ORIGINAL ARTICLE

Effectiveness between Duloxetine and Pregabalin for the Management of Neuropathic Chronic Low Back Pain

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Abstract

Background: Chronic low back pain has as a mixture of nociceptive and neuropathic component. This neuropathic component is often overlooked during management which increases the sufferings of patients. Prevalence of neuropathic pain is quite high and approximately 37% of chronic low back patients suffer from predominantly neuropathic pain. Treatment of neuropathic component of low back pain remains challenging and multiple modalities of treatments have been tried but not all of them are satisfactory. Among these, duloxetine and pregabalin have been shown to be promising in treatment of various neuropathic syndromes, but there is no direct comparative study between these two drugs in patients with back pain with neuropathic component. Objective of this study was to compare the effcetiveness between duloxetine and pregabalin which one reduce the pain and improve quality of life better.

Methods: This is a prospective, observational study. Chronic low back pain patients with neuropathic components were recruited according to inclusion and exclusion criteria. Pain was measured by visual analog scale and neuropathic component measured by painDETECT questionnaire score. Patients were randomly assigned to either duloxetine or pregabalin group. Both drugs were initiated with their lowest dose. Duloxetine was started with 20mg/day with optional up titration to 60mg/day (20mg, weekly increments) and pregabalin was started with 50mg/day with optional up titration to 300mg/day (50mg weekly increments) for six weeks. A fixed dose combination of paracetamol and tramadol (325mg + 37.5mg) was used as rescue medication for breakthrough pain. Follow up were carried out weekly by face to face visits or over phone. At week four and six, additional assessment of patients' quality of life was assessed by SF-36. The primary outcome parameter was mean VAS score and quality of life improvement by assessing SF-36 was secondary outcome parameter.

Results: Out of 80 patients enrolled, 62 completed trial, eight patients in duloxetine and ten patients in pregabalin group dropped out. In this study, a significant reduction of pain intensity was observed with both Duloxetine and Pregabalin compared with their baseline values, but there was no statistically significant difference between the two treatments. The SF-36 score at the end of each treatment phase was significantly improved with both treatments. But when comparing in between two groups, the changes of mean SF-36 score was not significant as well.

Conclusion: Both duloxetine and pregabalin are well-tolerated having good safety profiles. Further clinical trials with long term follow up are needed to determine their long term effect.

Keywords: CLBP, Neuropathic pain, Duloxetine, Pregabalin, VAS, pain DETECT, SF-36

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Introduction

CLBP often has as a mixture of nociceptive and neuropathic component. Prevalence of neuropathic CLBP is quite high and one study revealed, approximately 37% of CLBP patients suffer from predominantly neuropathic pain[1]. An analysis of claims recorded in a US health-insurance database indicated that back and neck pain with neuropathic involvement is probably the most frequent neuropathic disorder[2]. A recent survey among patients registered with general practitioners in the UK indicated a proportion of 17% patients suffering with neuropathic pain among persons with chronic back pain[3].

In chronic back pain the nociceptive component results from activation of nociceptors that innervate ligaments, small joints, muscles and tendons. And neuropathic component results from lesions of nociceptive sprouts within a degenerated disc, mechanical compression of the nerve root, or effects of inflammatory mediators arising from a degenerative disc that results in inflammation and damage to the nerve roots.

The International Association for the Study of Pain (IASP) taxonomy defines neuropathic pain as 'Pain resulting from a lesion or dysfunction of the peripheral or central nervous system'. A variety of nerve-damaging stimuli are likely to generate a neuropathic pain component in patients presenting with a CLBP, which mainly presents as radicular leg pain[4,5]. Radicular leg pain is defined as segmental pain that radiates below the knee[6,7]. It is also called as projected pain, which is caused by damage or irritation of peripheral nerves or nerve root. Mechanical compression of radicular nervous tissue may occur within or adjacent to the intervertebral foramina, within the lateral recess and within the spinal canal itself. In addition, the action of inflammatory mediators (cytokines, chemokines) originating from the degenerative disc has been implicated in the chemical pathomechanism of radicular neuropathic pain[1]. A smaller proportion of people have neurogenic claudication, in which the leg pain is associated with spinal stenosis and symptoms are exacerbated with extension activities and relieved by flexion[8].

