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ORIGINAL RESEARCH

# Outcomes and Predictors of Response of Duloxetine for the Treatment of Persistent Idiopathic Dentoalveolar Pain: A Retrospective Multicenter Observational Study

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**Background:** Duloxetine has been reported to significantly relieve the pain of persistent idiopathic dentoalveolar pain (PIDP); however, the number of studies available is scarce and no study has identified the predictors of response of duloxetine for the treatment of PIDP.

**Objective:** To report the efficacy, safety, and identification of positive predictors of duloxetine for PIDP patients through a retrospective multicenter observational study.

**Methods:** We retrospectively reviewed the clinical database of PIDP patients who were prescribed duloxetine at 3 hospitals between January 2018 and November 2021. Demographic and pain-related baseline data, efficacy of patients after 3 months of medication by visual analog scale (VAS) scores for pain and adverse events were extracted and analyzed. The predictors of pain-relieving effect of duloxetine were identified by logistic regression analysis.

**Results:** A total of 135 patients were included in this study. Side effects occurred immediately after taking duloxetine in 24 (17.8%) patients, and the treatment with duloxetine was discontinued on 13 of them because they could not tolerate the side effects. Other 11 (8.1%) patients gradually tolerated the side effects within 2 weeks. Ninety-four out of 122 (77.0%) patients obtained pain relief with VAS significantly decreased ($p < 0.01$) and the other 28 (23.0%) patients stopped taking the drug because of weak efficacy. Binary logistic regression analysis showed that short disease duration (OR = 1.017, 95% CI = 1.004–1.030, P = 0.012) was an independent predictor of the positive response of duloxetine.

**Conclusion:** This study confirmed that duloxetine can significantly improve chronic pain of PIDP patients, and the safety was tolerable. Patients with shorter disease duration had more benefit from duloxetine.

**Limitations:** This is a retrospective observational study. Long-term efficacy and safety of duloxetine in the treatment of PIDP patients were not evaluated.

**Keywords:** persistent idiopathic dentoalveolar pain, efficacy, safety, predictor of response, duloxetine

## Introduction

Persistent idiopathic dentoalveolar pain (PIDP) which is previously known as atypical odontalgia (AO) is defined as a persistent unilateral intraoral dentoalveolar pain localized to a dentoalveolar site, with deep, dull, pressure-like pain recurring daily for more than 2 hours per day for more than 3 months but in the absence of any clinical and radiographic evidence according to the International Classification of Orofacial Pain, 1st edition (ICOP-1).[1] PIDP may occur after endodontic treatment or other dental procedures such as tooth extraction or may occur spontaneously for no specific reason. Marbach et al previously reported that the incidence of AO in an undemonstrated population was 3% to 6%.[2] Miura et al reported that as much as 56.7% of 383 AO patients were related to dental treatment.[3] However, up to now, literature report on the actual prevalence of PIDP is scarce.

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PIDP is still a little-known chronic pain condition; many doctors do not see much PIDP in his or her career. Even when PIDP is diagnosed, some patients refuse to accept their diagnosis, so they often change doctors. Durham et al developed a new AO/persistent dentoalveolar pain disorder (PDAP) screening instrument and confirmed its effect preliminarily in detecting cases of AO/PDAP, however it still merits progression to field testing.[4] Even though the pathology and diagnostic criteria of PIDP have been clarified by the ICOP-1 for the past few years,[1] the differential diagnosis and definite diagnosis of PIDP is still very difficult, so patients are often misdiagnosed.[5] A retrospective multi-centric cross-sectional study including a total of 394 patients found that the average diagnostic delay of AO was much longer and costed more than patients with any other persistent idiopathic facial pain (PIFP).[6] When patients are misdiagnosed, they often take drugs that do not work, sometimes even undergo several unnecessary surgeries which does not alleviate but rather aggravate the pain. This rare clinical challenge, as one of the representative chronic orofacial pains,[7] result in unsatisfactory treatment outcomes and severely affect patients' quality of life. It may even lead to anxiety and depression.[8]

