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ORIGINAL ARTICLE

Efficacy of duloxetine and gabapentin in pain reduction in patients with knee osteoarthritis

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Abstract

Introduction Knee osteoarthritis (OA) is a common form of arthritis in elders which can lead to reduced daily activity and quality of life. It is important to administer a proper treatment with high efficacy and low side effects. In this study, we evaluated the efficacy of duloxetine and gabapentin in patients with moderate to severe knee OA.

Method In this randomized clinical trial, 150 patients with moderate to severe knee OA were randomly allocated to receive duloxetine 30 mg ($n = 50$), gabapentin 300 mg ($n = 50$), or acetaminophen 1000 mg ($n = 50$) all twice a day for 12 weeks. Pain severity using visual analogue scale (VAS) and functional status using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) were measured before, 2 weeks, 1 month, and 3 months after intervention.

Results WOMAC total and its subscale score were significantly lower in duloxetine compared to gabapentin in 2 weeks and 1 months after intervention, with no significant difference at the end of the third month. Both gabapentin and duloxetine groups had significantly more reduction in pain VAS and WOMAC and its subscales compared to acetaminophen group, with no significant difference between groups.

Conclusions Both gabapentin and duloxetine have similar and acceptable effects in pain reduction and improvement of functional status in patients with knee OA at the end of the third month's treatment. Duloxetine effects begin from the first weeks, while gabapentin effects begin gradually with the best at the end of the third month.

Key Points

- *Medical treatment is used for releiving pain in knee osteoarthritis.*
- *Gabapentin and duloxetine are both effective in reducing pain in knee osteoarthritis.*

Keywords Duloxetine · Gabapentin · Knee osteoarthritis · Pain

Introduction

Knee osteoarthritis (OA) is the most common form of arthritis in the elderly and is a common cause of pain and disability in these individuals, which is associated with a decrease in quality of life and increased risk of depression and anxiety. Pain relief is one of the principles of treatment for knee OA [1].

Pain is a major symptom in patients with OA [2]. Pain and decreased physical activity due to OA impose a significant psychosocial burden on the patient and the health system [2, 3]. Different medications suggested for pain control in knee OA are topical or oral NSAIDs, intra-articular injections of corticosteroids, and hyaluronate and opioids. Recently, duloxetine treatment was recommended for pain control in knee OA [4]. There is a need for proper treatments with acceptable efficacy and low side effects for pain relief in these patients.

Pain is often characterized by the presence of nociceptive and neuropathic inflammatory pain [5, 6]. OA is known as inflammatory pain and increased sensitivity to pain. Duloxetine is a selective norepinephrine and serotonin

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reuptake inhibitor which has acceptable efficacy in four types of chronic pain, such as diabetic peripheral neuropathic pain [7, 8], fibromyalgia [9, 10], chronic back pain [11, 12], and pain in knee OA [13, 14] in clinical studies. Duloxetine appears to inhibit pain by increasing serotonergic and noradrenergic activities in the central nervous system [15].

Gabapentinoid is a derivative of gamma aminobutyric acid neurotransmitter that blocks the voltage-dependent calcium channels. Gabapentin, originally developed for the treatment of epilepsy, is one of the other drugs that can help reduce pain in knee OA. Concerns about the use of gabapentinoid for the treatment of OA have been increased with respect to the role of gabapentin in inhibiting the sensitization of pain [16, 17]. The effectiveness of gabapentin in the treatment of chronic pain in diabetic neuropathy and fibromyalgia has also been shown [18, 19].

The study that evaluates the effect of gabapentin on the pain of patients with osteoarthritis is not available. However, researchers in animal studies have shown that gabapentin is effective in reducing the pain in OA [20, 21].

Several studies have been conducted to evaluate the efficacy of duloxetine compared with gabapentin for pain control, indicative of more efficacy for gabapentin in the treatment of diabetic neuropathy and fibromyalgia [22, 23]; although compliance and adherence to the duloxetine use in chronic back pain was more [24].

