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# A comparative study of the effectiveness and safety of pregabalin and duloxetine in the treatment of chemotherapy-induced neuropathic pain

## Abstract

**Background:** Chemotherapeutic medicines are among the several medication types that can cause peripheral neuropathy, a serious disorder marked by symmetrical, distal damage to the peripheral nerves. Chemotherapy-induced peripheral neuropathy (CIPN) is a significant problem that is becoming more prevalent as oncological treatments that use potentially neurotoxic chemotherapy improve the prognosis and cure of cancer. CIPN can need dose decrease or discontinuance, which can have an adverse effect on survival. Relieving the patient from CIPN is required because it enhances their quality of life as well as their mental and physical health.

**Patients and methods:** The patients who were diagnosed with chemotherapy-induced neuropathic pain were randomized into two groups after obtaining written informed consent. Group D received duloxetine 30 mg orally daily in the 1st week followed by 30 mg twice daily until 3 weeks and Group P received pregabalin 75 mg orally daily in the 1st week followed by 75 mg twice daily until 3 weeks. The intensity of pain was measured using the NRS (Numerical Rating Scale) and the DN4 questionnaire was used to evaluate the neuropathic component. Changes in pain score and neuropathic component were assessed at baseline and then at the 2nd and 4th week of follow-up. Data was collected and analyzed using SPSS 20.0 software at a level of significance $p < 0.05$.

**Results:** At baseline, the mean ± standard deviation (SD) of the NRS score in Group D was 7.12 ± 0.89; in Group P was 7.01 ± 0.66 at the end of the study 4th week, the mean ± SD of the NRS score in Group D was 4.04 ± 0.98; in Group P was 5.18 ± 0.64. At baseline, the mean ± SD of the DN4 score in Group D was 7.21 ± 0.80; in Group P was 6.93 ± 0.85 at the end of the study 4th week, the mean ± SD of the DN4 score in Group D was 4.73 ± 0.42; in Group P was 5.13 ± 0.82. The reduction in NRS scores and DN4 scores at the end of the study (4th weeks) when compared to baseline scores were statistically significant in each group ($p < 0.0001$).

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**Conclusions:** Both pregabalin and duloxetine are effective in improving the CIPN in patients with cancers. Both the drugs were well tolerated with mild side effects like headache, drowsiness, and sedation. However, duloxetine was found to be more favorable with fewer side effects than pregabalin.

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**Keywords:** duloxetine, pregabalin, pain, cancer, chemotherapy-induced neuropathic pain

## Introduction

Chemotherapy-induced peripheral neuropathy (CIPN) is a common neuropathic pain and a difficult side effect of several antineoplastic drugs that are regularly used [1]. The most prevalent medications that cause neuropathic pain include vinca alkaloids, such as vincristine, bortezomib, and thalidomide; they also include platinum compounds, such as carboplatin and cisplatin; and taxanes, such as paclitaxel [2]. Prolonged infusion periods, dose reductions, or early chemotherapy discontinuation may be brought on by the development of CIPN, which could have a detrimental effect on patient survival and treatment effectiveness [3]. CIPN is a crippling and dose-limiting adverse reaction that arises from a drug's cumulative dosage and is mostly experienced as a sensory, length-dependent process [4]. The severity of CIPN symptoms may need a decrease in medication dosage or an end to treatment, which can seriously impair the prognosis and long-term quality of life of the patient [5]. CIPN can be 40% prevalent, depending on the class of anticancer medications or drug combinations taken [6]. In a stocking-glove pattern, CIPN can manifest as sensory symptoms in the hands and/or feet, such as pain, tingling, numbness, motor problems, cranial nerve deficits, or autonomic neuropathy [7]. The amount of the chemotherapy drug, the length of time the patient was exposed, the cumulative dose, the usage of other medications at the same time, and the presence of associated conditions like diabetes, a vitamin $B_{12}$ deficiency, or alcoholism all affect how severe the neuropathy becomes [8]. The pathophysiology of CIPN is not fully understood. The following processes have been proposed: defects in the structure of peripheral nerves such as neuropathy, axonopathy, and/or myelinopathy; mitochondrial malfunction; oxidative stress; and neuronal death [9]. Relief from CIPN is necessary since it enhances the patient's Quality of Life (QOL), as well as their psychological and functional health [10]. Tricyclic antidepressants (TCA), gabapentin, pregabalin, serotonin and norepinephrine reuptake inhibitors (SNRIs), ketamine, and topical lidocaine are now the best treatments for CIPN [11].

