Retrospective Study

Effectiveness and Safety of Flupentixol and Melitracen Tablets for the Treatment of Patients with Persistent Idiopathic Facial Pain: A Retrospective Observational Study

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Background: Flupentixol and melitracen are being investigated for their potential effectiveness in managing persistent idiopathic facial pain (PIFP), based on their mechanisms of action as dopamine receptor antagonists and noradrenaline/serotonin reuptake inhibitors, respectively. The efficacy and safety of flupentixol and melitracen (FM) tablets in treating PIFP were retrospectively analyzed at our hospital.

Objectives: The aim of this study is to determine the effectiveness and safety of FM tablets in treating PIFP.

Study Design: Retrospective unicentric cohort design.

Setting: An academic university hospital.

Methods: A retrospective analysis was conducted on a cohort comprising 128 patients with a definite diagnoses of PIFP who were treated with FM tablets (flupentixol 0.5 mg and melitracen 10 mg tablet, ≤ 4 tablets/d) from January 2022 through May 2023 at an academic university hospital. Baseline conditions were statistically described, and Numeric Rating Scale (NRS-11) scores of pain levels before and during treatment were collected. Pain relief rates were calculated. Differences in baseline characteristics between responsive and unresponsive patients were evaluated using statistical tests. Additionally, the side effects experienced during treatment were summarized.

Results: Among the included 128 patients, 105 (82.0%) patients achieved pain relief (pain NRS-11 score reduction rate ≥ 50%). The median treatment onset time was 3 (1-7) days. NRS-11 scores of responsive patients at week 2, week 4, week 8, and week 12 were significantly lower than the baseline NRS-11 scores ($P < 0.001$), regardless of their Hamilton Depression Rating Scale score. Pain duration was the only factor that related to responsiveness (Wilcoxon rank sum test, $P < 0.001$; logistic regression, $P = 0.001$). No serious side effects that could affect patients' lives were observed during the first week of treatments.

Limitations: Due to its retrospective nature, this study is limited by its lack of a randomized control. The lack of data on nonresponders who did not achieve significant pain relief hinders assessing overall change and the placebo effects'. Patients previously treated with antidepressants were excluded, making it hard to determine if FM tablets were a better treatment for PIFP. Additionally, the small sample size in a single center may be influenced by chance variation in pain relief.

Conclusions: FM tablets showed its potential in the management of PIFP with considerable efficacy and safety. Early administration of FM tablets after a PIFP diagnosis may result in a high possibility of pain relief.

Key words: Flupentixol and melitracen, persistent idiopathic facial pain (PIFP), effectiveness, serotonin and norepinephrine reuptake inhibition (SNRIs)

Editor's Note: Flupentixol is not approved for use in the United States, either alone or in combination with melitracen.

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Persistent idiopathic facial pain (PIFP), previously termed atypical facial pain, is a persistent facial and/or oral pain that presents with highly variable symptoms, occurring daily for more than 2 hours per day over a period of more than 3 months. According to a primary care study conducted in the Netherlands, the incidence of PIFP is 4.4 (95% CI,3.2 – 5.9)/100,000 person-years. It predominantly affects women (75%) with an average age of 45.5 years (SD, 19.6) (1).

These patients experience a dull, burning, or pulling pain without precise localization that can be either deep or superficial. It primarily affects the distribution area of the trigeminal nerve in the face, and is commonly felt in the cheeks and maxilla region. In some cases, it may also radiate to other areas such as the jaw, occiput, ears, shoulders or arms over time. (2-5). Furthermore, the pain persists for prolonged durations and occurs throughout most of the day on a daily basis. Some patients with PIFP concurrently complain of other unexplained symptoms, such as other chronic pain, irritable bowel syndrome, etc., which may be related to health anxiety or other adverse psychological events (6). There are studies reporting that factors such as fatigue and anxiety can exacerbate pain, making it sharp (7,8).

In the third edition of the International Classification of Headache Disorders (ICHD-3), 2 disorders are treated as one entity: PIFP, with atypical odontalgia as a possible subtype. International Classification of Orofacial Pain, first edition (ICOP) criteria distinguish and define 2 entities: PIFP and persistent idiopathic dentoalveolar pain (9).

Since the etiology of PIFP has not been fully and scientifically validated, as well as the absence of randomized controlled trials for its treatment, a clear treatment plan is currently unavailable. Some therapies, such as cognitive behavioral therapy, active hypnosis, orthotic devices to maintain mandibular resting position, acupuncture, pulsed radiofrequency of the sphenopalatine ganglion, botulinum toxin A injection, implanted peripheral nerve field stimulators, and multimodal pain therapy have all been reported as potentially effective and safe treatments for PIFP (10-12).

