

Effect of duloxetine on neuropathic pain in patients intolerant to continuous administration of pregabalin

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Abstract:

Purpose: We examined duloxetine's effectiveness in the treatment of neuropathic pain in patients who were intolerant to continuous pregabalin administration. **Materials and Methods:** The present study is a retrospective study of patients diagnosed with neuropathic pain with neuropathic leg pain as the chief complaint. We analyzed 20 cases in which pregabalin was changed to duloxetine because of adverse effects (16 cases) or treatment failure (4 cases). The incidence of adverse events after duloxetine administration was used as the primary endpoint, with the secondary endpoint being the leg pain level based on a numerical rating scale (NRS). **Results:** The incidence of adverse events after starting duloxetine was 40%. Average leg pain scores measured on the NRS were 8.4 ± 1.4 , 6.4 ± 1.4 , and 4.1 ± 2.0 at the time of the patients' first visit, pregabalin discontinuation, and after switching to duloxetine, respectively. A significant difference in NRS scores was found between the first visit and pregabalin discontinuation and also between pregabalin discontinuation and after the switch to duloxetine ($p < 0.05$), indicating that pain decreases over time. Furthermore, NRS scores significantly declined between the patients' first visit and after the switch to duloxetine ($p < 0.05$). The improvement in NRS score was $20 \pm 12.8\%$ after pregabalin administration and $23 \pm 12.0\%$ after duloxetine administration compared with baseline scores (no significant difference between pregabalin and duloxetine; $p > 0.05$). **Conclusion:** When patients with neuropathic pain are unable to tolerate pregabalin because of adverse effects, changing the medication to duloxetine may be an option.

Keywords:

duloxetine, treatment failure with pregabalin, neuropathic pain

Spine Surg Relat Res 2017; 1(1): 40-43

dx.doi.org/10.22603/ssrr.1.2016-0012

Introduction

According to data summarized from 816 reports, the prevalence of chronic neuropathic pain in the lower back is as high as 36.6%¹⁾. Thus, orthopedists frequently encounter neuropathic pain in daily medical practice. The use of pregabalin for neuropathic pain has been shown to be effective, with its use increasing in recent years²⁾. Although the mechanism of analgesia is unclear, studies suggest that pregabalin inhibits the release of neurotransmitters such as glutamic acid and binds the calcium channel subunit- $\alpha 2\delta$, which plays a supplementary role in the function of voltage-dependent calcium channels in the central nervous system. This suppresses the expression of calcium channels and limits the calcium influx on the cellular surface of calcium

channels. In addition, there is evidence that pregabalin exerts an analgesic effect by inhibiting the descending pain modulatory system³⁻⁷⁾.

Despite its efficacy against neuropathic pain, pregabalin has a high frequency of adverse effects. According to the package insert in Japan, at least 20% of patients experience dizziness or drowsiness. Both effects can significantly lower compliance, sometimes forcing discontinuation before a therapeutic effect can be achieved.

Duloxetine, an antidepressant with serotonin-noradrenaline reuptake inhibitory activity, is reportedly effective against neuropathic pain. In fact, numerous foreign clinical studies have confirmed its analgesic effect, and several neuropathic guidelines, including one published by the International Association for the Study of Pain, have classified it as a first-

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Received: October 25, 2016, Accepted: December 12, 2016

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or second-line drug^{8,9}).

Because duloxetine is specific to serotonin and noradrenaline receptors, the drug characteristically has fewer adverse effects¹⁰. It follows that most adverse effects experienced by patients would be caused by serotonin and noradrenaline. For instance, the high frequency of nausea is caused by serotonin stimulation of the gastrointestinal tract¹¹.

To conclude, pregabalin and duloxetine possess different mechanisms of action, which may lead to different adverse effects. Therefore, we hypothesize that changing pregabalin to duloxetine could be an effective solution for patients who severely react to pregabalin. Here we report the effectiveness of duloxetine as a substitute for continuous administration of pregabalin for neuropathic pain.