Nowadays, duloxetine and pregabalin are being used as the preliminary management of CIPN in cancer. Duloxetine is a recognized serotonin and norepinephrine reuptake inhibitor [12, 13]. Duloxetine works by increasing noradrenergic and serotonergic activity in the central nervous system's descending pain inhibitory pathways [14]. Pregabalin is an anticonvulsant that reduces excitatory neurotransmitter release, which is connected to pain perception. It works by attaching itself to the calcium channels [15] in presynaptic neurons [16].

Till now, only a few comparative studies have been conducted assessing the role of duloxetine and pregabalin in CIPN. In the Indian population, very few studies have been conducted to date, comparing both duloxetine and pregabalin in CIPN among patients with cancer. The present study is conducted to assess and compare the effectiveness of duloxetine and pregabalin in managing the treatment of CIPN.

## Patients and methods

A prospective, randomized study was conducted in the tertiary care center, Sawai Man Singh (SMS) Medical College, Jaipur. Individuals who enrolled at a tertiary care center, those in the age range of 18 to 70 years, regardless of gender, and those experiencing moderate to severe neuropathic pain following the completion of a chemotherapy cycle. One or more of the following symptoms, such as a burning sensation, shooting or lancinating pain, dysesthesias, or allodynia, should be present in the location of the pain. The diagnosis of neuropathic pain will be made using the patient's history, clinical evaluation, electrophysiological evidence from a nerve conduction investigation, and written informed consent from those who are willing to participate in the study.

The patients who didn't give consent and not meeting inclusion criteria and declined to participate were excluded and patients having a history of documented medication hypersensitivity, women who are pregnant or lactating, neuropathic pain brought on by surgery, radiation damage, or compressed tumors, exclusions from the study included neuropathic pain resulting

from brachial plexopathy, diabetic neuropathy, radiculopathy, severe renal or liver impairment, drug use (antipsychotic, sedative-psychotic, atropine and its substitute), noncooperation, and refusal to give consent.

The sample size was calculated as 35 in each group with 80% power and 0.05 alpha error and an allowable absolute error of 20%. So total sample size chosen is 100 (50 in each group). Based on the inclusion and exclusion criteria, a total of 100 cases (N = 50 for each group) were chosen, and they were then randomly assigned to one of two treatment groups: Group D received duloxetine 30 mg orally daily in the 1st week followed by 30 mg twice daily [17] until 3 weeks and Group P received pregabalin 75 mg orally daily in the 1st week followed by 75 mg twice daily [18] until 3 weeks. The closed-envelope approach was used as the basis for randomization. The Numerical Rating Scale (NRS) [19] was used to quantitatively assess and record the level of pain using scoring criteria ranging from 0 (no pain) to 10 (very severe pain). Pain levels are classified as low (1–3), moderate (4–6), and severe (7–9). On the provided line, the patient is asked to indicate the level of pain.

The neuropathic component was assessed using the Douleur Neuropathic 4 questionnaire (DN4 questionnaire) [20]. Add up all of the "yes" responses at the end of the questionnaire to get a final score out of 10. The test suggests that patients are probably experiencing neuropathic pain if their result is greater than or equal to 4. This questionnaire comprises 10 items that depict both the signs related to bedside sensory assessment and sensory descriptors. It is a tool that is being used for diagnosing neuropathic pain. Its seven items are linked to symptoms like tingling, prickling and cold sensation, burning, electric shocks, itching, and numbness). The remaining three items are related to clinical assessment (hypoesthesia while injecting or touching, and pain while rubbing). Both scales are in English and are explained to the patients by the staff nurse in both English language and translated to the Hindi language.

The Helsinki Declaration's guiding principles were taken into consideration when designing the study. At baseline, as well as in the second and fourth follow-up weeks, changes in the pain score and neuropathic component were also evaluated and documented.

