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Comparison of the effects of duloxetine and pregabalin on pain and associated factors in patients with knee osteoarthritis

Ozge Gulsum Illeez[1*], Kubra Neslihan Kurt Oktay[2], Ilknur Aktas[1], Feyza Unlu Ozkan[1], Tuba Nazligül[3], Feyza Akan Begoglu[1], Meryem Yilmaz Kaysin[1], Arzu Atici[1], Pinar Akpinar[1]

SUMMARY

OBJECTIVES: This study aimed to investigate the effects of duloxetine and pregabalin primarily on pain and functional status in patients with knee osteoarthritis and secondarily on quality of life, depression, anxiety, and sleep disturbance.

METHODS: A total of 66 patients with knee osteoarthritis were randomized to use duloxetine or pregabalin. Patients were evaluated by Visual Analog Scale, Neuropathic Pain Diagnostic Questionnaire, Western Ontario and McMaster University Osteoarthritis Index, Short Form-36, Beck Depression Inventory, Beck Anxiety Inventory, and Pittsburg Sleep Quality Index before the treatment and after 4 and 12 weeks of treatment.

RESULTS: Improvements occurred in Visual Analog Scale, Neuropathic Pain Diagnostic Questionnaire, Western Ontario and McMaster University Osteoarthritis Index, Short Form-36 (with an exception of the mental health subgroup scores in duloxetine-treated group), Beck Depression Inventory, and Beck Anxiety Inventory scores in both groups from 4 weeks after baseline. Pittsburg Sleep Quality Index total scores and SF-36 mental health subgroup scores started to improve on the 4th and 12th weeks in pregabalin- and duloxetine-treated groups, respectively.

CONCLUSION: Osteoarthritis pain, a complex outcome with nociceptive and neuropathic components, leads to central sensitization in a chronic phase. Using centrally acting drugs in the control of pain and associated symptoms would increase the probability of treatment success.

KEYWORDS: Duloxetine hydrochloride. Knee. Osteoarthritis. Pain. Pregabalin.

INTRODUCTION

Osteoarthritis (OA) is a chronic, degenerative disease frequently seen in the middle-aged and elderly people. Knee OA is a particularly common type of OA and a major cause of disability[1]. OA pain is a mixed type of pain involving both nociceptive and neuropathic components. Pain is the most pronounced symptom in knee OA, being initially associated with activity and becoming continuous and severe as the disease progresses. This is thought to be due to the development of central sensitization. Central sensitization is a pain processing abnormality occurring in chronic pain due to persistent activation of the spinal and supraspinal neurons. This process may also cause comorbid conditions such as fear, anxiety, depression, and sleep disorders[2,3]. Central sensitization in knee OA has particularly been shown in patients describing severe pain but without radiological findings indicating the same pain severity[4,5].

Because of the mechanism involved in central sensitization in OA, the use of therapeutic agents that affect the central pain pathways may be required. Duloxetine, a selective serotonin and norepinephrine reuptake inhibitor, is found to be effective in the treatment of chronic pain because of its antidepressant and anxiolytic properties. Duloxetine has been reported to be effective in the treatment of diabetic peripheral neuropathic pain, fibromyalgia, and chronic musculoskeletal pain[6]. Pregabalin suppresses the release of excitatory neurotransmitters by combining with alpha-2-delta subunits of voltage-dependent calcium channels in the central nervous system. It also exhibits positive effects on neuropathic pain-related sleep disturbance, depression, and anxiety. Therapeutic guidelines recommend gabapentinoids (pregabalin-gabapentin) as the first choice medications in the treatment of neuropathic pain[7].