To date, treatment of CLBP with a neuropathic involvement remains challenging[8] and multiple modalities of treatments have been tried. The effect sizes of most nonsurgical treatments for nonspecific LBP are low to moderate (0.2-0.6) and unlikely to result in complete pain relief. Therefore, pain management is aimed at reducing dysfunction in physical, psychological and social dimensions while improving quality of life for patients and minimizing risks and adverse effects. Studies have found a 30% pain reduction to constitute clinically meaningful benefit[9].

The majority of published studies and guidelines stating the drugs used in neuropathic pain treatment include: paracetamol, NSAIDs, muscle relaxants, antidepressants, anticonvulsants, opioids. The therapeutic approach is primarily based on analgesics and paracetamol is the drug of choice in first intention. If paracetamol is not effective, weak opioid tramadol alone or in combination with acetaminophen may be used[10].

Compared with patients with non-neuropathic chronic pain, patients with neuropathic pain seem to have higher average pain scores and lower health related quality of life (HRQOL). The literature on neuropathic pain is evolving rapidly. A large number of randomized clinical trials (RCT) of different interventions for various neuropathic pain conditions have been published over the past several years but substantial gaps in the literatures remain. For these reasons, under the guidance of the International Association for the Study of Pain (IASP), Neuropathic Pain Special Interest Group (NeuPSIG), an international consensus process that included a diverse group of pain experts was formed to develop evidence-based guidelines for the pharmacologic treatment of neuropathic pain[11]. Additional consensus guidelines for the pharmacologic treatment of neuropathic pain were created simultaneously by the European Federation of Neurological Societies (EFNS)[12] and the Canadian Pain Society[13]. Tricyclic antidepressants, gabapentinoids (gabapentin, pregabalin) and selective serotonin noradrenaline reuptake inhibitor (SSNRI) duloxetine remain the most recommended drugs to treat various conditions of neuropathic pain according to these guidelines[13,14].

Duloxetine is a selective serotonin noradrenaline reuptake inhibitor which initiates the pharmacological response by reuptake inhibition of both serotonin and nor epinephrine in the central nervous system, thereby increases the activity of these neurotransmitters and subsequently reduces the perception for pain by modulating the pain signals[15]. Side effects with duloxetine are generally mild for the SNRI class which includes nausea, dizziness, somnolence, fatigue, sweating, dry mouth, constipation, and diarrhea[16]. Duloxetine may interact with tramadol, causing a serotonin syndrome, although this risk seems to be low in clinical practice[17]. A number of studies show that duloxetine is significantly superior to placebo in CLBP[18,19,20]. Duloxetine is a good choice for CLBP treatment with coexisting depression, anxiety, fibromyalgia or chronic musculoskeletal pain[21].

Pregabalin is a chemical analogue of the neurotransmitter Gamma Amino Butyric Acid (GABA) present in mammals. Pregabalin is inactive at GABA receptors and does not mimic GABA physiologically. Pregabalin binds with α2δ subunit of pre-synaptic, voltage dependent calcium channel which probably contributes to its anticonvulsant properties, since these activities correlates with a decrease in calcium channel function. Pregabalin was developed as an antiepileptic drug but has been reported to have clinical efficacy as an analgesic for neuropathic pain and fibromyalgia and as an anxiolytic in patients with generalized anxiety disorder[11,22]. The most common adverse effects associated with pregabalin are dizziness, somnolence, facial oedema, peripheral oedema and weight gain[21,22]. Pregabalin has proven efficacy in postherpetic neuralgia, painful diabetic neuralgia, and mixed or unclassified post-traumatic neuropathic pain. There are a number of studies showing pregabalin is also effective in CLBP[23-25].