Materials and Methods

In our retrospective study, we selected 20 patient cases from the records of 223 neuropathic pain patients who visited our institution from August 2014 to August 2015. The selection criteria included only patients who were diagnosed with neuropathic pain who came in with a chief complaint of neuropathic leg pain. In addition, we included only patients with obviously identified neuropathic pain through imaging and physical findings from magnetic resonance imaging (MRI) who were taking pregabalin but switched to duloxetine during the study period because of intolerance or treatment failure. Cases in which patients were administered gradually increasing doses of duloxetine and pregabalin were also included. The titration schedule for pregabalin began at 25 mg and increased to 50 mg, 75 mg, 150 mg, and 300 mg at intervals of 1 week or longer. For duloxetine, titration began at 20 mg and then increased to 40 mg and 60 mg at a 1-week interval or longer. Furthermore, duloxetine was administered before bedtime in all cases. In addition, all patients on duloxetine received an antiemetic agent as prophylaxis for nausea and vomiting.

Our primary endpoint was the incidence of adverse effects after administration of duloxetine, and our secondary endpoint was leg pain as measured on a numerical rating scale (NRS). Leg pain was evaluated at the time of patient's first visit, discontinuation of pregabalin, and after the switch to duloxetine. Improvement in leg pain was calculated from the NRS values obtained before and after administration of pregabalin and duloxetine. Statistical analysis for leg pain NRS scores and improvement rate at each time point was performed using the unpaired *t*-test, with $p < 0.05$ considered to be significant.

This study was performed in accordance with the Declaration of Helsinki.

Results

There were 6 male and 14 female patients in our study, with an average age of 51.5 ± 10.4 years. The causative disorders for neuropathic pain were lumbar disc hernia ($n=12$)

and lumbar spinal canal stenosis ($n=8$). The reasons for discontinuation of pregabalin were drowsiness ($n=10$), swelling ($n=4$), ineffectiveness ($n=4$), and nausea ($n=2$). For these patients, the average duration of treatment for pregabalin and duloxetine was 12.7 ± 15.2 weeks and 3.2 ± 1.0 weeks, and the average dose was 117.5 ± 97.4 mg and 30.0 ± 10.1 mg, respectively.

Although the incidence of adverse effects after duloxetine administration began was 40%, or 9 out of 20 cases (nausea in 5 cases and drowsiness/dry mouth/general physical weariness in 1 case), the effect of duloxetine on leg pain was very positive.

Average leg pain scores as measured using NRS were 8.4 ± 1.4 , 6.4 ± 1.4 , and 4.1 ± 2.0 at the time of patient's first visit, discontinuation of pregabalin, and after switch to duloxetine, respectively (Figure 1). A significant difference was found between NRS scores at the patients' first visit and discontinuation of pregabalin and between those at discontinuation of pregabalin and after the switch to duloxetine ($p < 0.05$), indicating that NRS scores decrease over time. Furthermore, leg pain NRS scores significantly declined between the time of patient's first visit and after the switch to duloxetine ($p < 0.05$). Compared with the baseline, leg pain NRS scores improved by $20 \pm 12.8\%$ after starting pregabalin and by $23 \pm 12.0\%$ after starting duloxetine, indicating that they did not significantly differ in effectiveness ($p > 0.05$; Figure 2).

Discussion

Because the incidence of adverse effects with duloxetine when used for depression is approximately 20%, the frequency of side effects with this drug in the treatment of neuropathic pain was expected to be similar¹². However, in our study, the incidence of adverse effects after duloxetine administration was 40%, or 9 out of 20 cases. This might be explained by the limitations of our study. It is a retrospective study with no control group and a small number of cases.

The expected primary side effect was nausea. In our study, the incidence of nausea was 25% (5 out of 20 cases) regardless of the combination of antiemetic drugs used. Symptoms appeared immediately after the drug change, confirming that sufficient countermeasures, such as combination with an antiemetic or gastrointestinal drug, should be taken. Nevertheless, because reports indicate that resistance to antiemetics can develop with continuous use, clinicians should consider a slow titration of duloxetine along with close monitoring for adverse effects¹³.