Tricyclic antidepressants (TCAs) are most commonly prescribed for treating PIFP (11,13). Additionally, combining TCAs like amitriptyline with nonselective β-blockers, such as pindolol, has resulted in a reduction in pain days (14,15). Selective serotonin reuptake inhibitors (SSRIs), and serotonin-norepinephrine reuptake inhibitions (SNRIs), such as duloxetine and venlafaxine, have also demonstrated effectiveness in small scale trials (15-18). Anticonvulsant drugs, including carbamazepine and phenytoin, and opioids not only have limited evidence for reducing chronic pain, but they may also cause adverse effects (19). In a recent meta-analysis by Do, et al (20), little evidence was found supporting using other pharmacologic agents for PIFP treatment. Therefore, there is an urgent need for clinical studies to enhance drug treatments for PIFP.

Flupentixol and melitracen (FM) tablets are a combination of flupentixol hydrochloride and melitracen hydrochloride. It is primarily utilized for treating depression and anxiety disorders. Flupentixol, acting as an antagonist on dopamine receptor 1 (D1) and particularly dopamine receptor 2 (D2), exhibits anxiolytic and antidepressant effects at low doses. A positron emission tomography study demonstrated increased D2 receptor density in the putamen, suggesting that dopaminergic neurotransmission may contribute to pain modulation in PIFP (21).

Based on this premise, we hypothesized that flupentixol could potentially play a role in managing PIFP. Melitracen is a tricyclic bipolar antidepressant, which blocks the reuptake of norepinephrine (NE) and 5-hydroxytryptamine (5-HT) by NE and 5-HT-ergic nerve terminals, thereby increasing monoamine transmitter concentrations within the synaptic cleft. Considering the potential efficacy of NE and 5-HT reuptake inhibitors in treating PIFP symptoms, it is plausible that melitracen might ameliorate PIFP manifestations. Accordingly, we hypothesized that FM tablets might be effective against PIFP. However, FM tablets have not been previously reported as a PIFP treatment. Therefore, we retrospectively analyzed its efficacy and safety in our hospital.

Methods

Our study was conducted in accordance with the World Medical Association Declaration of Helsinki, a set of ethical principles for human medical research. It was approved by the Institutional Review Board of our hospital, and was granted an informed consent waiver due to its retrospective nature.

In this retrospective study, patients were at minimal risk, and all data analyzed were de-identified. Waiver of consent did not have an adverse effect on the welfare and rights of the patients. We retrospectively reviewed the clinical database of patients with PIFP who were prescribed FM tablets at the Pain Management Department of an academic university hospital during the period from January 2022 through April 2023.

Inclusion and Exclusion Criteria

Inclusion criteria were: a PIFP diagnosis (22,23); 18 years or older; being fully involved in the FM tablets treatment process, taking medications as prescribed, and at least 3 months of follow-up data were available, unless the patient stopped taking the tablets because of side effects or poor efficacy.

Exclusion criteria were: a history of antidepressant drug use or current use of other medication or therapy; a history of mental illness, or those who have had psychoactive substance abuse; diabetic neuropathic pain.

Treatment

All patients adhered to a standardized medication regimen. FM tablets (flupentixol 0.5 mg and melitracen 10 mg per tablet, Chongqing Shenghuaxi Pharmaceutical Co., Ltd.) were administered at a dosage of 2 tablets daily: one in the morning and one at noon for approximately one week. If pain relief was not good and there were no adverse effects, the morning dose was increased to 2 tablets for approximately another week. If pain relief still remained insufficient, the midday dose was also escalated up to a maximum of 2 tablets.

Sedation was recommended during the acute phase for patients experiencing insomnia or severe restlessness. Symptom changes and adverse effects were closely monitored throughout the treatment period. Once complete pain relief was achieved, the dose of FM tablets was not increased but continued. However, if side effects related to the FM tablets occurred upon dose escalation, the dosage was promptly titrated back to the last tolerated level.

Data Acquisition

All data were available in a patient database which also included baseline characteristics and follow-up data. The baseline data were patients' age, gender, disease durations, affected side, comorbidities, history of dental operation before pain onset, and prior medication use after pain onset. The Numeric Rating Scale (NRS-11) was used to assess pain levels, while the Hamilton Depression Rating Scale (HDRS) was used to evaluate depression symptoms at baseline.

Additionally, the outpatient medical record system recorded the effect of medication based on patients' pain diaries or reports during their visit 2 weeks after the initial consultation. Typically, patients were requested to return to the clinic 2 weeks after the initial prescription of FM tablets; patients made additional visits to the outpatient clinic at 4 weeks, 8 weeks, and 12 weeks after taking the medication in order to monitor the therapeutic effect and continue their prescription. Efficacy and safety data were extracted from medical records documenting outpatient visits during FM tablet treatment which included variables such as visiting time, NRS-11 and HDRS scores at each visitation point, current FM tablet dosage administered; any observed side effects or complications encountered by patients along with other concurrent or subsequent treatments were also recorded.

The NRS-11 consists of a series of numbers with verbal anchors representing the entire range of pain intensity, where zero represents "no pain" and 10 represents the most intense level possible. Treatment onset time was defined as the time from treatment initiation to achieving a 30% reduction in the NRS-11 score. Based on treatment effect, patients were divided into responsive and nonresponsive groups. Significantly effective was an NRS-11 score reduction rate ≥ 75%; effective, a 75% – 50%reduction; ineffective, a < 50% reduction. The total effective rate = (significantly effective + effective)/total cases × 100%.