Depression, psychological disturbances such as emotional stress, anxiety, hypochondriac, and somatization are regarded as possible causative factors for AO.[9] However, the detailed etiological mechanisms and pathophysiology are far from clear. Clinically, there are somatosensory abnormalities, such as allodynia and hyperalgesia.[10] So, some studies have suggested that AO is a neuropathic syndrome.[8,11] Other mechanisms being proposed are currently believed to involve pathophysiological mechanism of AO in which the density of sodium channels in nerve endings increase, which leads to the increase of transmission of nerve impulses,[12] increased release of certain neurotransmitters may lead to central sensitization, lack of endogenous pain regulatory control can promote and maintain the pain, neuroinflammatory mechanisms involve chronic predominant orofacial pain and so on.[7] Just recently, Kawasaki et al reported the different clinical manifestations of PIFP (primarily AO) patients with or without neurovascular compression (NVC), which may enable a more precise understanding of the pathophysiology of AO and lead to improved treatment strategies.[13]

Until now the treatment guidelines for PIDP have not been established in the absence of high-quality controlled trials as sufficient evidence. Current pain management strategies are based on expert recommendations and the results of reported case series studies. Have long thought that tricyclic antidepressants (TCAs) and antiepileptics can treat AO, however, the curative effect is often insufficient.[8,14–16] The local anesthetics injected to block the painful area is another treatment recommendations, however, reported curative effects vary.[17] Local injection of Onabotulinumtoxin A (OnabotA) may be a therapeutic alternative for AO treatment. However, the conclusion is only obtained from the case series of very few patients.[18,19]

TCAs was still recommended as a first-line treatment for the management of AO,[15] despite the lack of randomized controlled trials or open-label studies in AO patients. In 2019, the real-world study of Trang et al, included the largest sample to date and confirmed the curative effect of TCAs as AO treatment.[16] It was however reported that the pain relief effect of serotonin-norepinephrine reuptake inhibitors (SNRIs) on AO was similar to that of TCAs[20] and the safety was better than TCAs.[21] In recent years, Ito and Nagashima have reported that SNRIs, such as milnacipran and duloxetine treatment significantly improve chronic nonorganic pain in the orofacial region including burning mouth syndrome (BMS) and AO.[22,23] Kobayashi et al found that the analgesic effect of duloxetine a common SNRIs for AO and BMS was not correlated with its plasma concentration.[24] Miyauchi et al found that duloxetine treatment for AO maybe through affecting plasma levels of neuroinflammation-related molecules.[7] However, the number of studies is scarce, and no study had identified the predictors of response of duloxetine for treatment. This study will explore the efficacy and safety of duloxetine in the treatment of PIDP patients through a retrospective multicenter observational study and identify the predictors of positive response of duloxetine in the treatment of PIDP patients.

# Methods

## Patients

This study was conducted in accordance with the Helsinki declaration of ethical principles for human medical research and was approved by the institutional review committee of Beijing Tiantan Hospital, Beijing Red Cross Peace Orthopedic Hospital and Beijing Puhua International Hospital. The risks to subjects in this retrospective study was no more than minimal. All the data analyzed were de-identified. Waiver of consent did not adversely affect the welfare and

rights of the subject. The institutional review committee of the 3 hospitals approved the waiver of informed consent in this study because of the retrospective nature of this study.

We retrospectively reviewed the clinical database for PIDP patients who were prescribed duloxetine at the department of pain management in the 3 hospitals between January 2018 and November 2021. Subjects who met the following inclusion criteria were eligible:

1. Patients older than 18 years;
2. Diagnosed as PIDP according to the criteria of the ICOP-1;[1]
3. Who had not previously taken antidepressants and were treated with duloxetine;
4. Available follow-up data for at least 3 months unless patients discontinued taking duloxetine because of side effects or poor efficacy.

The exclusion criteria were:

1. Patients with the history of mental illness, narcotic drug abuse;
2. Patients with incomplete medical records;
3. Other concomitant medication/treatment was taken by the patient while being treated with duloxetine;
4. Has diabetic neuropathic pain.