For the secondary endpoint, our study revealed a significant difference in average leg pain NRS scores between the patients' first visit and discontinuation of pregabalin as well as between pregabalin discontinuation and after the switch to duloxetine. This suggests that duloxetine could effectively relieve neuropathic pain, a conclusion supported by the Domestic Phase III Superiority Trial ($n=338$), in which the

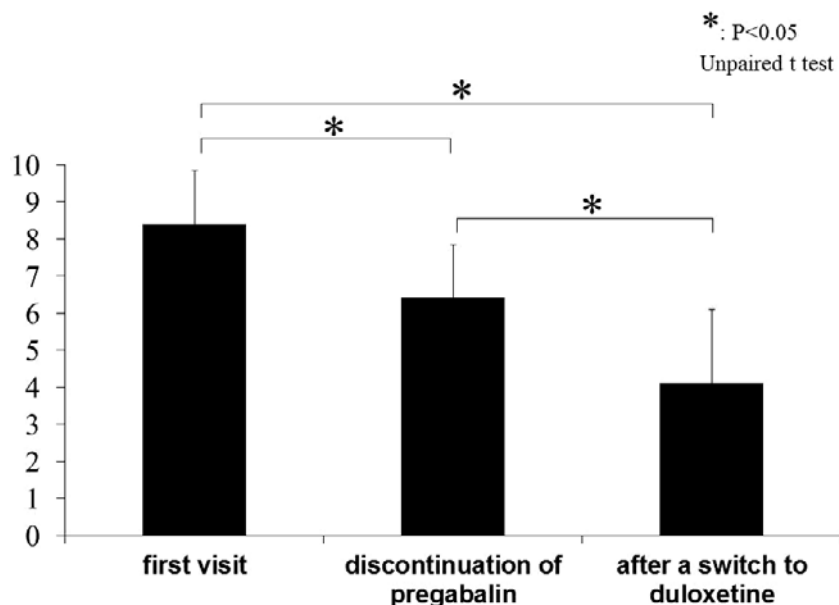


Figure 1. NRS values for leg pain.

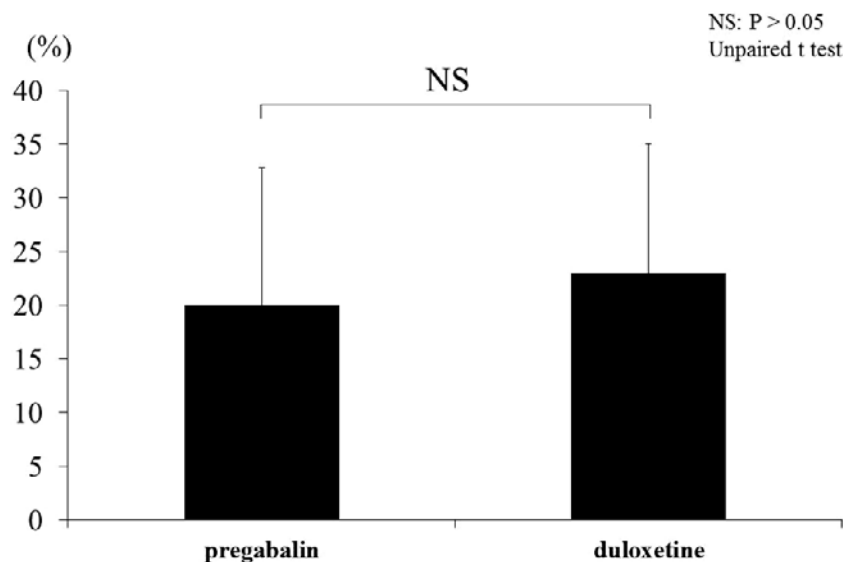


Figure 2. Improvement rates in NRS values for leg pain.

NRS scores in patients taking duloxetine significantly improved compared with those of the placebo group beginning from the 1st week of administration until the 12th week¹⁴.

In the future, we plan to conduct a large-scale prospective study with a control group for more conclusive results. However, from the results gathered thus far, we believe duloxetine is a viable option for neuropathic pain in patients with treatment failure or intolerance to pregabalin. The combined use of an antiemetic with duloxetine along with careful monitoring is recommended, and gradual dose titration should be considered.

Conflicts of Interest: The authors declare that there are no conflicts of interest.

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