This study was intended to compare the effects of duloxetine and pregabalin on pain and function in patients with OA. The secondary purpose of the study was to examine the effects of these central-acting drugs on anxiety, depression, and sleep disturbance frequently seen during chronic pain and on the

[1]University of Health Sciences Fatih Sultan Mehmet Training and Research Hospital, Department of Physical Medicine and Rehabilitation – Istanbul, Turkey.
[2]Yeditepe University Faculty of Medicine, Department of Physical Medicine and Rehabilitation – Istanbul, Turkey.
[3]University of Health Sciences, Van Training and Research Hospital, Department of Physical Medicine and Rehabilitation – Van, Turkey.
*Corresponding author: ozgeilleez@hotmail.com
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quality-of-life parameters. To the best of our knowledge, no previous studies have compared the efficacy of pregabalin and duloxetine in knee OA.

METHODS

This prospective, randomized clinical study was performed between October 2016 and December 2020. The study was approved by the Institutional Ethics Committee (FSMEAH-KAEK 9.06.2016/50), and informed consent was obtained from all patients before commencement. Inclusion criteria were age over 40, diagnosis with OA based on the American College of Rheumatology primary knee OA criteria; posterior–anterior X-ray examination showing grades 2–3 knee OA according to the Kellgren and Lawrence Radiological Classification System; a VAS score and a DN4 scale value of 4 or more; and more than 14 painful days a month for at least the past 3 months. Exclusion criteria were body mass index (BMI) higher than 40; the presence of diabetes mellitus, congestive heart failure, cancer, fibromyalgia, inflammatory arthropathy, or autoimmune disease; receipt of invasive treatment with a diagnosis of OA in the past 3 months; being nonambulatory or using assistant devices for walking; and the presence of psychiatric or neurological disease. Notably, 66 patients whose eligibility was confirmed were randomized to one of the two groups, and 3 patients from each group subsequently dropped out from the study; finally, only 60 patients participated in the study. One group was administered 60 mg/day duloxetine HCl, and another group was given 300 mg/day pregabalin, both for 12 weeks. In the duloxetine-treated group, the drug was administered as a single 30 mg dose in the first week and at 60 mg/day from the second week. Patients in the pregabalin-treated group received 75 mg orally twice a day in the first week, followed by 150 mg orally twice a day from the second week. Patient assessments were performed before the treatment and at the 4th and 12th weeks of the treatment. The primary outcome measures were VAS, DN4, and WOMAC, and the secondary outcome measures were BDI, BAI, PSQI, and SF-36. Side effects of the drug were questioned in the patients at the follow-ups.

Statistical evaluation

Data analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 23 software. Frequency and percentage values were calculated for categorical variables, while continuous variables were expressed as mean, standard deviation, median, minimum, and maximum values. Compatibility with a normal distribution of continuous variables was evaluated using the Kolmogorov–Smirnov test. Relationships between categorical variables were determined using the chi-square test. The Mann–Whitney U test was used to compare non-normally distributed variables between two independent groups, and the Friedman test was used for comparisons between more than two groups. Dunn's multiple comparisons test with Bonferroni correction was used for two-way comparisons. Statistical analyses were evaluated at a significance level of 0.05.

RESULTS

No significant difference was determined between the two groups in terms of age, gender, mean duration of disease, Kellgren and Lawrence grade, or initial scores for all the parameters examined. However, BMI was higher in the duloxetine-treated group than that in the pregabalin-treated group (p=0.017). Inter- and intragroup changes in VAS day and night pain, DN4, and WOMAC scores are shown in Table 1. Inter- and intragroup changes in SF-36 and subgroup scores are shown in Table 2. Inter- and intragroup changes in BDI, BAI, and PSQI scores are shown in Table 3.

Side effects were recorded prospectively throughout the study. A total of 16 side effects were observed in the duloxetine-treated group [i.e., constipation (4), dizziness (4), nausea (2), somnolence (1), peripheral edema (1), fatigue (1), pruritus (1), genitourinary symptoms (1), and diarrhea (1)], and 25 side effects were observed in the pregabalin-treated group [i.e., somnolence (6), constipation (4), dizziness (4), weight gain (3), nausea (2), peripheral edema (2), pruritus (1), skin eruption (1), dry mouth (1), and abdominal distension (1)]. In the duloxetine-treated group, three patients were withdrawn from the study (one patient due to pain persisting at the same level of severity, one patient due to constipation, and one patient due to dizziness). In the pregabalin-treated group, 3 patients were dropped out from the study (one patient due to peripheral edema in the bilateral lower extremities and two patients due to somnolence). Other side effects were not severe enough to prevent patients from continuing treatment.