## Medication Regimen

All patients at the 3 study centers took the drugs in the same way. The initial dose of duloxetine (YouBiLuo 20mg per piece, NHWA, China) was 20 milligrams once daily,[23] taken with breakfast for about one week. The dose of duloxetine was titrated up to 40mg, 60mg, 80mg, 100mg, until a maximum of 120 mg per day was reached at intervals of about 1 week, while taking into account the changes in symptoms and adverse reactions. If the patient's pain did not improve and there were no adverse reactions, the dose of duloxetine was increased.[23] If the patient's pain was completely relieved, the dose of duloxetine did not increase but was continued. Once the side effects associated with duloxetine occurred when the dosage was increased, the dose of duloxetine was reverted to the last tolerable dose. To treat the early adverse event of anxiety and insomnia after taken duloxetine, alprazolam or brotizolam could be combined with duloxetine as needed and the use of alprazolam or lorazepam including their doses were also collected.[23] Dentists performed oral examinations at baseline, weeks 2, 4, 8, and 12 to confirm no organic abnormalities.

## Data Extraction and Collection

All data were available in a patient database which also included baseline characteristics and follow-up data. Patients with PIDP were routinely followed up after their first use of duloxetine at the pain management departments of the 3 study centers for quality management. We extracted and collected patients' age, gender, disease durations, affected side (unilateral (left/right-sided)/bilateral), comorbidities, history of dental operation before pain onset, baseline visual analogue scale (VAS) scores for pain (0 means no pain at all, 10 means the most pain imaginable), quality of pain, baseline Hamilton Depression Rating Scale (HDRS) scores for depression symptoms, number of patients with HDRS $\leq 7$ (normal) or $\geq 8$ (with depressive symptoms), prior medication use after pain onset, and prior invasive treatment after pain onset as baseline data. VAS scores for pain, adverse events at 2, 4, 8, 12 weeks were also reviewed. The treatment onset time, defined as the time from the start of treatment to a reduction of 30% of pain VAS score after treatment had been collected. Pain relief was defined as a VAS scores reduced by more than 50% compared with the baseline after treatment, otherwise was considered as unresponsive. The final doses of duloxetine among continuous medication patients included in this study and the reasons for withdrawal from the study were also collected. Patients were divided into responsive group and nonresponsive group according to the treatment effect.

## Statistical Analysis

We used IBM SPSS Statistics Version 25 to perform statistical analysis. All measurement data were tested for normality. Distributed variables were described as means ± standard deviation (SD), non-normal distribution data were shown as medians and interquartile ranges (IQRs). Categorical data were described as numbers (percentages). Differences between responsive group and unresponsive group were compared using the *t*-test (normal distributions continuous variables). Mann–Whitney *U*-test (non-normal distributions continuous variables) and the Chi-square test or the Fisher's exact test (when the expected values were <5) were used for categorical variables.

Binary logistic regression analysis was used to determine the predictors of positive response of duloxetine in PIDP patients, and the adjusted odds ratios (ORs) with 95% confidence intervals (CI) were calculated. All continuous variables were tested for linearity using the Box-Tidwell method and included in the model as a linear variable. The final multivariate model was determined by the stepwise backward (Likelihood Ratio) method. The time course of VAS score in patients' positive response of duloxetine before and after the start of drug administration were compared using repeated-measures ANOVA analysis. A variable was entered into the model if the probability of its score statistic was less than 0.05 and was removed if the probability was greater than 0.1. $P < 0.05$ was regarded as significant.

# Results

Between January 2018 and November 2021, 143 PIDP patients were treated with duloxetine in the pain clinic of the 3 hospitals. Eight patients were excluded because their follow-up data were incomplete. In total, 135 patients were included in this study. All the patients had received medications such as non-steroidal anti-inflammatory drugs (NSAIDs), aminophenol oxycodone, gabapentin or pregabalin etc. before taking duloxetine but did not have good pain-relieving effect.

Seventy-eight patients (63.93%) had been treated with dental procedures after pain onset including tooth extraction because they were misdiagnosed as dental disease. About 29.5% of the patients in this study were misdiagnosed as TN and had prior invasive treatment such as microvascular decompression (MVD), gamma knife, radiofrequency thermocoagulation and percutaneous balloon compression (PBC). Some patients underwent more than two operations, but their symptoms did not change after the neurosurgery. The demographics and pain-related baseline data are listed in Table 1.