Comparative study between duloxetine and pregabalin are very few, all are conducted in diabetic neuropathic pain, fibromyalgia showing similar efficacy and safety profile of these two drugs[26,27]. However, there is no direct comparison between duloxetine and pregabalin in neuropathic CLBP. So, this study was designed to compare the effectiveness of duloxetine and pregabalin in the treatment of neuropathic CLBP.

Methods

Study place, participants and design

This prospective observational study was carried out on patients with chronic low back pain with neuropathic components identified by painDETECT questionnaire score ≥12, recruited from Pain Medicine Outpatient Clinics, in the Department of Anaesthesia, Analgesia and Intensive Care Medicine, BSMMU, Dhaka from March 2018 to September 2020. Prior to the commencement of this study, the research protocol was approved by the Institutional review board (IRB). An informed written consent was taken from all the participants after fulfilling inclusion and exclusion criteria. Demographic characteristics of all subjects were recorded. Patients exposed to medications for neuropathic pain e. g. amitriptyline was gone through two weeks washout period during which they were treated with a combination of paracetamol and tramadol (325mg + 37.5mg) 3 times per day.

Clinical and functional assessment was done for all patients by full history taking, general examination and complete back examination at the first visit. The severity of pain was assessed by visual analogue scale (VAS) and quality of life by SF-36.

The patients were randomly assigned into two groups. The randomization was performed by independent members of the Department. They used eighty (80) opaque sealed envelopes containing group names (duloxetine or pregabalin group) and a code number of the patients (01 to 80). The patients drew an envelope by lottery. The research stuff opened the envelope and recorded the patient's name, group and code number. In this way, the total eighty (80) patients were randomly assigned into two groups as follows:

Duloxetine Group = Duloxetine titrated from 20 mg/day to a maximum 60 mg/day at bedtime (20mg weekly increments) for six weeks.

Pregabalin Group = Pregabalin titrated from 50 mg/day to a maximum 300 mg/day in two divided doses (50mg weekly increments) for six weeks.

Treatment was started with the lowest dose of both drugs that is used in previous studies[14,20]. The

uptitration of doses of duloxetine and pregabalin were flexible i.e. the doses were increased in them whose severity of pain did not reduced from baseline or from previous week and there were no severe adverse events. If pain is reduced at a satisfactory level (30% from baseline) with a lower dose, then that dose was continued up to six weeks without attaining the maximum titrating dose to minimize possibility of side effects.

The primary endpoint was expected change of pain intensity from baseline at four weeks and six weeks measured by VAS scores. Secondary endpoint was expected change in patient's quality of life from baseline to weeks four and six measured by short-form 36-item general health survey (SF-36). At the beginning and end of each treatment, a safety laboratory check, including electrolytes, creatinine, liver parameters (alanine aminotransferase, aspartate aminotransferase), and a complete blood count were performed. Patients were recommended not to seek any other treatment during trial period except rescue medication; a combination of paracetamol and tramadol (325mg + 37.5mg) 3 times per day, if required.to control break through pain.

Follow up were carried out weekly, by visiting the patients in pain clinic or over phone. At weekly follow up, intensity of pain was measured using VAS and assessment done for any adverse events. At week four and week six, patients' quality of life was also assessed by SF-36. In the event that a patient used rescue medication within 12 hours of the clinic visit, the patients were requested to respond to the VAS, SF-36 questions based on their functional ability for the 24-hour period preceding the rescue medication.

Study measures

A pre-tested structured questionnaire was used for data collection. The questionnaire had two parts, demographic characteristics and assessment of pain and functional ability.

Visual analogue scale (VAS): A 10 cm Visual analogue scale is a tool used to rate the intensity of pain. A straight line is drawn between two extremes with one end meaning "no pain" at 0 and the other end meaning "maximum pain" at 10. The patients will be asked to rate their pain by placing a mark along the scale between these two extremes.