DISCUSSION

In this study, significant improvement was observed compared with pre-treatment values in all parameters in both drug groups from the fourth week. Two exceptions were that total sleep scores and SF-36 MH scores in the duloxetine-treated group only improved compared with baseline in the 12th week. A significant difference between weeks 4 and 12 was also present in a small number of parameters, functional status, and

Table 1. Inter- and intragroup changes in VAS, DN4, and WOMAC scores.

Parameters	Duloxetine (n=30) Mean±SD Median (min–max)	Pregabalin (n=30) Mean±SD Median (min–max)	p*	*Post hoc* test†	Duloxetine	Pregabalin
VAS daytime 0	6.77±1.43 7 [4–10]	7.03±1.54 7 [5–10]	0.476	0 vs. 4	p<0.0001	p<0.0001
VAS daytime 4	3.4±1.92 3 [0–8]	3.4±1.73 3 [1–8]	0.893	0 vs. 12	**p<0.0001**	**p<0.0001**
VAS daytime 12	2.7±2.1 3 [0–8]	2.1±2.12 1 [0–9]	0.179	4 vs. 12	NS	NS
p**	**p<0.0001**	**p<0.0001**				
VAS nighttime 0	6.83±1.7 7 [4–10]	6.73±2.53 8 [0–9]	0.647	0 vs. 4	**p<0.0001**	**p<0.0001**
VAS nighttime 4	3.57±1.96 3.5 [0–8]	2.97±1.94 3 [0–8]	0.242	0 vs. 12	**p<0.0001**	**p<0.0001**
VAS nighttime 12	2.6±2.14 2.5 [0–8]	1.9±2.02 2 [0–9]	0.152	4 vs. 12	NS	NS
p**	**p<0.0001**	**p<0.0001**				
DN4-0	5.27±1.6 5 [4–9]	4.9±1.21 4 [4–8]	0.410	0 vs. 4	**p<0.0001**	**p<0.0001**
DN4-4	3.03±1.63 3 [0–7]	1.47±1.2 1 [0–5]	**p<0.0001**	0 vs. 12	**p<0.0001**	**p<0.0001**
DN4-12	2.73±1.62 3 [0–7]	1.43±1.28 1 [0–5]	**0.001**	4 vs. 12	NS	NS
p**	**p<0.0001**	**p<0.0001**				
WOMAC 0 pain	13.37±3.83	12.47±4.36	0.377	0 vs. 4	**p<0.0001**	**p<0.0001**
WOMAC 4 pain	8.67±4.36	6.53±3.72	**0.038**	0 vs. 12	**p<0.0001**	**p<0.0001**
WOMAC 12 pain	7.2±5.61	4.2±4.29	**0.020**	4 vs. 12	NS	**0.024**
p**	**p<0.0001**	**p<0.0001**				
WOMAC 0 stiffness	5±2.27	4.03±2.16	0.101	0 vs. 4	**p<0.0001**	**p<0.0001**
WOMAC 4 stiffness	3.33±2.2	2±1.82	**0.016**	0 vs. 12	**p<0.0001**	**0.001**
WOMAC 12 stiffness	3±2.17	1.37±1.69	**0.002**	4 vs. 12	NS	NS
p**	**p<0.0001**	**p<0.0001**				
WOMAC 0 function	40.6±14.66	38.1±14.56	0.662	0 vs. 4	**p<0.0001**	**p<0.0001**
WOMAC 4 function	26.2±13.58	21.03±14.3	0.141	0 vs. 12	**p<0.0001**	**p<0.0001**
WOMAC 12 function	22.93±17.08	14.5±14.98	**0.043**	4 vs. 12	NS	NS
p**	**p<0.0001**	**p<0.0001**				
WOMAC 0 total	60.62±19.17	56.52±20.3	0.473	0 vs. 4	**p<0.0001**	**p<0.0001**
WOMAC 4 total	39.3±19.47	30.9±19.59	0.109	0 vs. 12	**p<0.0001**	**p<0.0001**
WOMAC 12 total	34.02±23.81	20.9±21.28	**0.022**	4 vs. 12	NS	**0.029**
p**	**p<0.0001**	**p<0.0001**				