In 13 (9.6%) patients, side effects occurred immediately after taking the drug and the drug was discontinued. After excluding the 13 patients mentioned above, 94 (77.0%) out of 122 patients achieved pain relief, 28 (23.0%) patients stopped taking the drug because of weak efficacy. There were no significant differences between the two groups with regards to age, gender, affected side (unilateral (left/right-sided)/bilateral), comorbidities, history of dental operation before pain onset, baseline VAS scores for pain, baseline HDRS scores for depression symptoms, number of patients with HDRS ≤ 7 or ≥8, prior medication use after pain onset and prior invasive treatment after pain onset ($p > 0.05$, Table 2). The disease duration was significantly shorter in the responsive group than in the nonresponsive group ($P = 0.005$). A univariate comparison of the demographics and pain-related baseline data between the responsive group (n = 94) and the nonresponsive group (n = 28) are showed in Table 2. Binary logistic regression analysis showed that short disease duration (OR=1.017, 95% CI =1.004–1.030, $P = 0.012$) was an independent predictor of the positive response of good analgesic efficacy of duloxetine.

The final doses (12 weeks) of duloxetine among the responsive group patients included in this study was 60 (60–80) mg/day. When analyzing the 94 patients in the responsive group with 12-week follow-up data, repeated-measures ANOVA revealed that a significant result ($df = 2.190$, $F = 948.903$, $P < 0.001$), indicating that the mean VAS scores at each time point were not all equivalent. Contrast analysis indicated that VAS at 2-, 4-, 8- and 12-weeks taking duloxetine was all significantly lower than the baseline value (Figure 1). The median treatment onset time was 5(1–14) day.

Of the 135 enrolled patients, adverse reactions of duloxetine were experienced by 24 patients (17.7%). The highest incidence of side effects in PIDP patients in this study was nausea (21 patients, 15.6%). Other side effects included vomiting in 2 patients (1.5%), constipation in 11 (8.1%), diarrhoea in 6 (4.4%), somnolence in 11 (8.1%), dry mouth in 4 (3.0%), urinary retention in 4 (3.0%), insomnia in 2 (1.5%), dizziness in 4 (3.0%), fatigue in 5 case (3.7%) and muscle twitch in 1 patient (0.7%). The adverse reaction of insomnia in the early days was solved by took alprazolam

**Table 1** Demographics and Pain-Related Baseline Data of the Patients Enrolled

| Variables | Total (n=135) |
|---|---|
| **Age (years, mean ± SD)** | 56.21 ± 11.34 |
| **Gender (No. (%))** | |
| **Male** | 48(35.6%) |
| **Female** | 87(64.4%) |
| **Disease durations (median month with IQR)** | 27(12 to 60) |
| **Side affected (no. (%))** | |
| **Unilateral** | 92(68.1%) |
| **Left-sided** | 66(48.9%) |
| **Right-sided** | 26(19.3%) |
| **Bilateral** | 43(31.9%) |
| **Quality of pain (no. (%))** | |
| **Deep, pressure-like quality** | 95(70.4%) |
| **Dull, aching or nagging quality** | 40(29.6%) |
| **Comorbidities (no. (%))** | |
| **Hypertension** | 12(8.9%) |
| **Dyslipidemia** | 9(6.7%) |
| **Diabetes** | 4(3.0%) |
| **Cerebrovascular disease** | 3(2.2%) |
| **Previous history of dental procedure before pain onset [n (%)]** | 105(77.8%) |
| **Baseline VAS Scores (mean ± SD)** | 6.64±1.15 |
| **Baseline HDRS Scores [median (IQR)]** | 14(7 to 15) |
| **Baseline HDRS scores ≥ 8 (no. (%))** | 97(71.9%) |
| **Baseline HDRS scores ≤ 7 (no. (%))** | 38(28.1%) |
| **Analgesic use after pain onset (no. (%))** | 135(100%) |
| **NSAIDs** | 128(94.8%) |
| **Antiepileptics** | 50(37.0%) |
| **Muscle relaxants** | 13(8.6%) |
| **Aminophenol oxycodone** | 15(11.1%) |
| **Tramadol** | 23(17.0%) |
| **Invasive treatment after pain onset (no. (%))** | 92(68.1%) |
| **Dental procedures [n (%)]** | 87(64.4%) |
| **MVD for TN** | 6(4.4%) |
| **Radiofrequency thermocoagulation for TN** | 22(16.3%) |
| **Gamma knife for TN** | 4(3.0%) |
| **PBC for TN** | 7(5.2%) |