Both gabapentin and duloxetine are effective in pain control, with higher efficacy for gabapentin. Reducing the pain of patients with knee OA is one of the most important therapeutic goals of these patients, but proper cost-effective and tolerable treatment has not been recommended yet. There is also no study on the efficacy of gabapentin in controlling pain in patients with knee OA. Therefore, for the first time, we aimed to evaluate the effectiveness of gabapentin in comparison with duloxetine in reducing pain patients with knee OA.

Patients and methods

In this double-blinded randomized controlled trial, 150 patients with moderate to severe knee OA visiting rheumatology clinics of Ardabil University of Medical Sciences were recruited.

Patients between 45 and 75 years old with moderate to severe idiopathic knee OA able to walk with knee pain more than five by visual analogue scale (VAS) or more than 48 score in the Western Ontario and McMaster Universities Osteoarthritis (WOMAC) were included in the study. The patients had radiographic evidence of OA with Kellgren-Lawrence score of III to IV (moderate to severe) on X-ray. Exclusion criteria were those patients with other rheumatologic diseases, including fibromyalgia, other knee or periarticular disease, lower limb fracture with knee joint involvement, OA of the hip and ankle, history of knee surgery or trauma, radicular pain, intraarticular corticosteroid injection or physiotherapy in the previous three months and hyaluronic injection in the previous six months, and psychologic disorders, including depression, balanced control deficit, sensory and motor neurologic deficits, and cancers. We also excluded those patients with underlying systemic disease, such as renal, hepatic, or heart failure, uncontrolled blood pressure, diabetes mellitus, and severe asthma in need of corticosteroid use. Those patients who used corticosteroids in the last 6 weeks prior to the study and those with allergic reactions to any of the study medications were also excluded. The ethics committee of Ardabil University of Medical Sciences approved the study protocol, and all patients gave their informed written consent.

The sample size for each group was calculated as 44 cases considering an effect size of $d \geq 0.5$ as statistically significant in a two-tailed test with $\alpha = 0.05$ and power of 0.90. As there was possibility that some patients do not complete the study, we included 50 patients in each group. After excluding 7 patients, 150 were included. Using random number blocks and sealed envelopes, the patients were randomly allocated to duloxetine ($n = 50$), gabapentin ($n = 50$), or acetaminophen ($n = 50$) groups according to sample size (Fig. 1). All patients completed the study period, and none of the patients discontinued the intervention or lost to follow-up.

Three groups received duloxetine 30 mg, gabapentin 300 mg, or acetaminophen 1000 mg daily; the drug dosage was increased to maximum of 60, 600, and 2000 mg daily, respectively, after two weeks. All the patients receive the maximum dosage of each of the given medication after two weeks. The participants and the physician assessing the outcome of the study were blinded to the allocated group. Opioid usage was not allowed during the intervention period. The patients were asked to continue their previous medications for OA, except corticosteroids. Patients were asked to report the use of NSAIDS (ibuprofen with maximum dose of 2400 mg daily, naproxen with maximum dose of 1500 mg daily, and indomethacin 150 mg daily) during the study period for pain reduction.

The study period was three months; the patients were evaluated before the intervention, 2 weeks, one month, and three months after the intervention for their pain severity using the visual analogue scale (VAS) and physical status using the Western Ontario and McMaster Universities Osteoarthritis (WOMAC) questionnaire. The VAS is a standard scale for pain measurement using a 10-cm instrument. Each subject rated knee pain on a scale of 0 to 10, where zero indicates the absence of pain and 10 indicates the worst pain imaginable [25].

The WOMAC questionnaire includes 24 questions that measures the three dimensions of pain (5 items), stiffness (2 items), and physical function (17 items). Each question is based on 5-point Likert scale resulting in total number range of 0 to 96. With increase in the severity of the disease, the points are increased [26]. The Persian format of the WOMAC questionnaire was validated previously [27].