SF-36: The Short Form (36) Health Survey is a 36-item, patient-reported survey of patient health. The SF-36 consists of eight domains of health, which are the weighted sums of the questions in their section. All questions are scored on a scale from 0 to 100, on the assumption that each question carries equal weight. The scores from those questions that address each specific domains of health are then averaged together, for a final score. The lower the score the more the disability. The higher the score the less the disability.

Pain DETECT questionnaire: It is a validated screening tool specifically developed for the identification of a neuropathic component in CLBP patients, with a high sensitivity and specificity (80 and 83%) to neuropathic pain. Distribution and quality of pain perceived by the patient can be obtained and rated on a 38-point scale. Patients with a score of greater than 19 points are very likely to have a neuropathic component with their low back pain (> 90%), and in patients with a score from 12 to 18 points, a neuropathic component may be present.

Ethical consideration

Prior to the commencement of this study, the research protocol was approved by Institutional review board (IRB). The aims and objective of the study along with its procedure, alternative diagnostic methods, risk and benefits were explained to the patients in easily understandable local language and then informed consent had been taken from each patient. It was assured that all records would be kept confidential and the procedure would be helpful for both the physician and patients in making rational approach regarding management of the case.

Statistical analysis

Data were statistically described in terms of mean ± standard deviation (SD) (continuous variables) and percentages/frequencies (qualitative observations) when appropriate. Comparison of numerical variables were done using the Student's t-test or fisher exact test. For comparing categorical data, Chi-square (X2) test was performed. $P < 0.05$ were considered statistically significant. All statistical calculations were done using the

computer programs SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 25 for Microsoft Windows.

Results

A total of 80 patients were included in this study. Eight patients in duloxetine group and ten patients in pregabalin group were dropped out in follow up.

Demographic and Baseline data were statistically not significant among the two groups (p>0.05).The mean age was 41.65±11.98 years in duloxetine group and 43.06±13.27 years in pregabalin group. 46.9% patients were male in duloxetine group and 53.3% patients were male in pregabalin group. Regarding height, the mean height was 161.31±5.34 cm in duloxetine group, 164.00±7.57 cm in pregabalin group. The mean weight was 66.87±8.11 kg in duloxetine group and 70.76±11.51 kg in pregabalin group. Baseline characteristics shows, the mean VAS was 5.53±0.94 and 5.66±0.92 in duloxetine and pregabalin group respectively. Duration of pain was 11.50±7.60 and 12.00±8.61 months, SF-36 score 37.24±8.29 and 40.86±8.79, Pain DETECT score 13.12±2.10 and 13.53±2.06 in duloxetine and pregabalin group respectively. Table I described the Demographic and Baseline data of the two groups.

Table I: Demographic and Baseline data of duloxetine and pregabalin groups:

Demographic & baseline data	Duloxetine group (n=32)	Pregabalin group (n=30)	P value
Age (years)	41.65±11.98	43.06±13.27	0.661
Sex			
Male	15(46.9)	16(53.3)	0.611
Female	17(53.1)	14(46.7)	
Height (cm)	161.31±5.34	164.00±7.57	0.110
Weight (kg)	66.87±8.11	70.76±11.51	0.127
PainDETECT score	13.12±2.10	13.53±2.06	0.451
Duration of pain (months)	11.50±7.60	12.00±8.61	0.681
VAS at baseline	5.53±0.94	5.66±0.92	0.572
SF-36	37.24±8.29	40.86±8.79	0.100

Values are expressed as mean ± SD or absolute number. Within parenthesis are percentages over column total.Statistical analysis is done by unpaired student t-test and chi square test where applicable. P value of <0.05 is considered as significant.

Pain intensity after each week quantified by VAS score (ranges from 0 to 10, lower scores indicate less pain). In duloxetine group, mean VAS reduced from 5.53±0.94 to 2.96±0.89 at week four and 2.87±0.70 at week six. The P value was 0.001. In pregabalin group, mean VAS reduced from 5.66±0.92 to 3.06±1.01 at week four and 3.00±0.98 at week six. The P value was 0.001. But when comparing the VAS in between two groups, the P value was more than 0.05. (Table II)

Figure 1 showed the gradual increment of doses in two groups in relation to treatment time period. Here, in first week, the mean dose of duloxetine and pregabalin was 20.00±0.00 mg and 50.00±0.00 mg respectively. At fourth week, the dose was increased to 22.81±4.56 mg in duloxetine and 106.66±40.96 mg in pregabalin group. And in final week, the mean dose of duloxetine and pregabalin group was 26.87±4.70 mg and 123.33±34.07 mg respectively.