The HDRS is commonly used for assessing depression. Scores ranging from 0 to 4 are assigned based on symptom absence, mildness, moderation, or severity; these scores are then summed up to obtain the total score for each item. The total score range for the 17-item variant is from 0 to 54: scores from 0 – 7 indicate no depression; scores from 8 – 13 denote mild depression; scores from 14 – 18 represent moderate depression; scores from 19 – 22 signify severe depression; and any score equal to or greater than 23 indicates very severe depression (24).

Safety assessments included monitoring adverse events, which were documented by physicians through direct observation and spontaneous reports from patients throughout the trial. Adverse events included headache, dizziness, drowsiness, dry mouth, nausea, gastrointestinal discomfort, insomnia, somnolence, constipation, diaphoresis, nervousness, and fatigue. The incidence of these events was recorded during visits and throughout the treatment period. Additionally, the reasons for patient withdrawal and final medication dosage in discontinuation cases were also recorded.

Statistical Analysis

Data were entered and analyzed using IBM SPSS Statistics 25.0 (IBM Corporation). Descriptive statistics

tools were applied for the analysis. Each collected variable underwent analysis, with mean and SD calculated for normally distributed measurements, while nonnormally distributed data are represented by median and interquartile range. Disaggregated data are presented as a number or percentage indicating the proportion of patients who responded or did not respond to treatment. It should be noted that no normal distribution was observed in this study. The Mann-Whitney U test was used to compare nonnormally distributed continuous variables between the responsive group and the nonresponsive group, while categorical variables were assessed using either the χ^2 test or Fisher's exact test when expected values were less than 5.

For patients who responded, NRS-11 scores at 2 weeks, 4 weeks, 8 weeks, and 12 weeks posttreatment were compared with baseline NRS-11 scores using the paired Friedman test. A significance level of < 0.05 was considered statistically significant. Univariate and multivariate binary logistic regression analyses were conducted to identify predictors of the degree of response; adjusted odds ratios were calculated along with their corresponding 95% CIs. All continuous variables underwent linear testing using the Box-Tidwell method before being included in the model as linear variables. Additionally, information regarding side effects was also provided.

Results

Demographic Data

From January 2022 through April 2023, we identified a total of 140 patients with PIFP who were administered FM tablets for pain management at our hospital's pain clinic. Among these patients, 6 also received other analgesics, 4 had incomplete follow-up data, and 2 discontinued the medication due to concerns about potential side effects despite experiencing pain relief, but not side effects. Consequently, our study included a total of 128 patients who met the inclusion criteria (Fig. 1). All participants had received analgesic drugs such as nonsteroidal anti-inflammatory drugs (NSAIDs), oxycodone/acetaminophen, gabapentin or pregabalin, and others before taking FM tablets, but these drugs were unsuccessful in controlling their pain. Additionally, dental misdiagnosis led to dental treatment including tooth extraction in 78 patients (74.3%) after the onset of pain. Demographic and baseline data related to pain are presented in Table 1.

Efficacy of FM Tablets

Among the 128 patients included in our study, pain relief was achieved in 105 patients (82.0%), while 23 patients (18.0%) withdrew from treatment due to their being nonresponders to treatment with FM tablets. No patient discontinued treatment because of side effects. Table 2 shows univariate comparisons of demographic and pain-related baseline data between responders (n = 105) and nonresponders (n = 23).

These results reveal that there was only a significant difference in pain duration between these 2 patient subgroups ($P = 0.000$; $P < 0.001$, respectively), indicating that the mean NRS-11 scores at each time point were not equivalent. Contrast analysis shows that NRS-11 scores at weeks 2, 4, 8 and 12, while taking FM tablets were all significantly lower than baseline values. The median onset time for effective treatment response was 3 (SD, 1-7) days.

In order to investigate the effect of baseline depressive symptoms on the pain-improving effect of the study treatment, we compared changes in the NRS-11 score over time between the 2 subgroups of patients based on their HDRS scores at initial examination; those with an HDRS score of 7 or lower (patients without depression, n = 28) and those with a score of 8 or higher (patients with depression, n = 77). The results showed a significant difference (df = 4, F = 2187.920, $P < 0.001$), indicating that the mean NRS-11 scores at each time point were not equivalent. A contrast analysis showed that NRS-11 scores at weeks 2, 4, 8 and 12 while taking FM tablets were all significantly lower than baseline values. There was no significant mood (nondepressed or depressed) × time interaction between the 2 groups (df = 4; F= 0.210; $P = 0.864$; Fig. 2).

When analyzing the responsive group consisting of only patients with depression with complete data for a follow-up period of 12 weeks (n = 77), the Friedman nonparametric repeated measures analysis of variance (ANOVA) test yielded a significant result (df =4; F = 306.022; $P < 0.001$), suggesting that the mean HDRS scores at each time point were not equivalent. A contrast analysis demonstrated that NRS-11 scores at weeks 2, 4, 8, and12 while taking FM tablets were all significantly lower than baseline values (Fig. 3).