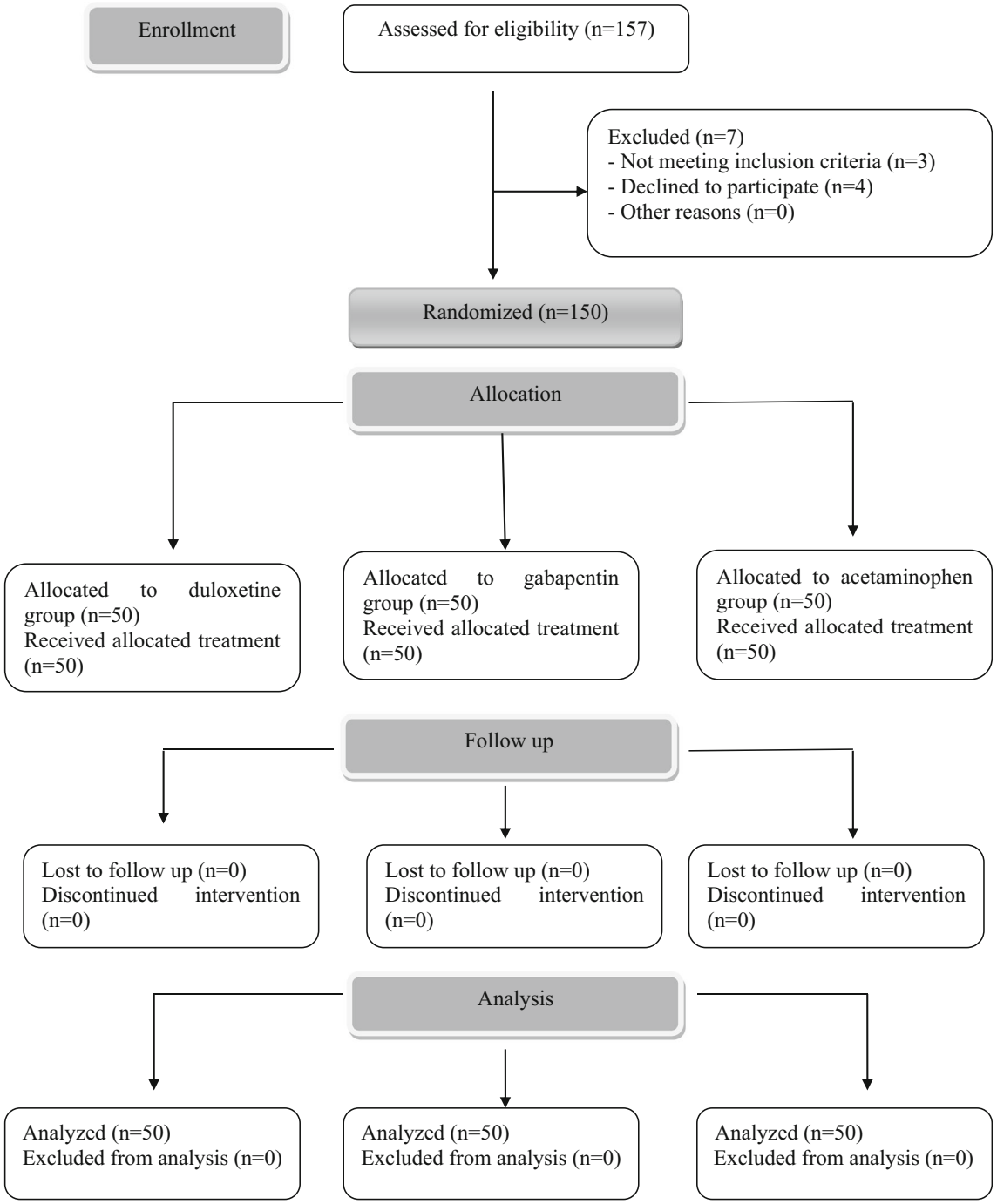

Fig. 1 Study flow diagram

Statistical analysis

All data were analyzed using SPSS20 (version 22; SPSS Inc., Chicago, IL). The results are expressed as mean ± standard deviation or percentage. Kolmogorov–Smirnov test was used to assess normal distribution of data. Chi-squared test, Fisher's exact test, independent *t* test, or Mann–Whitney *U* test was used to compare data between groups. Repeated measure of ANOVA was used to compare serial changes in parameters during the study period in each and between groups. *p* values of less than 0.05 were considered statistically significant.