**Abbreviations**: VAS, visual analog scale; HDRS, Hamilton Depression Rating Scale; NSAIDs, non-steroidal anti-inflammatory drugs; MVD, microvascular decompression; TN, trigeminal neuralgia; PBC, percutaneous balloon compression.

with the dosage no more than 1.2 mg/day. The incidence of duloxetine withdrawal due to adverse effects was in 13 patients (9.6%) taking duloxetine. The other 11 (8.1%) patients had adverse reactions, which mainly occurred in the early stages of taking the medicine, and the adverse reactions were relieved or disappeared after 2 weeks of treatment (Table 3).

**Table 2** Comparison of the Demographics and Pain-Related Baseline Data Between the Responsive Group and the Nonresponsive Group

| Variables | Responsive Group (n=94) | Unresponsive Group (n=28) | P value |
|---|---|---|---|
| **Age (years, mean ± SD)** | 56.47±11.37 | 55.54±11.83 | 0.869 |
| **Gender (n (%))** | | | |
| **Male** | 34(36.2%) | 10(35.7%) | 0.686 |
| **Female** | 60(63.8%) | 18(64.3%) | |
| **Disease durations (median month with IQR)** | 24(12 to 36) | 42(24 to 72) | **0.005** |
| **Side affected (no (%))** | | | 0.361 |
| **Unilateral** | 66(70.2%) | 17(60.7%) | |
| **Left-sided** | 48(51.0%) | 10(35.7%) | |
| **Right-sided** | 18(19.1%) | 7(25.0%) | |
| **Bilateral** | 28(29.8%) | 11(39.3%) | |
| **Comorbidities (no. (%))** | 23(24.5%) | 3(10.7%) | 0.119 |
| **Hypertension** | 9(9.6%) | 2(7.1%) | |
| **Dyslipidemia** | 8(8.5%) | 0(0.0%) | |
| **Diabetes** | 4(4.3%) | 0(0.0%) | |
| **Cerebrovascular disease** | 2(2.1%) | 1(3.6%) | |
| **No comorbidity** | 49(52.1%) | 22(78.6%) | |
| **Previous history of dental procedure before pain onset [n (%)]** | 72(76.6%) | 22(78.6%) | 0.827 |
| **Baseline VAS Scores (mean ± SD)** | 6.64±1.15 | 6.57±1.26 | 0.537 |
| **Baseline HDRS Scores (median score with IQR)** | 14.5(7 to 15) | 14(7.75 to 15.25) | 0.924 |
| **Baseline HDRS scores ≥ 8 (no. (%))** | 68(72.3%) | 21(75.0%) | 0.781 |
| **Baseline HDRS scores ≤ 7 (no. (%))** | 26(27.7%) | 7(25.0%) | |
| **Analgesic use after pain onset (no (%))** | 94(100%) | 28(100%) | 0.751 |
| **NSAIDs** | 89(94.7%) | 27(96.4%) | |
| **Antiepileptics** | 35(38.1%) | 14(52.6%) | |
| **Muscle relaxants** | 9(9.6%) | 2(7.1%) | |
| **Aminophenol oxycodone** | 11(11.7%) | 3(3.6%) | |
| **Tramadol** | 14(14.9%) | 5(17.9%) | |
| **Invasive treatment after pain onset (no (%))** | 64(68.1%) | 18(64.3%) | 0.707 |
| **Dental procedures [n (%)]** | 61(64.9%) | 17(60.7%) | |
| **MVD for TN** | 4(4.3%) | 1(3.6%) | |
| **Radiofrequency thermocoagulation for TN** | 16(17.0%) | 4(14.3%) | |
| **Gamma knife for TN** | 4(4.3%) | 0(0.0%) | |
| **PBC for TN** | 5(5.3%) | 2(7.1%) | |

**Note:** Bold value indicates P<0.01.

**Abbreviations:** VAS, visual analog scale; HDRS, Hamilton Depression Rating Scale; NSAIDs, non-steroidal anti-inflammatory drugs; MVD, microvascular decompression; TN, trigeminal neuralgia; PBC, percutaneous balloon compression.