Table II: Comparison of VAS score between duloxetine and pregabalin groups with P value:

Weeks	Duloxetine group (n=32)	Pregabalin group (n=30)	P value (In between group)
Pre-treatment	5.53±0.94	5.66±0.92	0.572
After 1st week	4.43±0.94	4.86±1.33	0.147
After 2nd weeks	3.75±1.01	4.13±1.30	0.200
After 3rd week	3.34±1.03	3.70±1.26	0.228
After 4th weeks	2.96±0.89	3.06±1.01	0.688
After 5th weeks	2.87±0.70	3.00±0.98	0.566
After 6th weeks	2.87±0.70	3.00±0.98	0.566
P value (Within group)	0.001	0.001	

Values are expressed as mean ± SD. Statistical analysis in between groups is done by unpaired student t-test and within groups by ANOVA test. P value (P<0.05) is considered as statistically significant.

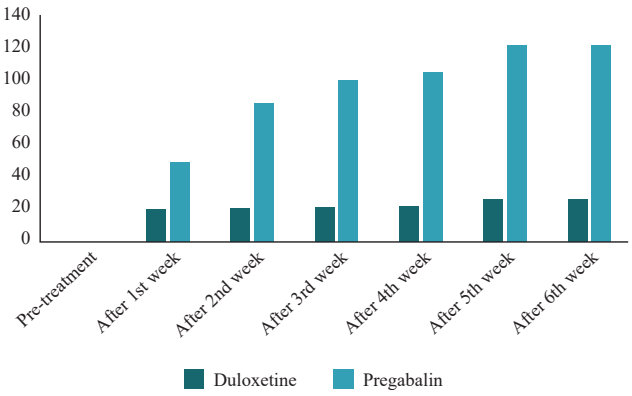

Fig. 1: Weekly increments of doses of Duloxetine and Pregabalin

In pregabalin group, the average dose was 106.66±40.96mg and VAS reduced 2.60 points. At week six, average dose of duloxetine was 26.87±4.70mg and VAS reduced 2.66 points from baseline. In pregabalin group, the average dose was 123.33±34.07mg and VAS reduced to 2.66 points form baseline. It took two weeks for duloxetine and three weeks for pregabalin to achieve 30% reduction of pain in VAS scale counting from baseline.

The Quality of life was measured by SF-36 (ranges from 0 to 100, higher scores indicate better health). Table III shows that mean SF-36 score increases in both groups after intervention. SF-36 increased from 37.24±8.29 to 42.55±8.99 at week four and 42.61±8.59 at week six in duloxetine group. In pregabalin group, SF-36 increased from 40.86±8.79 to 46.03±9.74 at week four but decreased slightly to 45.65±10.52 at week six. In both groups the P value was 0.001 and it was statistically significant ($p<0.05$). But when comparing in between two groups, the changes of mean SF-36 score was not significant ($P>0.05$).

Table III: Comparison of SF-36 score at week four and six between Duloxetine and Pregabalin group:

Weeks	Duloxetine group (n=32)	Pregabalin group (n=30)	P value (In between group)
Pre-treatment	37.24±8.29	40.86±8.79	0.100
After 4th weeks	42.55±8.99	46.03±9.74	0.149
After 6th weeks	42.61±8.59	45.65±10.52	0.217
P value (Within group)	0.001	0.001	

Values are expressed as mean ± SD. Statistical analysis in between group is done by unpaired student t-test and within group by ANOVA test. P value ($P<0.05$) is considered as statistically significant.