Results

One-hundred and fifty patients were randomly allocated to gabapentin, duloxetine, and acetaminophen groups. These

Table 1 Patients' demographic findings

		Gabapentin ($N = 50$)	Duloxetine ($N = 50$)	Acetaminophen ($N = 50$)	p value
Age (years)		54.76 ± 8.58	55.00 ± 5.89	53.56 ± 6.70	0.56
Gender	Male	12 (24%)	14 (28%)	14 (28%)	0.87
	Female	38 (76%)	36 (72%)	36 (72%)	
Disease duration (years)		8.08 ± 3.48	8.56 ± 4.05	8.68 ± 4.59	0.73
BMI (kg/m^2)		28.13 ± 4.47	27.05 ± 4.91	27.71 ± 5.55	0.56
Kellgren-Lawrence score	II	22 (44%)	20 (40%)	21 (42%)	0.92
	III	28 (56%)	30 (60%)	29 (58%)	

BMI, body mass index

Data are expressed as frequency (percentage) or mean ± standard deviation

three groups were similar regarding demographic findings (Table 1).

Both gabapentin and duloxetine groups had significantly lower pain VAS compared to acetaminophen group in the first ($p < 0.001$, both) and third months ($p < 0.001$, both) after intervention, with no significant differences between these two groups ($p = 0.11$, $p = 0.59$, respectively) (Fig. 2). Gabapentin and duloxetine also had more reduction in VAS after treatment compared to the acetaminophen group ($p < 0.001$), while there was no significant difference between groups ($p = 0.33$) (Table 2).

Serial changes in WOMAC score and its subscales in different periods between groups are demonstrated in Fig. 3. There was no significant difference between groups before intervention ($p > 0.05$). Gabapentin had significantly higher WOMAC total score than duloxetine ($p = 0.006$) and acetaminophen ($p = 0.002$), with no significant difference between duloxetine and acetaminophen ($p = 0.77$). In the first month after treatment, duloxetine group had significantly lower WOMAC total compared to gabapentin ($p < 0.001$) and acetaminophen ($p < 0.001$) groups, with no significant difference between gabapentin and acetaminophen ($p = 0.25$) groups. At the end of the third month, both gabapentin and duloxetine had significantly lower total score compared to acetaminophen group ($p < 0.001$, for both), with no significant difference between these two groups ($p = 0.56$).

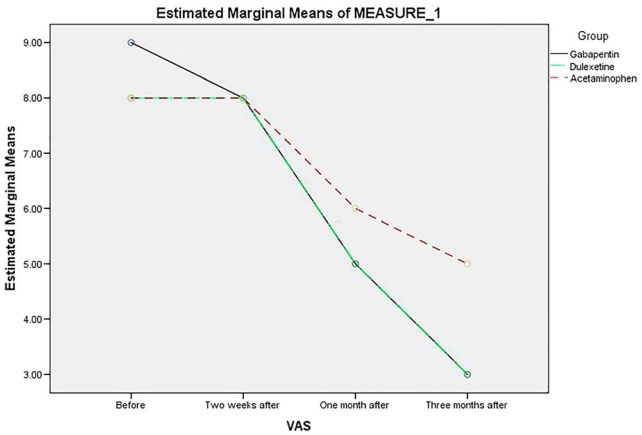

Fig. 2 VAS changes during study period between groups

Duloxetine and acetaminophen had significantly lower score in pain subscale ($p = 0.04$ and $p = 0.02$, respectively) and physical state subscale ($p = 0.03$ and $p = 0.009$) than gabapentin in the first two weeks; there was also lower score in pain and physical state subscale in duloxetine compared to gabapentin ($p < 0.001$) and acetaminophen ($p < 0.001$) in the first month. At the end of the third month, both gabapentin and duloxetine groups compared to acetaminophen ($p < 0.001$ for both) had significantly lower pain and physical state score, with no significant difference between other groups in the evaluated periods.