### Statistical analysis

SPSS 20.0 software was used for analyzing data. Qualitative normally distributed data was expressed in percentage and proportions and quantitative data was expressed in mean ± SD. The significance of difference in proportions was inferred by the chi-square test and the significance of difference in two means was inferred by unpaired t-test. For significance, a p-value less than 0.05 was considered as significant.

## Results

A total of 100 patients were included in the study out of which 5 patients in Group D and 6 patients in Group P were lost to follow-up. So, data from 45 patients of Group D and 44 patients of Group P were analyzed. The Consolidated Standards of Reporting Trials (CONSORT) flow diagram is presented in Figure 1.

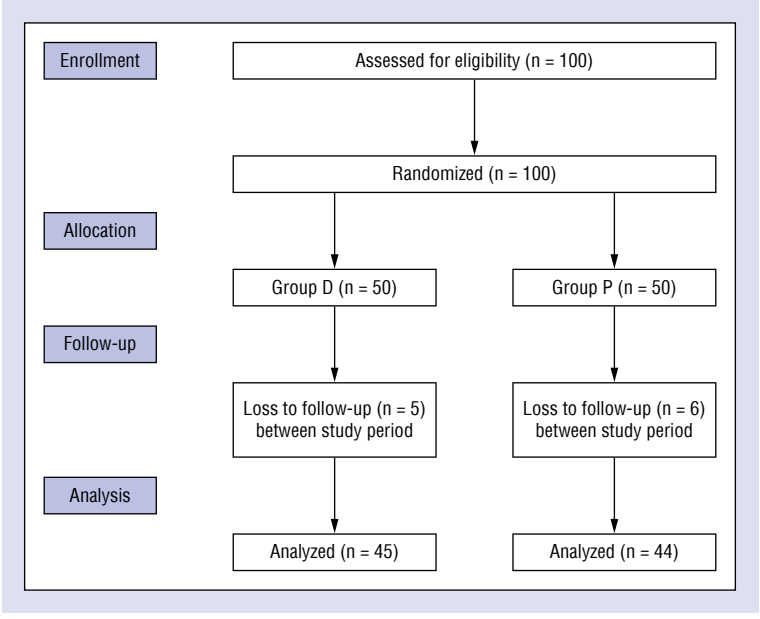


**Figure 1.** CONSORT flow diagram

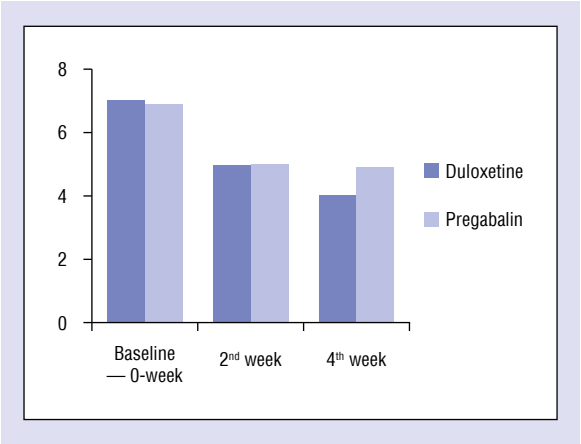


**Figure 2.** Comparison of mean NRS scores in both groups

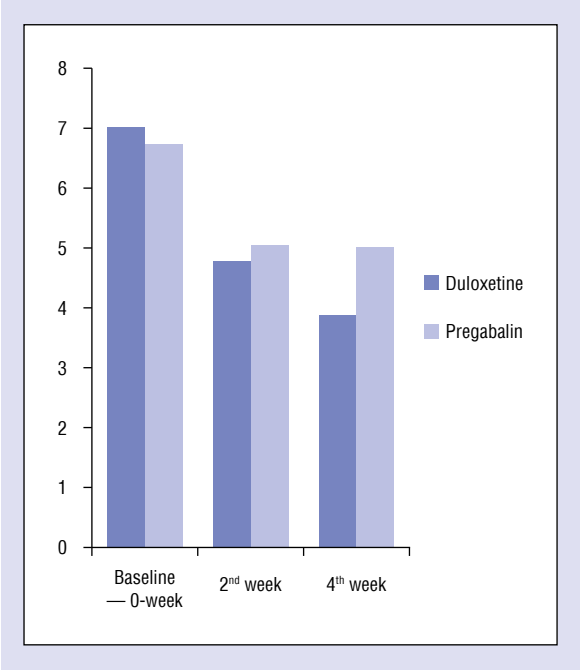


**Figure 3.** Comparison of mean DN4 questionnaire scores in both groups

The comparison of the mean NRS scores is presented in Figure 2. The comparison of the mean DN4 questionnaire scores is shown in Figure 3.