*Mann–Whitney U test; **Friedman test. †Dunn's multiple comparisons test with Bonferroni correction. Min: minimum; Max: maximum; SD: standard deviation; VAS: Visual Analog Scale; NS: nonsignificant. Bold indicates statistically significant values.

quality-of-life subscores. A comparison of duloxetine and pregabalin treatment revealed that pregabalin was superior in terms of its effects on the neuropathic component of pain, functional status, and some quality-of-life parameters.

Earlier, OA pain was generally regarded as a peripherally mediated nociceptive pain. However, inflammatory mediators have been shown to modulate both peripheral and central nociceptors following intra-articular release from damaged tissues[8].

Table 2. Inter- and intragroup SF-36 and sub-parameter changes.

Parameters	Duloxetine (n=30) Mean±SD	Pregabalin (n=30) Mean±SD	p*	*Post hoc* test†	Duloxetine	Pregabalin
SF-36 PF 0	43.17±17.79	41.67±21.15	0.917	0 vs. 4	**p=0.001**	**p=0.001**
SF-36 PF 4	64±22.22	64±20.98	0.870	0 vs. 12	**p<0.0001**	**p<0.0001**
SF-36 PF 12	71.08±21.69	76±22.61	0.237	4 vs. 12	NS	**0.035**
p**	**p<0.0001**	**p<0.0001**				
SF-36 PRF 0	20.22±35.97	20.83±34.79	0.844	0 vs. 4	**0.002**	**0.002**
SF-36 PRF 4	62.21±40.75	69.17±44.37	0.414	0 vs. 12	**p<0.0001**	**p<0.0001**
SF-36 PRF 12	68.44±39.31	83.33±33.69	0.112	4 vs. 12	NS	NS
p**	**p<0.0001**	**p<0.0001**				
SF-36 ERF 0	38.87±35.1	31.09±28.93	0.450	0 vs. 4	**p<0.0001**	**p<0.0001**
SF-36 ERF 4	69.96±25.31	71.1±37.89	0.463	0 vs. 12	**0.007**	**0.011**
SF-36 ERF 12	80.53±26.31	85.55±29.93	0.184	4 vs. 12	NS	NS
p**	**p<0.0001**	**p<0.0001**				
SF-36 V 0	40.11±22.39	36.73±24.34	0.276	0 vs. 4	**p<0.0001**	**p<0.0001**
SF-36 V 4	48±22.54	55.33±22.7	0.194	0 vs. 12	**0.014**	**0.014**
SF-36 V 12	58.27±21.55	64±18.82	0.357	4 vs. 12	**0.024**	NS
p**	**p<0.0001**	**p<0.0001**				
SF-36 MH0	49.5±23.49	50.8±24.14	0.716	0 vs. 4	NS	**p<0.0001**
SF-36 MH 4	55.83±17.53	66.4±18.98	**0.014**	0 vs. 12	**0.006**	**0.002**
SF-36 MH 12	61.23±21.4	71.67±14.73	0.055	4 vs. 12	NS	NS
p**	**p<0.0001**	**p<0.0001**				
SF-36SRF 0	56.85±24.19	49.58±26.16	0.187	0 vs. 4	**0.020**	**0.001**
SF-36 SRF 4	69.5±25.15	72.92±21.3	0.799	0 vs. 12	**p<0.0001**	**p<0.0001**
SF-36 SRF 12	75.03±22.12	78.75±17.1	0.689	4 vs. 12	NS	NS
p**	**p<0.0001**	**p<0.0001**				
SF-36 BP 0	31.33±18.47	23.17±17.37	0.061	0 vs. 4	**p<0.0001**	**p<0.0001**
SF-36 BP 4	58.42±24.05	62.25±21.79	0.336	0 vs. 12	**p<0.0001**	**p<0.0001**
SF-36 BP 12	63.75±29.41	66.83±25.02	0.911	4 vs. 12	NS	NS
p**	**p<0.0001**	**p<0.0001**				
SF-36 GHP 0	36.5±20.14	42.1±23.47	0.509	0 vs. 4	**p<0.0001**	**0.002**
SF-36 GHP 4	50.23±16.62	59.57±18.02	0.063	0 vs. 12	**p<0.0001**	**p<0.0001**
SF-36 GHP 12	56.92±20.59	69.07±14.62	**0.022**	4 vs. 12	NS	NS
p**	**p<0.0001**	**p<0.0001**				