In the stiffness subscale, duloxetine had significantly lower score than gabapentin in the first two weeks ($p = 0.03$) and lower score than gabapentin and acetaminophen in the first month ($p < 0.001$, both). Both gabapentin and duloxetine had lower score compared to acetaminophen group at the end of the third month ($p < 0.001$, both), with no significant difference between the two groups ($p = 0.08$).

The percent of reduction in WOMAC total and its subscale scores in both gabapentin and duloxetine were significantly higher than acetaminophen ($p < 0.001$ for all), but gabapentin and duloxetine had no significant difference ($p > 0.05$). It seems that duloxetine effects begin from the first weeks of treatment, but gabapentin needs three months for showing its full efficacy. Acetaminophen efficacy reduces significantly after first month.

Although the patients were instructed to use defined NSAIDS in the case of pain, none of them reported using these drugs during the intervention period.

Drug side effects were seen in 9 patients (18%) of gabapentin group and 8 patients (16%) of duloxetine group, with no significant difference between groups ($p = 0.79$). Side effects in the gabapentin group were dry mouth in 5 cases, drowsiness in 2, and fatigue in 2, while in duloxetine group were drowsiness in 5, fatigue in 2, and dry mouth in 1. No side effects were seen in the acetaminophen group.

Table 2 Percent of changes in VAS and WOMAC score and its subscales between groups

	Gabapentin	Duloxetine	Acetaminophen	*p* value
Visual analogue scale	− 63.36 ± 8.87	− 61.45 ± 7.65	− 31.20 ± 12.58	< 0.001
WOMAC total	− 70.67 ± 8.97	− 71.11 ± 10.05	− 41.48 ± 6.74	< 0.001
Pain subscale	− 73.94 ± 12.79	− 78.29 ± 10.06	− 50.32 ± 10.78	< 0.001
Stiffness subscale	− 72.91 ± 20.55	− 78.10 ± 16.49	− 47.30 ± 21.28	< 0.001
Physical activity subscale	− 69.53 ± 8.85	− 68.36 ± 11.69	− 58.82 ± 8.54	< 0.001

WOMAC, Western Ontario & McMaster Universities Osteoarthritis Index

Data are expressed as mean ± standard deviation

Discussion

In this study, we found that both gabapentin and duloxetine had an acceptable efficacy compared to acetaminophen in relieving pain and improving the function of patients with moderate to severe knee OA at the end of the third month's treatment.

Various oral and topical medications have been used for OA treatment, but none of them has proven to be the most effective one. Given that the majority of patients with knee OA are elders that would have other illnesses, it is important to prescribe a drug that has the highest efficacy with the least side effects and drug interactions. NSAIDs and acetaminophen are among the most commonly used drugs to treat knee OA [28]. Despite short-term efficacy, it has been shown that acetaminophen has low efficacy compared to NSAIDs and is not superior to placebo in the treatment of patients with moderate to severe knee OA [28, 29]; thus, it is not recommended in these patients.

Similarly, we observed that acetaminophen was more effective only in the first month of treatment, and improvement