The research assessed various demographic variables. The mean age of Group D is 49.3 ± 5.2 and of Group P is 51.6 ± 9.4. Most of the patients resided in rural areas, belonging to the Hindu religion, and were illiterate. In both the groups, the maximum cases were having a habit of tobacco chewing (Table 1).

Most of the patients were suffering from carcinoma of the lung (22.4%) in Group D and carcinoma of buccal mucosa (20.5%) in Group P (Table 2).

In Group D (44.5%) and Group P (40.8%), injection carboplatin + paclitaxel was the most often used anti-cancer medication that resulted in CIPN (Table 3).

We evaluated the improvement in pain scores after using duloxetine and pregabalin with the help of NRS scoring criteria. It was observed that pain scores significantly decreased from baseline to 4$^{th}$ week in both groups (Table 4).

Neuropathic improvement was assessed using the DN4 questionnaire. It was observed that although mean score significantly decreased from baseline to 4$^{th}$ week in both groups (Table 5).

Besides assessing the effectiveness of both drugs, also were noticed their side effects. It was found that pregabalin had more side effects than duloxetine. Patients suffered from more episodes of drowsiness, sedation, and blurring of vision with the use of pregabalin, whereas with duloxetine few patients suffered from headache, nausea, and constipation (Table 6).

## Discussion

The present study was conducted to assess and compare the effectiveness of duloxetine 30 mg orally daily in the 1$^{st}$ week followed by 30 mg twice daily until 3 weeks and pregabalin 75 mg orally daily in the 1$^{st}$ week followed by 75 mg twice daily until 3 weeks in managing the CIPN in cancer patients. Demographic variables like age, gender, habit, education, area, etc. were evaluated and found to be similar in both groups. Begum et al. [21] compared the safety and efficacy of tablet duloxetine 60 mg with tablet gabapentin 300 mg in patients suffering from diabetic polyneuropathy. They observed that baseline characteristics were observed to be similar in both groups.

The improvement in pain score was evaluated after using duloxetine and pregabalin with the help of NRS scoring criteria. Duloxetine is a known antidepressant that raises the levels of 5-hydroxytryptamine (5-HT) and nor-epinephrine in CNS, thus decreasing neuropathic pain. Pregabalin is a known anticonvulsant that acts by inhibiting the pain sensors and channels of calcium ions in the pain fibers of the postsynaptic dorsal root. It also increases the threshold of pain in patients. In the present study, with both the drugs pain score significantly decreased from baseline to 4$^{th}$ week, but the mean improvement in pain was found to be significantly more in patients subjected to duloxetine than pregabalin. In contrast to the present study, Salehifar et al. [22] found that by the end of 6$^{th}$ week, pregabalin showed a significant improvement in NRS scores than duloxetine. Similar to the present study, Begum et al. [21] observed that although both duloxetine and gabapentin were well tolerated and

**Table 1. Comparison of demographic variables in the study groups**

| Parameters | | Group D | | Group P | |
|---|---|---|---|---|---|
| | | Frequency (n) | Percentage [%] | Frequency (n) | Percentage [%] |
| **Age (mean ± SD)** | | 49.3 ± 5.2 | | 51.6 ± 9.4 | |
| **Gender** | **Female** | 12 | 26.7 | 9 | 20.5 |
| | **Male** | 33 | 73.3 | 35 | 79.5 |
| **Education** | **Illiterate** | 27 | 60 | 23 | 52.3 |
| | **Literate** | 18 | 40 | 21 | 47.7 |
| **Area** | **Rural** | 26 | 57.7 | 28 | 63.7 |
| | **Urban** | 19 | 42.3 | 16 | 36.3 |
| **Religion** | **Hindu** | 34 | 75.5 | 35 | 79.5 |
| | **Muslim** | 11 | 24.5 | 9 | 20.5 |
| **Addiction** | **No** | 10 | 22.3 | 9 | 20.5 |
| | **Alcohol** | 11 | 24.4 | 10 | 22.7 |
| | **Smoking** | 9 | 20 | 12 | 27.3 |
| | **Tobacco** | 15 | 33.3 | 13 | 29.5 |
| **Total** | | 45 | 100 | 44 | 100 |