In duloxetine group, 68.8% participants required dose up titration and 90.6% needed rescue medication. In pregabalin group 80% participants needed dose up titration and 93.3 % needed rescue medication.

The frequency of adverse effects in two groups was shown in Figure 2. In duloxetine group, most common adverse effects were somnolence (12.5%) and fatigue (12.5%) followed by dry mouth (3.12%), nausea (3.12%) and headache (3.12%). In pregabalin group, fatigue was most common (23.33%), followed by somnolence (16.7%), nausea (6.7%), peripheral oedema (3.33%).

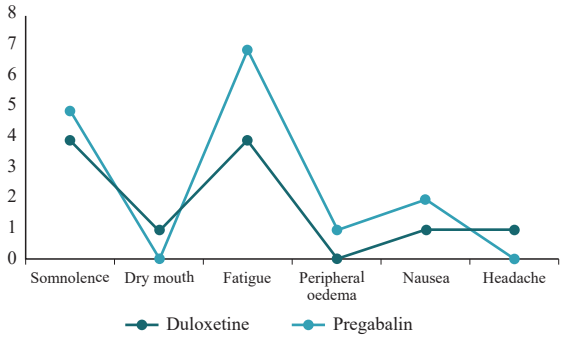

Fig. 2: Frequency of adverse effects of the two studied groups

Discussion

In this study, the demographic characteristics of patients of duloxetine and pregabalin group were statistically similar in the context of age, sex, height and weight ($P>0.05$). So, demographic variables didn't significantly alter the outcome of the study. Demographic characteristics of a similar study of duloxetine in neuropathic CLBP patients conducted in Austria[18] and found higher mean age and weight of CLBP patients. This differences in demographic features are due to different geographic locations of study populations.

The current trial demonstrates that both duloxetine and pregabalin are efficacious in the treatment of neuropathic CLBP. The average dose of duloxetine and pregabalin at week six was 26.87mg and 123.33mg respectively. There was no significant difference between duloxetine and pregabalin groups ($P >0.05$) in relation to pretreatment VAS. It took two weeks for duloxetine and three weeks for pregabalin to achieve 30% reduction of pain in VAS scale

counting from baseline. However, at the endpoint, at week four and six there was significant reduction of pain in both groups (P = 0.001) evident by change of VAS. Though VAS reduced more in duloxetine group of population than pregabalin, this difference was not significant (P>0.05) when compared the two groups statistically.

These results correlate well with the findings of previous studies. Shahid et al.[25] compared efficacy of duloxetine and pregabalin in diabetic peripheral neuropathy by comparing mean VAS. They used a fixed dose for duloxetine (60mg/day) and pregabalin (300mg/day). The mean change of VAS from baseline to week four was 1.21 for duloxetine and 0.98 for pregabalin, (p<0.05 for all). In our study, change of VAS at week 4 was 2.5 for duloxetine and 2.6 for pregabalin (p<0.05). Their result shows both duloxetine and pregabalin reduced VAS significantly (P<0.0001), but there was no significant intergroup difference (P=0.90). However, the larger dose requirements maybe due to difference in disease process, as diabetes mellitus causing more neuropathy than CLBP and also different demographic features of study population.

In a placebo controlled randomized crossover trial[18] studied effectiveness of duloxetine in neuropathic CLBP patients. They started duloxetine with 30mg/day and titrated up to 120mg/day. The mean change of VAS from baseline to week four for duloxetine phase was 2.7±2.5 (p<0.05), that is consistent with the findings of our study where, change of VAS at week four was 2.5 for duloxetine and 2.6 for pregabalin (p<0.05). The larger dose requirement is due to larger average weight (80.5kg) of their study population (vs. 66.87kg in our study) and more neuropathic features present evident by painDETECT score. Their pain DETECT score at baseline was 20±3.1 compared to 13.12±2.10 in our study.