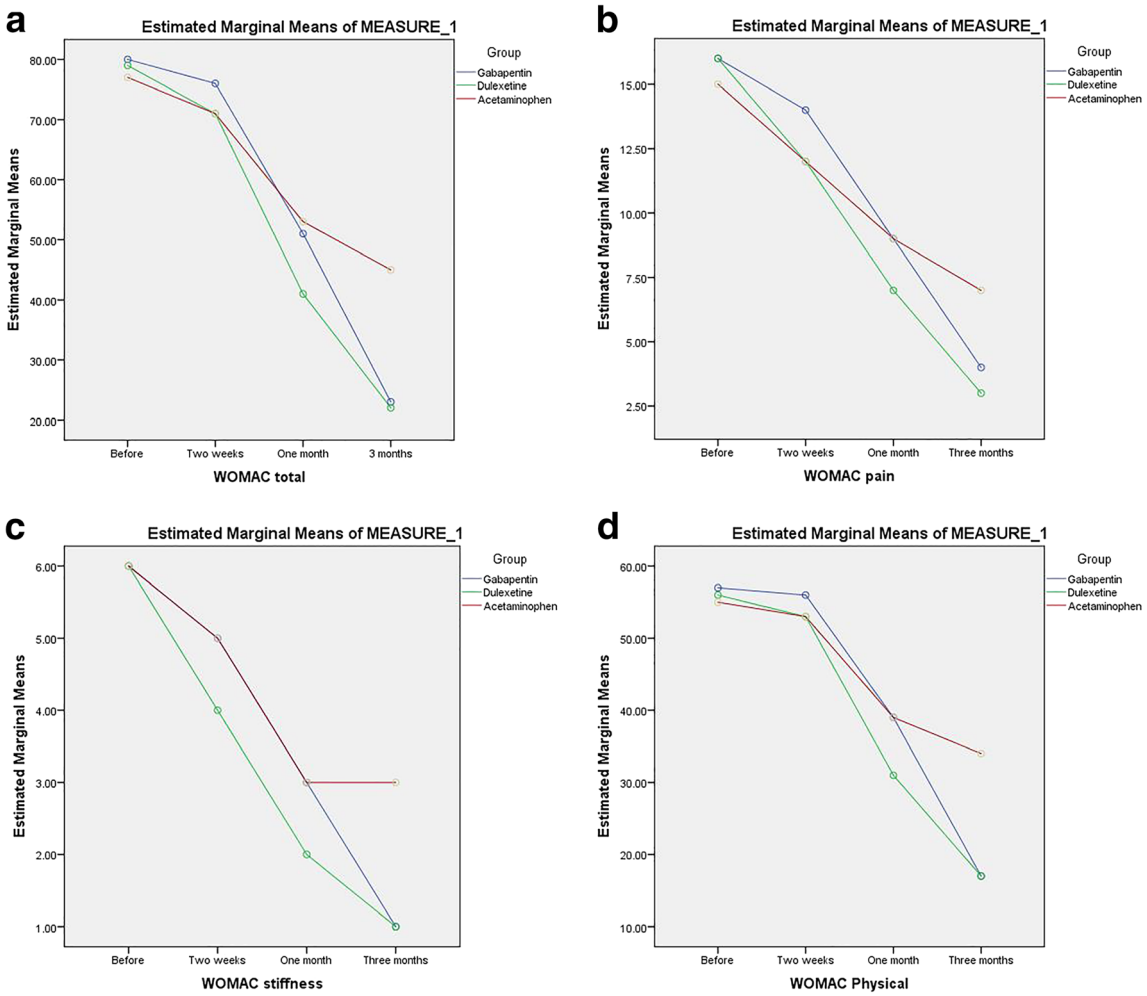

Fig. 3 WOMAC total (**a**), pain (**b**), stiffness (**c**), and physical function (**d**) subscale changes during study period between groups

in the severity of the symptoms was observed afterwards compared to the other two drugs.

Recent studies have indicated that central pain processing system may be involved in causing peripheral or nociceptive pains, such as OA [30]. Studies have also shown that neuropathic mechanisms are activated during the development of OA, and many OA patients report neuropathic pain. Administering drugs that would affect neuropathic pain could be used for relieving OA-associated pain [20].

Duloxetine and gabapentin are shown to be effective in the treatment of different neuropathic pain syndromes [22–24, 31]. OA guidelines recommend duloxetine for the treatment of poly-articular OA with or without underlying disease and for knee OA without any associated illness [4]. Several studies have reported a significant improvement in pain in patients with knee OA treated with duloxetine compared to placebo [13, 14, 32]. In the experimental studies, gabapentin had variable effects on the OA pain depending on the model, dose, and nociceptive test [20].

