W4                                                           | 11            | 15.0 $\pm$ 2.7 <sup>a</sup> | 10         | 23.1 $\pm$ 3.6 <sup>ab</sup> | 0.070   |
| W8                                                           | 10            | 16.8 $\pm$ 3.1 <sup>a</sup> | 8          | 27.6 $\pm$ 5.1 <sup>bc</sup> | 0.068   |
| W12                                                          | 8             | 16.9 $\pm$ 3.2 <sup>a</sup> | 6          | 31.3 $\pm$ 4.8 <sup>c</sup>  | 0.013   |
| Variation W12-Baseline (CI 95%)                              |               | 1.2 (-2.3 to 4.6)           |            | 11.8 (4.3 to 19.2)           | 0.063   |
| p value                                                      |               | 0.506                       |            | 0.002                        |         |

a,b,c,d Same letters do not differ according to *Least Significant Difference* (LSD) test at 5% of significance level

HE: home-based exercise; SE: standard error

## DISCUSSION

To the best of our knowledge, this is the first study designed to assess the effects of chronic pain management on sarcopenia in patients with KOA. According to our findings, duloxetine was not superior to placebo in improving physical performance of sedentary patients with painful KOA treated with exercise. Both groups equally improved SPPB and WOMAC throughout the 12-week period of follow-up. There was a significant improvement in pain VAS only in HE + duloxetine group, but that was not accompanied by muscle mass or muscle strength increment. Interestingly, muscle mass and muscle strength were significantly better only in HE + placebo group.

Despite the reported associations between pain and muscle mass or strength in KOA, the overall

association between pain and sarcopenia remains elusive. Allegedly, knee pain could be associated with either muscle mass, muscle strength or physical performance at most in subgroups of KOA patients. In the study by Scott, et al., greater knee pain predicted lower leg strength and muscle quality only in women<sup>7</sup>. In the KNHANES study, lower muscle mass was independently associated with greater knee pain only in radiographically mild KOA patients<sup>14</sup>. In the SPSS-OK study, pain was not associated with sarcopenia, defined by muscle mass, handgrip strength and walking speed<sup>29</sup>, but could be moderating the association between muscle mass and muscle strength in radiographically severe KOA patients<sup>30</sup>.

Our results indicate that exercise improves function in KOA patients and this finding is consistent with the

literature<sup>6</sup>. However, the effect of exercise in muscle mass and muscle strength could only be appreciated without duloxetine. Also, there was a greater amount of time dedicated to home exercise in the placebo group. This difference could mainly have been due to three reasons. First, pain improvement induced by duloxetine could have been interpreted as an exemption from strict exercise adherence, since, during study visits, both interventions were mentioned as associated with symptoms amelioration. Second, although not statistically different, a numerically greater number of milder adverse events in duloxetine users, such as nausea and dizziness, could have played a role in refraining from exercising. In other words, duloxetine-induced adverse events could have impaired exercise adherence, but our sample was probably not large enough to demonstrate a true difference of adverse events between groups. Despite the small sample size, results were according to a parametric distribution, because Shapiro-Wilk's test was not statistically significant and there was homoscedasticity in both groups. Finally, the greater number of participants lost to follow-up in the placebo group could have been due to lack of efficacy and the observed differences in muscle mass and strength subjected to attrition bias.

The present study has some limitations. Firstly, despite achieving the estimated sample size, our results could have been affected by a greater than expected dropout rate, which raises the possibility of a type 2 error<sup>31</sup>. Also, the substantial number of losses to follow-up prevented any inference of the direction of the treatment effect and any conclusion needs studies with larger sample sizes. Notwithstanding our attempt to sustain study endurance by regular phone calls, the high number of participants lost to follow-up could be attributed to the greater mobility impairment inherent to a clinical scenario that combines low physical performance with painful KOA at baseline. Futures studies should consider a greater than expect dropout rate to circumvent this relevant limitation. To minimize the biases of losses to follow-up, we used GEE, that allows the inclusion of every participant in the analysis, not only those that completed the study<sup>32</sup>. In addition, although the study was designed to find a clinically significant difference in SPPB, our final sample size was not large enough to allow any subgroup or regression analysis. Therefore, the longitudinal association between pain and sarcopenia, as well as how this interaction could be moderated by sex, body composition and radiographic osteoarthritis severity could not be properly addressed herein. At last, the numerous exclusion criteria adopted to assure participants' safety before study interventions ultimately limited the generalizability of our findings to different populations.

In the present study, duloxetine did not additionally improve physical performance, pain, stiffness and

physical function of patients with lower physical performance and painful knee osteoarthritis treated with exercise. Regarding pain, only duloxetine group showed a statistically significant improvement during the 12-week follow-up, even though this variation was not statistically different from the variation observed in the placebo group. Muscle mass and muscle strength gains were only observed in the placebo group perhaps due to exercise adherence issues in the duloxetine group and/or attrition bias, even though we were not able to demonstrate any of these inferences, due to a limited sample size. For these reasons, our results are not enough to change clinical practice protocols towards duloxetine prescription intended to improve physical function, muscle mass or pain management in KOA patients. Therefore, larger studies are needed to specify the eventual additional benefits of central sensitization drug therapy over and above exercise in an osteoarthritis population that benefits from both interventions.

### **Declarations**

Ethics approval and consent to participate

The study protocol was approved in 2015 by local ethics committee (Comitê de Ética em Pesquisa do Grupo de Pesquisa e Pós-Graduação do Hospital de Clínicas de Porto Alegre – 15-0549; CAAE: 50785715000005327). All participants were above 16 years of age and signed written informed consent before entering the study. All of the procedures were in accordance with the Helsinki Declaration.

### **Availability of data and materials**

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

### **Competing interests**

The authors declare that they have no conflicts of interest/competing interests.

Conflicts of interest: none.

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### **Authors' Contributions**

RMDSC participated in the conception of the work, acquisition, analysis and interpretation of data, drafting and critically revising the work. RCDES, KPS and MMDS participated in the acquisition, analysis and interpretation of data, and critically revising the work. LPDS participated in the acquisition and interpretation of data, and critically revising the work.

MEDM, JB, PSC, AAG and VH participated in the acquisition and interpretation of data, and critically revising the work. All authors read and approved the final manuscript.

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