Side Effects

A total of 25 patients (19.5%) had side effects from taking FM tablets. Most patients had mild side effects, including headache/dizziness/drowsiness in 10 cases (7.8%), dry mouth in 8 cases (6.25%), nausea in

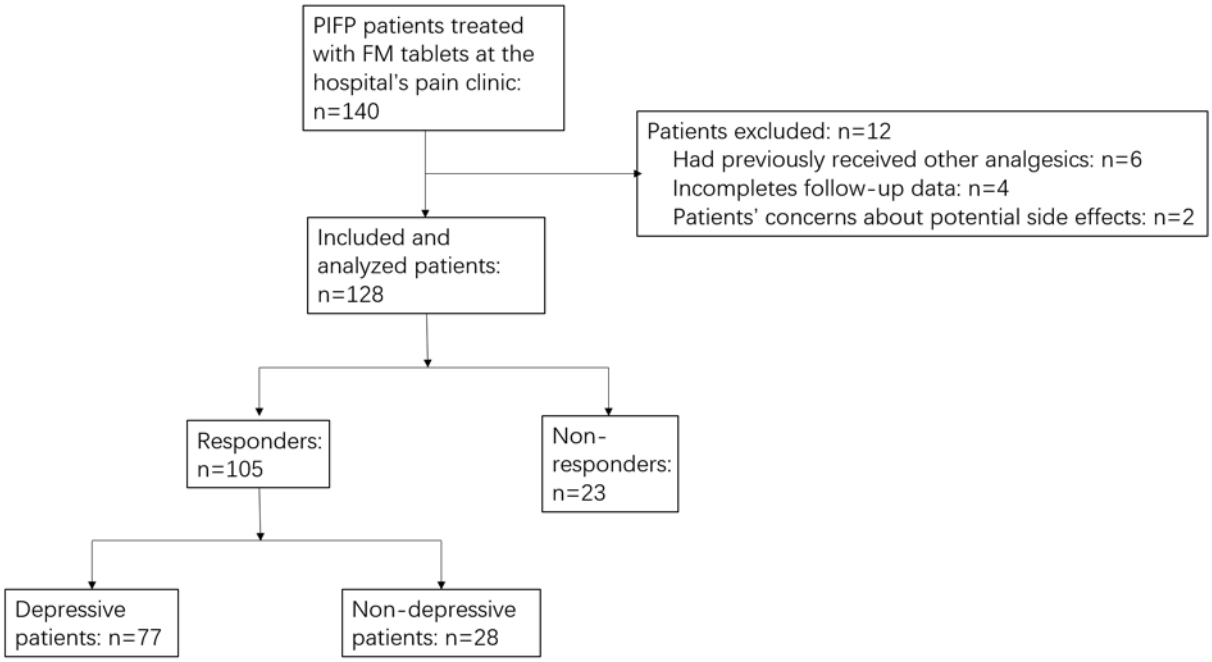

Fig. 1. *Study enrollment flow chart.*

5 cases (3.90%), and gastrointestinal discomfort in 2 cases (1.56%). All of the above adverse reactions were transient, which were quickly relieved by rest and were tolerated. All patients were able to complete the course of treatment.

Discussion

This retrospective observational study included a population of 128 patients diagnosed with PIFP, mainly affecting middle-aged and elderly women with a mean age of 48 years. These findings align with previous literature indicating that PIFP is a chronic pain condition primarily affecting this demographic group (25-29).

In this retrospective observational study, our first main finding was that 105 (82.0%) out of 128 patients continued to take FM tablets for at least 12 weeks and obtained some degree of pain relief, which is comparable to previous studies using SNRI drugs such as duloxetine and venlafaxine. These 2 studies reported pain relief rates of 77.0% and 80.6%, respectively (17,18). In our study, by the end of the 12 weeks of treatment, there was a remarkable reduction of 84.97% in the mean NRS-11 score compared to baseline values.

These promising results suggest that FM tablets could effectively alleviate pain in patients with PIFP. To the best of our knowledge, this is the first observa-

Table 1. *Baseline data summary of included patients (n = 128).*

Variables	Values
Age (IQR)	48 (41 – 57)
Gender (Women/Men)	80/48 (62.5%/37.5%)
Pain Duration (months, IQR)	24.0 (15.0 – 36.0)
NRS-11 (IQR)	6.3 (6 – 7){range? IQR?}
Affected Side Unilateral	
Left Side	53 (41.4%)
Right Side	68 (53.1%)
Bilateral	7 (5.5%)
HDRS	12.24; (IQR, 7– 16)
Low score group (≤ 7)	n = 33 (25.8%); 5.73 (IQR, 5 – 7)
High score group (≥ 8)	n = 95 (74.2%); 14.51 (IQR, 13–17)
Analgesic use before FM	128 (100%)
NSAIDs	125 (97.7%)
Antiepileptics	62 (48.4%)
Oxycodone/Acetaminophen	23(18.0%)
Tramadol	18 (14.1%)
Previous dental procedure(s)	88(68.8%)

Abbreviations: IQR = interquartile range; NRS-11 = Numeric Rating Scale; HDRS = Hamilton Depression Rating Scale; FM = flupentixol and melitracen; NSAIDs = nonsteroidal anti-inflammatory drugs

tional study evaluating the effects of FM tablets on patients with PIFP. These results will help address existing literature regarding the treatment of these patients, and may provide new ideas for their treatment and management.