In another study by Roy et al.[21] found similar efficacy of pregabalin and duloxetine in reduction of Diabetic Neuropathic Pain. They showed that that both duloxetine and pregabalin reduced neuropathic pain but effect of duloxetine was 1.27 times more than that of pregabalin. However, they measured pain in neuropathic pain scale (NPS).

In this study, result shows that, mean SF-36 scores increased significantly from pretreatment to week four and six both in duloxetine and pregabalin group. So, the improvement of quality of life with both drugs group was significant (P = 0.001). Though pregabalin increased SF-36 scores slightly more than duloxetine but the difference between the two groups was not statistically significant (P>0.05).

Roy et al.[21] also found similar improvement in quality of life in patients of diabetic peripheral neuropathy following treatment by duloxetine and pregabalin measured by Neuro-QoL (quality of life) scores. But they showed duloxetine improved quality of life 1.44 times more than that of Pregabalin. This difference may be due to differences in disease process and different scale used to measure quality of life.

Rahimzadeh et al.[26] in a randomized clinical trial investigated the effectiveness of duloxetine and pregabalin on quality of life of breast cancer patients with taxane-induced sensory neuropathy. They measured mean global health status/QOL, pain, insomnia, and emotional functioning scores after a 6-week treatment period. They found that, both pregabalin and duloxetine improved the global health status/QOL scale significantly after 6 weeks (P = 0.002). However, between pregabalin and duloxetine groups, no significant difference was seen (P = 0.91).

In the current study, 90.6% participants in duloxetine group and 93.3% in pregabalin group used rescue medication. In the study by Schukro et al.[18] showed that out of 21 patients, 13 (61.9%) used rescue medication in duloxetine phase. The explanation of relatively large amounts of patients' use of rescue medication in our study maybe due to the fact that we started with the minimum dose and chronic low back patients often have neuropathic and nociceptive pain components. So, duloxetine, pregabalin reduced the neuropathic component and tramadol, paracetamol reduced the nociceptive component.

In this study the side effects were noted in 21.8% patients in duloxetine and 26.7% patients in pregabalin group. The common side effects in duloxetine group were somnolence 12.5% and fatigue 12.5%, whereas in the pregabalin group, the common side effects were fatigue 23.3%, somnolence 16.7% and nausea 6.7%. The side effects between the two

groups were not significantly different (P>0.05). No patients in any group discontinued therapy due to adverse events.

Similar study by Shahid et al.[25] reported the side effects in 17.9% of the participants. Lethargy/ somnolence 8.1% and peripheral edema 3.4% were commonly reported in the pregabalin group and constipation 6.9% and orthostatic hypotension 4.6% were commonly reported in the duloxetine group. The composite side effects between the two groups were not significantly different. Two patients in duloxetine group and no patients in pregabalin group discontinued therapy due to adverse events.

In the study conducted by Schukro et al.[18], 65% patients in duloxetine phase experienced side effects. Dry mouth (35%), fatigue (35%), sweating (26%), constipation (19%), nausea (19%), and loss of appetite (19%), dizziness (16%) were common. Five patients in duloxetine group of first phase and four patients in crossover phase discontinued therapy due to adverse effects. Rahimzadeh et al.[26] had found adverse effects were mild in both duloxetine and pregabalin group and no participants discontinued therapy due to adverse events. Somnolence (22.5%), dizziness (17.5%) in duloxetine group and nausea (9.5%), somnolence (4.8%) were common in pregabalin group. The difference in discontinuation and adverse events between current study and the abovementioned studies maybe due to difference in sample size and difference in doses.

Conclusion

Both duloxetine and pregabalin are well-tolerated having good safety profiles. Further clinical trials with long term follow up are needed to determine their long term effect.

Declaration

Ethics approval

The study was approved by the Ethical Review Committee of BSMMU. Informed written consent was taken from the participants before inclusion.

Author contributions

Conception and development of the idea *AKMA, MMR*
Data analysis *MMR, MMK*
Data collection *MMR, GD, SS, MZ*
Writing- Original draft preparation *MMR, MMK*
Review and Editing *MMR, MMK, AKMA*

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Conflict of interests None

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