SD — standard deviation

**Table 2. Distribution of patients according to type of malignancy**

| Malignancy | Group D | | Group P | |
|---|---|---|---|---|
| | Frequency (n) | Percentage [%] | Frequency (n) | Percentage [%] |
| Buccal mucosa | 8 | 17.8 | 9 | 20.5 |
| Lung | 10 | 22.4 | 8 | 18.2 |
| GB | 6 | 13.4 | 4 | 9.1 |
| Rectum | 2 | 4.4 | 3 | 6.8 |
| Larynx | 1 | 2.2 | 2 | 4.5 |
| Tongue | 5 | 11.2 | 6 | 13.7 |
| Breast | 4 | 8.8 | 4 | 9.1 |
| Prostate | 3 | 6.6 | 2 | 4.5 |
| Gynic (ovary, cervix) | 4 | 8.8 | 3 | 6.8 |
| Rcc | 2 | 4.4 | 3 | 6.8 |
| **Total** | 45 | 100 | 44 | 100 |

GB — gall-bladder; Rcc — renal cell carcinoma

**Table 3. Anti-cancer drugs causing neuropathic pain**

| Chemotherapy drugs given | Group D | | Group P | |
|---|---|---|---|---|
| | Frequency (n) | Percentage [%] | Frequency (n) | Percentage [%] |
| Paclitaxel + carboplatin | 20 | 44.5 | 18 | 40.8 |
| Paclitaxel | 12 | 26.6 | 13 | 29.5 |
| Oxaliplatin | 2 | 4.5 | 2 | 4.6 |
| Cisplatin | 6 | 13.3 | 4 | 9.2 |
| Vincristine | 2 | 4.5 | 2 | 4.6 |
| Bortezomib | 3 | 6.6 | 5 | 11.3 |
| **Total** | 45 | 100 | 44 | 100 |

**Table 4. Comparison of NRS scores in the study groups**

| | Baseline mean ± SD | 2nd week mean ± SD | 4th week mean ± SD |
|---|---|---|---|
| Duloxetine | 7.04 ± 0.903 | 4.96 ± 0.878 | 4.04 ± 0.99 |
| Pregabalin | 6.89 ± 0.920 | 5.02 ± 0.876 | 4.91 ± 0.960 |
| Level of significance | t-value: 0.818 | t-value: −0.361 | t-value: −4.16 |
| | p-value: 0.416 | p-value: 0.719 | p-value < 0.001 |

**Table 5. Comparison of DN4 questionnaire scores in the study groups**

| | Baseline mean ± SD | 2nd week mean ± SD | 4th week mean ± SD |
|---|---|---|---|
| Duloxetine | 7.02 ± 0.917 | 4.78 ± 0.974 | 3.87 ± 0.694 |
| Pregabalin | 6.73 ± 0.973 | 5.05 ± 0.806 | 5.02 ± 1.023 |
| Level of significance | t-value: 1.472 | t-value: −1.41 | t-value: −6.25 |
| | p-value: 0.145 | p-value: 0.161 | p-value: < 0.001 |

**Table 6. Side effects among the study groups**

| Adverse effects | Duloxetine | | Pregabalin | |
|---|---|---|---|---|
| | Frequency (n) | Percentage [%] | Frequency (n) | Percentage [%] |
| Sedation | 2 | 4.5 | 3 | 6.8 |
| Drowsiness | 1 | 2.2 | 4 | 9.1 |
| Blurred vision | 0 | 0 | 2 | 4.5 |
| Nausea | 2 | 4.4 | 1 | 2.3 |
| Headache | 3 | 6.6 | 2 | 4.5 |
| Insomnia | 1 | 2.2 | 1 | 2.3 |
| Constipation | 2 | 4.5 | 0 | 0 |
| No adverse effect | 34 | 75.6 | 31 | 70.5 |
| Total | 45 | 100 | 44 | 100 |

effective in controlling pain, duloxetine was found to be more effective than gabapentin in cases suffering from diabetic polyneuropathic pain. In a study by Bucher et al. [23], it was found that there was no difference when medications like gabapentin, pregabalin, and venlafaxine were compared to duloxetine statistically for control of neuropathic pain. In the present study, duloxetine was compared with pregabalin, but it was found that both pregabalin and gabapentin share a common mechanism by modulation of alpha-2 delta subunit of voltage-gated calcium channels. Thus, the results of the above studies can be applied and are comparable with the present study.