Table 2. *Statistical tests and logistic regression to identify risk factors for responsiveness.*

	Description		Comparison
	Responsive (n = 105)	**Unresponsive (n = 23)**	***P***
Age (IQR)	49.0 (41.5 – 57.0)	44.0 (39.0 – 55.5)	0.114
Gender (Women/Men)	65/40 (61.9%/38.1%)	15/8 (65.2%/34.8%)	0.766
Pain Duration	24 (12,30)	38 (30,42)	0.000**
Affected Side			1.000
Unilateral	99 (94.3%)	22 (95.7%)	
Left	42 (40%)	11 (47.8%)	
Right	57 (54.3%)	11 (47.8%)	
Bilateral	6 (5.7%)	1 (4.3%)	
Baseline NRS-11	6 (6, 7)	6 (6, 7)	0.970
Baseline HDRS	13 (7,16)	15 (9,16)	0.447
HDRS			0.794
Low score group (≤ 7)	28 (26.7%)	5 (21.7%)	
High score group (≥ 8)	77 (73.3%)	18 (78.3%)	
Analgesic use before FM	105 (100.0%)	23 (100%)	
NSAIDs	103 (98.1%)	22 (95.7%)	0.451
Antiepileptics	52 (49.5%)	10 (43.5%)	0.650
Oxycodone/Acetaminophen	20 (19.0%)	3 (13.0%)	0.764
Tramadol	15 (14.3%)	3 (13.0%)	1.000
Previous dental procedure(s)	73(69.5%)	15 (65.2%)	0.687

Abbreviations: NRS-11 = Numeric Rating Scale; HDRS = Hamilton Depression Rating Scale; FM = flupentixol and melitracen tablets; NSAIDs = nonsteroidal anti-inflammatory drugs

In this study, all enrolled patients exhibited no analgesic response to previous treatments with multiple analgesics including NSAIDs, oxycodone/acetaminophen, gabapentin, pregabalin, and others. No analgesics were used during the study period in order to prevent interference with the results. After initiating FM tablet treatment, pain relief was achieved within an average of 3 (interquartile range [IQR], 1-7) days after beginning treatment, which was faster than 5 (IQR, 1-14) days after duloxetine reported by Jia, et al (17), and 9 (IQR, 8-11) days after venlafaxine reported by Xiao, et al (18), thus avoiding the rush of hasty medication changes. Furthermore, the NRS-11 core continued to decline over time after FM tablet treatment.

There is a strong link between depression and chronic pain, which has been shown to be interrelated by Foerster, et al (11). Among our patients, nearly

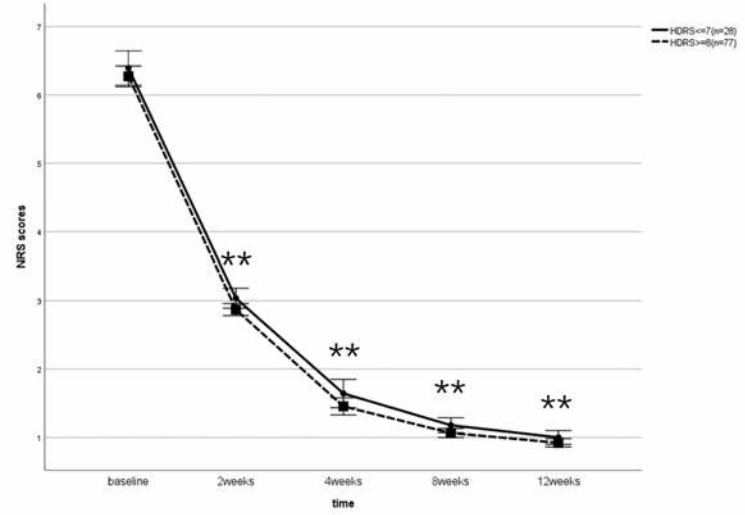

Fig. 2. *NRS-11 scores during the 12 weeks of treatment in the 2 subgroups of patients with a baseline HDRS score of 7 or lower (patients without depression) and 8 or more (patients with depression). **Compared with the baseline value, $P < 0.01$.*
Abbreviations: NRS-11 = Numeric Rating Scale; HDRS=Hamilton Depression Rating Scale.