## Discussions

We present a retrospective multicenter cohort study of a large sample of PIDP patients treated with duloxetine 20–120 mg daily in clinical practice. Our first main finding is that 94 (77.0%) out of 122 patients continued to take medication for at least 12 weeks and obtained some degree of pain relief. Furthermore, by 12 weeks of treatment, the mean VAS score reduced by 89.16% compared with baseline value. These promising results suggest that duloxetine could effectively relieve PIDP patients' pain degree. To our knowledge, this was the largest scale observational study

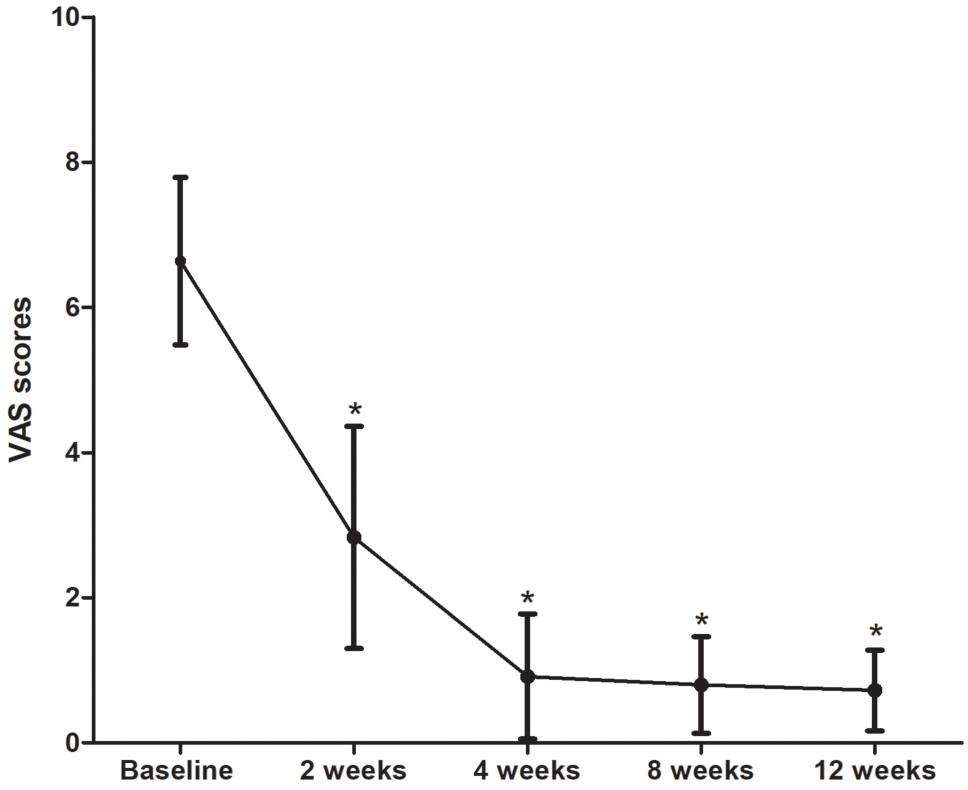


**Figure 1** The time course of VAS scores in 94 patients who were responsive to duloxetine. Each point represents the mean±SD score. Repeated-measures ANOVA revealed a significant result (df = 2.190, F = 948.903, P<0.001), indicating that the mean scores at each point were not all equivalent. Contrast analysis indicated that the VAS score significantly decreased from 2 weeks after taking duloxetine. *Compared with the baseline value, p<0.01.

evaluating the effects of duloxetine in PIDP patients so far. These results will help fill in some gaps in the literature regarding the treatment of PIDP patients.

The pain relief effect of duloxetine in PIDP patients is consistent with the reports of Nagashima et al[23] in which the initial dose of duloxetine was established as 20 mg/day. In Nagashima's study,[23] after 2 weeks or later, if symptom did not change and no adverse effects were observed, the dose of duloxetine was increased to 40 mg/day, which was the maximum dose recommended for major depressive disorder in their country. Unlike their study, the appropriate dose of duloxetine in our study was titrated to 40, 60, 80, or 100, even 120 mg/day in some patients according to the effects and side effects experienced by each patient. In the present study, the median daily dose of duloxetine at 12 weeks was 60 mg/day, which was higher than Nagashima's study.[23] The VAS score declined further over time after duloxetine