Quilici et al. [24] compared the tolerability and efficacy of duloxetine with both pregabalin and gabapentin in patients suffering from diabetic peripheral neuropathic pain. They found that there was no statistical difference between all three drugs in relation to safety and efficacy. In a metanalysis by Rudroju et al. [25] the safety and efficacy of five drugs (duloxetine, amitriptyline, gabapentin, venlafaxine, and pregabalin) are compared in relation to the treatment of diabetic neuropathic pain. They found that gabapentin was observed to be the most effective drug among others in controlling pain. Studies by Shah et al. [26] and Shahid et al. [27] found that both duloxetine and pregabalin reduced the peripheral neuropathic pain related to diabetes, but duloxetine was more efficient than pregabalin, but the outcome was not statistically significant.

In the present study, neurological improvement was assessed using DN4 questionnaire [28]. It was found that although the mean score of DN4 significantly decreased from baseline to 4th week in both the groups, the mean improvement in neurological component was found to be significantly more in patients

subjected to duloxetine than pregabalin. Avan et al. [29] found that duloxetine and pregabalin both raise the overall quality of life (QOL) of taxane-induced peripheral neuropathy breast cancer patients. A meta-analysis by Widyadharma et al. [30] found that duloxetine is an excellent choice for treating CIPN since it effectively reduces neuropathic pain in particular. In contrast to the present study, Salehifar et al. [22] found that as compared to duloxetine, sensory neuropathy was significantly improved in patients using pregabalin than duloxetine. Begum et al. [21] used the McGill pain questionnaire to assess neuropathic pain symptoms and they found that duloxetine was found to be more effective than gabapentin in terms of reduction of pain at follow-up periods.

In the present study, it was found that pregabalin had more side effects than duloxetine. Patients suffered from more episodes of sedation, drowsiness, and blurring of vision with the use of pregabalin than duloxetine. Salehifar et al. [22] found that both duloxetine and pregabalin had mild adverse effects. Similar to the present study, Begum et al. [21] revealed that nausea was the most prevalent side effect in patients using duloxetine and this could be because of lack of dose titration. The present study revealed that both pregabalin and duloxetine were well tolerated by patients with CIPN in cancer patients. Duloxetine revealed better efficacy in relieving neuropathic pain and had fewer side effects than pregabalin. The present study was a single-center study conducted on less sample size with a limited follow-up of 4 weeks. Thus, further multi-center studies should be conducted on large sample size, and with longer follow-up. In future clinical trials should be conducted to study and compare various other drugs to manage CIPN in cancer cases. In the present study fixed doses of drugs were used instead of comparing different dose ranges by dose titration. Thus, future studies should be conducted to assess the efficacy of drugs at various dose ranges.

## Conclusions

Both pregabalin and duloxetine are effective in improving the CIPN in patients with cancers. Both the drugs were well tolerated with mild side effects like headache, drowsiness, and sedation. However, duloxetine was found to be more favorable with fewer side effects than pregabalin. Patients were assessed using readily available evaluation scales. In the future there is a need to conduct multicentric studies, having a large sample size with long follow-up periods using even better scales, on different drug combinations to get more authentic, conclusive, and accurate results.

## Article information and declarations

### *Acknowledgments*
None.

### *Data availability statement*
None.

### *Ethics statement*
The study was conducted by the Declaration of Helsinki. All the participants provided signed informed consent before participating in the study.

### *Author contributions*
Conception and design, manuscript writing — YG; manuscript writing, data collection, and analysis — SKP; data collection, analysis, and interpretation — PA; manuscript writing — AM; final approval of manuscript — all authors.

### *Conflict of interest*
The authors declare no conflict of interest.

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### *Supplementary material*
None.

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