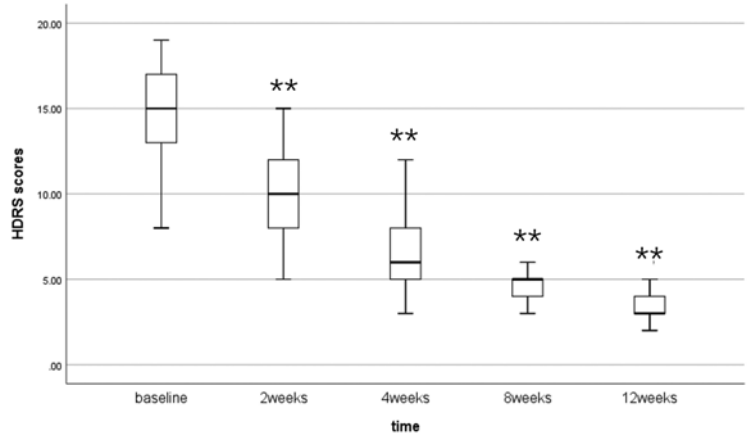

Fig. 3. *HDRS scores during the 12 weeks of treatment in 77 patients with a baseline HDRS score of 8 or more (patients with depression). **Compared with the baseline value, $P < 0.01$.*
Abbreviations: HDRS = Hamilton Depression Rating Scale; NRS = Numeric Rating Scale.

three-quarters (95/128, 74.2 %) showed signs of depression preceding the onset of their orofacial pain. This finding is in line with earlier reports indicating a high prevalence of depressive disorders before orofacial pain onset (30).

In this study, age, gender and depression were not observed to be related to the efficacy of FM tablets. We found that the pain duration is a risk factor for unresponsiveness to FM tablets. Similar findings were reported by Jia, et al (17) and Xiao, et al (18), suggesting that patients with persistent idiopathic dentoalveolar pain with a shorter disease duration had more benefit from duloxetine and venlafaxine.

In the last decade, studies have highlighted the significance of dopaminergic pathways in PIFP and related clinical pain conditions. Specifically, it is the hypofunction of dopaminergic pathways in the basal ganglia that may contribute to PIFP (10). It is proposed that the high psychiatric morbidity in chronic idiopathic orofacial pain can be best understood in terms of shared vulnerability to both chronic pain and specific psychiatric disorders, most likely mediated by abnormal brain dopamine function (30). It is widely recognized that pain sensation input to the brain is controlled by the descending pain inhibitory system, which courses from the central nervous system to the spinal cord. This system is modulated by the function of both the serotonergic and noradrenergic nervous systems (31).

A mixture of melitracen (10 mg) and flupentixol (0.5 mg), of which agents are accordingly a kind of tricyclic antidepressant and classic antipsychotic component, has been proven to have a rapid onset with both anxiolytic and antidepressant properties in low doses (32).

Melitracen, similar to imipramine and amitriptyline, is a bipolar thymoleptic with activating properties that can act on both depression and anxiety. It acts on the presynaptic membrane to increase the concentration of norepinephrine and 5-HT related receptors in the synaptic space (33). Flupentixol specifically antagonizes D1 and D2 receptors, along with various dopamine, serotonin, adrenaline, and histamine receptors, resulting in an important antipsychotic effect without affecting muscarinic acetylcholine receptors, and directly stimulates dopamine secretion in the synaptic space by acting on the related postsynaptic membrane receptors (34-36). Additionally, it significantly improves the symptoms of patients with mild-to-moderate depression and has comparable effects at low doses to amitriptyline, but with a more rapid onset of action (34,37).

Melitracen and flupentixol can promote the improvement of depression and take effect quickly, thus avoiding drug dependence addiction with a certain biosafety (38,39).

In our study the responsive group patients were classified into 2 subgroups: one with depression at the start of the study treatment, and the other without it. Their NRS-11 scores were monitored over time during the study treatment, and both groups showed essentially the same score decline tendency. The results suggest that patients with PIFP respond to FM tablet therapy with a comparable pain-relieving effect regardless of whether any depressive symptoms are present.

By the end of the second week of treatment, 92.2% of the patients' NRS-11 scores decreased by ≥ 50%; all patients had a lower score by the end of the fourth week of treatment. However, at the end of the second

week, their HDRS scores only decreased by more than 25% in 75.3% of patients; all patients had a lower score by the end of the fourth week. These results show that the analgesic effect occurred significantly earlier than the antidepressant effect. This suggests that the analgesic effect of FM tablets on patients with PIFP might be independent from their antidepressant effects. The exact mechanism of action of FM tablets in treating PIFP is still unclear, particularly given the fact that some of our study patients did not suffer from anxiety or depression as evidenced by their HDRS scores.

In our study, patients reported few side effects, which were comparable to the proportion of patients experiencing side effects in Jia, et al's (17) investigation on the efficacy of duloxetine in patients with PIFP (17.7%), and significantly lower than Xiao, et al's (18) research on the effectiveness of venlafaxine in patients with PIFP (49.6%). However, these side effects were only observed during the initial stages of drug use. Unlike the 13 individuals in Jia et al's (17) study who discontinued the medication due to side effects, our patients found these side effects tolerable and did not withdrew from treatment. This is consistent with previous reports suggesting that the combination drug has rare and well-tolerated side effects in the treatment of diarrhea-type irritable bowel syndrome (40). Additionally, a previous clinical trial of short-term treatment for functional dyspepsia also showed a positive clinical response and good tolerance among patients receiving FM tablets. Therefore, we believe that the treatment of PIFP with FM tablets is safe.