**Table 3** Adverse Events with Duloxetine (n = 135)

| Adverse Event | Number of Patients (%) |
|---|---|
| **Nausea** | 21 (15.6%) |
| **Vomiting** | 2 (1.5%) |
| **Constipation** | 11 (8.1%) |
| **Diarrhoea** | 6 (4.4%) |
| **Somnolence** | 11 (8.1%) |
| **Dry mouth** | 4 (3.0%) |
| **Urinary retention** | 4 (3.0%) |
| **Insomnia** | 2 (1.5%) |
| **Dizziness** | 4 (3.0%) |
| **Fatigue** | 5 (3.7%) |
| **Muscle twitch** | 1 (0.7%) |

treatment. TCAs have long been considered effective in treating AO, Trang et al recently reported that about two-thirds of patients experienced moderate pain relief after 16 weeks of amitriptyline, one of the TCAs treatments in AO.[16] From our results, the response rate reached 77.0% after 12 weeks of treatment, signifying that duloxetine may be a more effective drug in this field. Prospective controlled studies are needed for comparison.

Currently, there are reports of predictors of duloxetine response in patients with several chronic pain disorders such as chronic low back pain,[25] fibromyalgia,[26] neuropathic cancer pain,[27] chemotherapy-induced peripheral neuropathy,[28] etc. However, predictors of duloxetine response for PIDP patients have not been reported yet. Our second main finding is that the study firstly screened the predictive factors of response of duloxetine in the treatment of PIDP patients. The patient's demographic data and pain-related baseline data may have affected the efficacy of duloxetine. The results through Binary logistic regression analysis show that only disease duration is an independent positive predictor of the efficacy of duloxetine treatment in PIDP patients. We inferred that duloxetine may be more effective when applied in the early stages of PIDP. However, the odds ratio was 1.017 which was not a high value. Therefore, the results of the study should be taken with caution. Baseline VAS pain scores for pain and other variables were not the predictors of analgesic effects of duloxetine. In future studies, further exploration of other possible predictive factors is expected to improve clinical strategies for the use of duloxetine in treatment of PIDP patients.

In this study, all the included patients had no pain relief effect from the previous treatment with multiple analgesics such as NSAIDs, aminophenol oxycodone, gabapentin, pregabalin etc. Therefore, no patients used analgesics during the study period. Analgesics were avoided in this study to prevent interference with the results. After taking duloxetine, pain was relieved by an average of 5(1–14) days after beginning treatment. These results are consistent with the results reported by Yasuda et al's study[29] which reported the pain relief efficacy of duloxetine in patients with diabetic neuropathy (DNP) in the first week of administration. The results indicate that duloxetine can be effective relatively quickly in PIDP patients. However, after all, it takes nearly a week for the drug to take effect, and some patients take even longer to take effect. Clinicians should tell patients to wait patiently for the drug to take effect, and to avoid rushing to change the drug.

Since duloxetine is a SNRI, the mechanism of duloxetine in the treatment of PIDP raises the levels of serotonin and norepinephrine which plays a role in pain control by activating the descending pain inhibitory pathway. Kobayashi et al[24] reported that pain is resolved through a similar temporal process, regardless of the presence of baseline depressive symptoms. In this study we found that baseline HDRS score was not the predictor of performance of pain relief of duloxetine. Thereafter, we also assumed that duloxetine's effect on pain relief in PIDP patients was independent of its antidepressant effect. In addition to PIDP patients, the analgesic effect of duloxetine on other diseases such as fibromyalgia and PDN have long been reported in the literature as a direct effect rather than a secondary analgesic effect associated with its antidepressant effect.[30]

Kobayashi et al[24] reported that no association was observed between the pain-relieving effects of duloxetine and its plasma concentrations. Unlike Venlafaxine and other SNRIs, which only has the effect of an SNRI with sufficient effects on noradrenaline reuptake in a high dose,[31] duloxetine may act as an SNRI at a low dose/concentration.[32] Therefore, this could explain why some patients have pain relief effect within the first week when the dose of duloxetine was only 20 mg/day, however, the mechanism involved in it remains to be elucidated.