All previous studies on gabapentin have been performed on experimental OA models. In this study, we evaluated the efficacy of gabapentin compared to duloxetine among patients with moderate to severe knee OA for the first time. Our results indicated significant efficacy of gabapentin in reducing the pain and improving WOMAC's total and its subscale scores at the end of the three-month treatment. Gabapentin had similar efficacy to acetaminophen in the first month, but the effectiveness of the drug was significantly increased afterwards.

In the experimental models, Adães et al. [20] observed that the use of gabapentin improved pain responses within 6 weeks. Gong et al. [21] concluded that gabapentin may be helpful in the treatment of OA-induced pain. Vonsy and colleagues [33] also observed that gabapentin improves pain through neuronal pathways and therefore can be used to treat OA patients.

In this study, patients receiving duloxetine also experienced an acceptable efficacy during the three-month period. The severity of pain in these patients began to decrease from the very beginning and the patient's performance status based on WOMAC improved accordingly.

Similarly, Wang et al. [32] found that treatment with duloxetine 60 mg daily for 13 weeks resulted in a significant reduction in pain intensity compared to the placebo group. In another study, Uchio et al. [34] observed that the treatment of patients with duloxetine 60 mg daily for 14 weeks resulted in a significant reduction in pain severity compared to placebo, along with improved quality of life. However, no significant changes were observed in knee range of motion nor radiological changes between the two groups.

Wang et al. [35] in a review of 1011 patients from three clinical trials found that duloxetine 60/120 mg daily compared to placebo was associated with a greater reduction in pain and significant improvement in the physical function subgroup of WOMAC with acceptable side effects.

In previous studies, the effectiveness of the gabapentin and duloxetine in chronic pain disorders has been evaluated, but there is no such study in OA patients. In one study, Sofat et al. [36] reported significant improvement in pain and physical function after 13 weeks of treatment with pregabalin compared with placebo and duloxetine, while there was no significant difference between the duloxetine and placebo groups. Although this study was conducted on hand OA, but due to the similarity between gabapentin and pregabalin, it could be presumed that gabapentin is more effective than duloxetine in treating hand OA.

In the present study, we observed that both gabapentin and duloxetine had an acceptable efficacy at the end of the 3-month period in reducing pain and improving WOMAC score and its subscales, with no significant difference between groups. However, the time required for duloxetine to produce significant effects was from the first weeks, while the effects of gabapentin occurred after first month. These indicate that duloxetine seems a better choice in patients with more severe disease in need of early pain relief. In the case of treatment with gabapentin, another drug is necessary to be administered especially in the first month until gabapentin effects occur.

It is necessary to choose a medication with less side effects for the treatment of knee OA. The common reported side effects for gabapentin are dizziness, drowsiness, peripheral edema, and imbalance [37], while common reported side effects of duloxetine are drowsiness, constipation, dry mouth, nausea, fatigue, and appetite loss [37]. In the present study, side effects were observed in 18 and 16% of gabapentin and duloxetine patients, including oral dryness in 5 cases, drowsiness in 2, and fatigue in 2 in the gabapentin group and drowsiness was also reported in 5 cases, feeling tired in 2, and dry mouth in one in the duloxetine group. Most of these complications were negligible and did not result in discontinuation of treatment in any of the patients.

Conclusion

Both gabapentin and duloxetine have similar and acceptable effects in pain reduction and improvement of functional status in patients with knee OA at the end of the third month's treatment. Duloxetine effects begin from the first weeks, while gabapentin effects begin gradually with the best at the end of the third month.

Author contribution All the authors edited and critically reviewed the manuscript drafts and approved the final version submitted for publication. AEM was the principal investigator, performed a literature search, and was involved in the study design, collection, analysis, and interpretation of data and in writing the manuscript. AH and PJ were involved in the collection and interpretation of data and writing the manuscript. KI contributed to the conception and design of the study, the data interpretation, and the critical revision of the manuscript. HM was involved in collection and interpretation of data, performed a literature search, and in writing the manuscript.

Compliance with ethical standards

Disclosures None.

Patient consent Obtained

Ethics approval The study was conducted in accordance with the Declaration of Helsinki and good clinical practice guidelines and with local requirements.

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