Limitations

Our study has a few limitations due to its retrospective and observational nature. In terms of efficacy, there was limited information on nonresponsive patients who had no significant pain relief, making it difficult to assess the overall change from baseline and the influence of placebo effects on the results. Additionally, since patients who had previously taken antidepressants were excluded from this study and TCAs are commonly used for PIFP, we were unable to demonstrate that FM tablets are superior to conventional TCAs. Moreover, due to the small number of patients involved in this single-center study, it should be noted that changes in NRS-11 scores and FM tablet doses may have occurred by chance due to low statistical power. Despite these limitations, we believe that FM tablets show promise as an effective and safe treatment option for patients with PIFP. The real-world data obtained in this study provide valuable insights into its potential efficacy.

Conclusions

Our short-term outcomes demonstrate that in a 12-week follow-up period, FM tablets showed potential for managing PIFP with considerable efficacy and safety. Patients with a shorter disease duration benefited more from FM tablets administration.

Authors' Contributions

YXW made substantial contributions to conception and design, drafting the article, analyzing data, and revising it critically for intellectual content; NS and YS participated in the study design, collected data and performed critical revision of the manuscript. All authors were involved in data interpretation. FL is the principal investigator of the entire study, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. FL participated in conceiving and designing the study, reviewing and analyzing data, revising the manuscript, and securing funding. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

The Institutional Review Board of Beijing Tiantan Hospital (Approval Number: KY2020-100-07) approved the planned protocol. Informed consent was required from all patients before inclusion in the study, and each participant was informed that their participation would be voluntary and that they could withdraw from the study at any time.

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References

1. Koopman JS, Dieleman JP, Huygen FJ, de Mos M, Martin CG, Sturkenboom MC. Incidence of facial pain in the general population. *Pain* 2009, 147:122-127
2. Bahra A, Goadsby J. Diagnostic delays and mis-management in cluster headache. *Acta neurologica Scandinavica* 2004; 109:175-179.