*Mann–Whitney U test; **Friedman test. †Dunn's multiple comparisons test with Bonferroni correction. Bold indicates statistically significant values. SF-36: Short Form-36; PF: physical functioning; PRF: physical role functioning; ERF: emotional role functioning; V: vitality; MH: mental health; SRF: social role functioning; BP: bodily pain; GHP: general health perceptions; SD: standard deviation; VAS: Visual Analog Scale; NS: nonsignificant.

Patients with OA are now known to experience varying degrees of both nociceptive and neuropathic pain[9]. Significant scientific evidence also reports a role for central sensitization in OA pain. The presence of central sensitization confuses the clinical picture and makes it less likely to respond to conventional treatments[10]. The addition of centrally acting agents to conventional therapies in the treatment of OA has been shown to increase the response to treatment[11].

Table 3. Inter- and intragroup changes in BDI, BAI, and Pittsburg scores.

Parameters	Duloxetine (n=30) Mean+SD	Pregabalin (n=30) Mean+SD	p*	*Post hoc* test†	Duloxetine	Pregabalin
BDI 0	17.2±8.72	16.53±9.21	0.841	0 vs. 4	**p<0.001**	**p<0.017**
BDI 4	11.63±7.65	10.47±8.11	0.501	0 vs. 12	**p<0.0001**	**p<0.0001**
BDI 12	10.13±7.88	7.83±6.26	0.310	4 vs. 12	NS	NS
p**	**p<0.0001**	**p<0.0001**				
BAI 0	17.63±13.63	17.63±9.98	0.594	0 vs. 4	**0.002**	**0.001**
BAI 4	13.07±11.23	10.87±7.59	0.706	0 vs. 12	**p<0.0001**	**p<0.0001**
BAI 12	11±9.67	7.3±6.18	0.109	4 vs. 12	NS	NS
p**	**p<0.0001**	**p<0.0001**				
Pittsburg total-0	8.93±4.87	11±4.99	0,119	0 vs. 4	NS	**0.001**
Pittsburg total-4	7.13±5.11	6.93±4.37	0.795	0 vs. 12	**0.001**	**p<0.0001**
Pittsburg total-12	6.27±5.09	5.9±3.52	0.522	4 vs. 12	NS	NS
p**	**p<0.0001**	**p<0.0001**				

*Mann–Whitney U test; **Friedman test. †Dunn's multiple comparisons test with Bonferroni correction. Bold indicates statistically significant values. BAI: Beck Anxiety Inventory; BDI: Beck Depression Inventory; NS: nonsignificant.

There have been very few studies of the use of pregabalin in knee OA. Rahman et al. described pregabalin as useful against pain resulting from knee OA in an animal model and demonstrated modified physiology of deep dorsal horn wide dynamic range neurons, suggesting an association between heightened neuronal activity and hypersensitive behavioral responses[12]. In another study using a lower pregabalin dosage than in this study, patients with knee OA were randomized into groups receiving meloxicam 10 mg, meloxicam 10 mg/day+pregabalin 25 mg/day, and pregabalin 25 mg/day only. Significant improvements were recorded in the meloxicam+pregabalin group in terms of pain and functional status scores, showing that knee OA represents a combination of both nociceptive and neuropathic pain[11]. In another study, the same number of patients as in this study were randomized into aceclofenac- and aceclofenac+pregabalin-treated groups, and significant improvement in both pain severity and functional status was observed in the combination therapy group compared with the monotherapy group[13].