The recommended way to take duloxetine is to titrate gradually from a small dose to a satisfactory dose, with continuous careful monitoring to avoid the associated side effects of the drug. Once the side effects start to appear, the dosage needs to be reduced to the patients' medication compliance. The incidence of adverse effects is about 20% when duloxetine is used as an antidepressant for treating patients with depressive disorder and painful physical symptoms.[33] The incidence of side effects in patients with PIDP treated with duloxetine was expected to be similar. In our study, we found that the incidence of adverse effects after duloxetine administration was 18%, 24 out of 135 cases. Due to proper counseling, only 13 patients discontinued treatment.

The expected adverse reactions to duloxetine have been reported to mainly be nausea. It appeared immediately after taking the drug. In this study, the incidence of nausea was 17.2% (21 out of 122 cases) which was consistent with that reported by Nagashima et al (17%),[23] but their result was well below the 34.29% reported by Bidari et al.[34] This may be because the population in our study was PIDP patients and in Nagashima's study was BMS and AO patients,[23] while the

population observed by Bidari et al[34] were women with Fibromyalgia. Bitter et al indicate that the antiemetics are resistant to continuous use, and it is clinically recommended to slowly titrate duloxetine while closely monitoring its adverse reactions.[35] In this study, none of the patients receive prophylactic antiemetic agents. In accordance with Nagashima et al,[23] to treat the early adverse event of anxiety and insomnia after taken duloxetine, 2 patients (1.5%) took alprazolam with the dosage no more than 1.2 mg/day. Pain physicians who prescribed duloxetine asked patients to take duloxetine with meals and slowly increased the dose of duloxetine to reduce the incidence nausea. In this study, the incidence of dry mouth was 3.2%, which was consistent with the report by Kobayashi et al.[25] The incidence of dry mouth in duloxetine group (5.2%) was far lower than that of TCA amitriptyline when prescribed to patients with chronic orofacial pain (26.7%)[36] as the affinity of duloxetine for muscarinic receptors was lower.[22] So, for PIDP, duloxetine has fewer oral cavity side effects and patient compliance is higher. Hence, duloxetine may be more useful than TCAs for the treatment of diseases with oral symptoms, such as PIDP. Consistent with Bidari et al's findings, most of the adverse events in patients taking duloxetine occurred in the first and second weeks after taking the drug in women with fibromyalgia. Doctors should inform the patient before taking the medicine to improve compliance.[34]

The limitations of this study are as follows. First, in our study, a part of PIDP patients were misdiagnosed as TN in other hospitals and received the neurosurgery. Their pain quality did not change or got pain relieved after the neurosurgery. But those patients who received surgery for TN still has the possibility to develop to post-traumatic trigeminal neuropathy (PTTN). Further, the hierarchical analysis of the increased sample size of data is needed to avoid the influence on results by the patients' heterogeneity. Because of the lack of human resources, the efficacy and safety assessments in this study were conducted by pain physicians who were responsible for examinations/treatments of PIDP patients. This study only observed a VAS score reduction within the first 3 months and some short-term adverse events after taking duloxetine. Furthermore, catastrophizing score and other related information of PIDP patients, especially long-term efficacy of duloxetine on PIDP patients should be studied. Prospective randomized placebo-controlled trials, which can separately establish individuals responsible for the assessment and examinations/treatments must be conducted in the future, to obtain a more definitive result and achieve a higher level of recommendation. Moreover, we only discussed the efficacy of duloxetine in the treatment of PIDP. In the future, the efficacy of other potential effective drugs in the treatment of PIDP patients should also be discussed, along with screening for better drug choices. Finally, how to improve the efficacy of PIDP by drug compatibility remains to be further studied.

## Conclusion

The results of this study are consistent with those previously observed in PIDP patients. A short-term outcome showed that in a 3 month follow up, the administration of duloxetine could significantly reduce the degree of pain. Oral administration of duloxetine may be an effective and safe option for the treatment of PIDP patients with minimal side effects. Patients with shorter disease duration had more benefit from duloxetine.

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## Author Contributions

Jia Zipu and Yu Jinyong contributed equally to this work and should be considered co-first authors. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work. This retrospective study was designed by Luo Fang and with important contribution from Jia Zipu and Yu Jinyong. Jia and Yu contributed equally to this work.

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