3. Cademartiri C, Torelli P, Cologno D, Manzoni GC. Upper and lower cluster headache: Clinical and pathogenetic observations in 608 patients. *Headache* 2002; 42:630-637.
4. Gaul C, Gantenbein AR, Buettner UW, Ettlin DA, Sándor PS. Orofacial cluster headache. *Cephalalgia* 2008; 28:903-905.
5. van Vliet JA, Eekers PJ, Haan J, Ferrari MD, Dutch RUSSH Study Group. Features involved in the diagnostic delay of cluster headache. *J Neurol Neurosurg Psychiatry 2003;* 74:1123-1125.
6. Aggarwal VR, McBeth J, Zakrzewska JM, Lunt M, Macfarlane GJ. The epidemiology of chronic syndromes that are frequently unexplained: Do they have common associated factors?. *International J Epidemiology* 2006; 35:468-476.
7. Clarkson E, Jung E. Atypical Facial Pain. *Dent Clin North Am* 2020; 64:249-253.
8. Brailo V, Zakrzewska JM. Grading the intensity of nondental orofacial pain: Identification of cutoff points for mild, moderate, and severe pain. *J Pain Res* 2015; 8:95-104.
9. International Classification of Orofacial Pain, 1st edition (ICOP). *Cephalalgia* 2020; 40:129-221.
10. Weiss AL, Ehrhardt KP, Tolba R. Atypical facial pain: A comprehensive, evidence-based review. *Curr Pain Headache Rep 2017;* 21:8.
11. Foerster Z, Kleinmann B, Schlueter N, Vach K, Wolter T. Multimodal pain therapy for persistent idiopathic facial pain - A pilot study. *BioPsychoSocial Medicine* 2022; 16:25.
12. Didier HA, Cappellari AM, Gaffuri F, et al. Predictive role of gnathological techniques for the treatment of persistent idiopathic facial pain (PIFP). *Neurol Sci* 2020; 41:3315-3319.
13. Güler N, Durmus E, Tuncer S. Long-term follow-up of patients with atypical facial pain treated with amitriptyline. *N Y State Dent J 2005;* 71:38-42.
14. Harrison S, Glover L, Maslin L, Feinmann C, Pearce S, Harris M. A comparison of antidepressant medication alone and in conjunction with cognitive behavioral therapy for chronic idiopathic facial pain. In: Proceedings of the 8th World Congress on Pain. Volume 8. Jensen T, Turner J, Weinsenfeld-Halin Z (Eds). IASP Press, Seattle, WA, USA (1997) 21 chronic tension-type facial pain. *Rhinology* 2013; 51:143-153.
15. Forssell H, Tasmuth T, Tenovuo O, Hampf G, Kalso E. Venlafaxine in the treatment of atypical facial pain: A randomized controlled trial. *J Orofacial Pain* 2004; 18:131-137.
16. Nakamura M, Yoshimi A, Mouri A, et al. Duloxetine attenuates pain in association with downregulation of platelet serotonin transporter in patients with burning mouth syndrome and atypical odontalgia. *Human Psychopharmacol* 2022; 37:e2818.
17. Jia Z, Yu J, Zhao C, Ren H, Luo F. Outcomes and predictors of response of duloxetine for the treatment of persistent idiopathic dentoalveolar pain: A retrospective multicenter observational study. *J Pain Res* 2022; 15:3031-3041.
18. Xiao X, Chai G, Wang B, Luo F. Treatment of persistent idiopathic dentoalveolar pain with venlafaxine: A multicentric retrospective study on its effectiveness and safety. *J Pain Res* 2023; 16:2487-2495.
19. Ganzberg S. Pain management part II: pharmacologic management of chronic orofacial pain. *Anesth Prog* 2010; 57:114-118.
20. Do TM, Unis GD, Kattar N, Ananth A, McCoul ED. Neuromodulators for atypical facial pain and neuralgias: A systematic review and meta-analysis. *Laryngoscope* 2021; 131:1235-1253. .
21. Hagelberg N, Forssell H, Aalto S, et al. Altered dopamine D2 receptor binding in atypical facial pain. *Pain* 2003; 106:43-48.
22. Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. *Cephalalgia* 2018; 38:1-211.
23. Benoliel R, Gaul C. Persistent idiopathic facial pain. *Cephalalgia* 2017; 37:680-691.
24. Hirschfeld RM, Montgomery SA, Aguglia E, et al. Partial response and nonresponse to antidepressant therapy: Current approaches and treatment options. *J Clin Psychiatry* 2002; 63:826-837.
25. Benoliel R, Gaul C. Persistent idiopathic facial pain. *Cephalalgia* 2017; 37:680-691.
26. Woda A, Pionchon P. A unified concept of idiopathic orofacial pain: Clinical features. *J Orofac Pain* 1999; 13:172-184.
27. Woda A, Tubert-Jeannin S, Bouhassira D, et al. Towards a new taxonomy of idiopathic orofacial pain. *Pain* 2005; 116: 396-406.
28. Didier H, Marchetti C, Borromeo G, Tullo V, Bussone G, Santoro F. Persistent idiopathic facial pain: Multidisciplinary approach and assumption of comorbidity. *Neurol Sci* 2010; 31:S189
29. Schweiger V, Nocini R, De Santis D, et al. Persistent Idiopathic Facial Pain (PIFP) in Patients Referred to a Multidisciplinary Centre in Italy: A Retrospective Observational Study. *J Clin Med* 2022; 11:3821.
30. Taiminen T, Kuusalo L, Lehtinen, L et al. Psychiatric (axis I) and personality (axis II) disorders in patients with burning mouth syndrome or atypical facial pain. *Scand J Pain* 2011; 2:155- 160.
31. Basbaum AI, Fields HL. The origin of descending pathways in the dorsolateral funiculus of the spinal cord of the cat and rat: Further studies on the anatomy of pain modulation. *J Comp Neurol* 1979; 187:513-531.
32. Hashash JG, Abdul-Baki H, Azar C, et al. Clinical trial: A randomized controlled cross-over study of flupenthixol + melitracen in functional dyspepsia. *Aliment Pharmacol Ther* 2008; 27:1148-1155.
33. Zhang T, Yu GD. [Observation of Flupentixol and melitracen on curative effect of sudden deafness patients with anxiety and depression in different stages]. *Lin Chuang Er Bi Yan Hou Tou Jing Wai Ke Za Zhi* 2018; 32:643-646. Chinese.
34. Høstmaelingen HJ, Asskilt O, Austad SG, et al. Primary care treatment of depression in the elderly: A double-blind, multi-centre study of flupenthixol ('Fluanxol') and sustained-release amitriptyline. *Curr Med Res Opin* 1989; 11:593-599.
35. Juel C. Pre- and postsynaptic effects of dopamine antagonists on dopaminergic synaptic transmission in Helix pomatia. *Comp Biochem Physiol C Comp Pharmacol Toxicol* 1983; 76:203-208.
36. Gottschling C, Geissler M, Springer G, Wolf R, Juckel G, Faissner A. First and second generation antipsychotics differentially affect structural and functional properties of rat hippocampal neuron synapses. *Neurosci* 2016; 337:117-130.
37. Wang L, Zhong Z, Hu J, et al. Sertraline plus deanxit to treat patients with depression and anxiety in chronic somatic diseases: A randomized controlled trial. *BMC Psychiatry* 2015; 14;15:84.
38. Zheng JR, Xie YM. [HIS-based analysis of comorbid characteristics and combined treatment of Chinese and western medicine in patients with depressive disorder]. *Zhongguo Zhong*

Yao Za Zhi 2014; 39:3454-3461. Chinese.

39. Yi ZG, Yang XH, Ren JJ, Peng WH, Liang QL. [Clinical observation of flupentixol and melitracen combined with specific immunotherapy for treatment of allergic rhinitis patients with anxiety and depression]. *Lin Chuang Er Bi Yan Hou Tou Jing Wai Ke Za Zhi* 2017; 31:34-37. Chinese.
40. Qin L, Qin J, Yang Q, Lv X, Huang L. Efficacy and safety of pinaverium bromide combined with flupentixol-melitracen for diarrhea-type irritable bowel syndrome: A systematic review and metaanalysis. *Medicine (Baltimore)* 2019; 98: e14064.