There have been more studies investigating the use of duloxetine in knee OA than pregabalin. A meta-analysis of three randomized controlled studies involving a total of 1011 patients reported significant improvement in pain and functional status in patients using 60/120 mg duloxetine following approximately 10–13 weeks of treatment compared with a placebo group. Similar to this study, tolerable levels of side effects such as nausea, fatigue, constipation, hyperhidrosis, somnolence, dizziness, diarrhea, insomnia, and dry mouth were reported in the three studies in that meta-analysis[14]. A double-blinded randomized, controlled study of 354 patients reported no change in knee joint movement and x-ray findings in a duloxetine-treated group but observed significant improvement in pain and functional status compared with a control group[6]. Another study of 288 patients with knee OA aged over 65 reported significant improvements in pain, functionality, and geriatric depressions scores in a duloxetine-treated group compared with a placebo group[15]. A study comparing the efficacy of pregabalin and duloxetine in patients with hand OA reported that both agents were effective against chronic hand OA pain, with pregabalin being superior to duloxetine. However, in contrast to the findings of this study, neither of the two drugs was reported to produce any improvement in either depression or anxiety scores[16].

Chronic pain developing in association with OA can result in impairment of health-related quality of life and daily activities, and psychological distress, including depression[17] and sleep disturbances[18]. The prevalence of depression is estimated to be two to three times higher in patients with OA[19-20]. Sarıyıldız et al. reported impairment of sleep quality in patients with knee OA and that this was particularly associated with knee pain, age, depressive symptoms, and radiological grade[21]. Alkan et al. reported lower SF-36 scores among patients with OA compared with healthy controls[22]. In this study, treatment with both duloxetine and pregabalin improved anxiety, depression, and sleep disturbance symptoms, together with the quality of

life. Despite not reaching statistical significance, pregabalin was superior to duloxetine in all these parameters, and pregabalin also exhibited its effect on sleep disturbance earlier. Studies examining the effectiveness of pregabalin on anxiety and depression have reported inconsistent findings regarding pain, but similar results in terms of its effect on sleep. Gilron et al. reported that pregabalin yielded a small but significant difference in sleep interference, anxiety, and depression scores[23]. This study has some limitations. The first limitation is the absence of a control group. Although we knew that using a placebo group would make our study more valuable, we did not use a placebo group because we thought that the quality of life of the patients might be affected by this process. The second one is the short follow-up period, since more informative results might have been yielded by a longer follow-up period. The third limitation is that BMI was higher in the duloxetine group than that in the pregabalin group. This may partially account for the superiority of pregabalin in terms of knee functionality.

CONCLUSION

Pain in OA is a complex event involving both nociceptive and neuropathic components. According to the results of our study, both duloxetine and pregabalin are effective in reducing mixed type of pain and improving functions. These agents also are useful against depression, anxiety, and sleep disorder, which frequently accompany the chronic process, and can thus contribute to an improvement of the patient's quality of life.

ETHICAL APPROVAL

The study was approved by the Institutional Ethics Committee (FSMEAH-KAEK 9.06.2016/50). Clinical trial ID: NCT04532684, retrospectively registered 25.01.2021.

AUTHORS' CONTRIBUTIONS

OGI: Conceptualization, Data Curation, Formal Analysis, Investigation, Methodology, and Writing – Original Draft. **KNKO:** Data Curation, Investigation, Methodology, Validation, and Visualization. **IA:** Project Administration, Methodology, Supervision and Writing – Review & Editing. **FUO:** Methodology, Supervision, and Writing – Review & Editing. **TN:** Data Curation, Investigation, and Resources. **FAB:** Data Curation, Investigation, and Resources. **MYK:** Data Curation, Investigation, And Resources. **AA:** Data Curation, Investigation, and Resources. **PA:** Data Curation, Investigation, and Resources.

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