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Original Article

Verapamil and venlafaxine combined as an effective and well-tolerated adjunct for cancer pain management

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Abstract: Aims: To evaluate the efficacy of combining verapamil and venlafaxine in cancer pain management. Methods: This retrospective study included 203 patients with cancer pain treated between March 2022 and March 2025. The patients were divided into a control group (n = 98) receiving verapamil alone and an observation group (n = 105) receiving a combination of verapamil and venlafaxine. Pain relief was assessed using the Numeric Rating Scale (NRS), Visual Analogue Scale (VAS), and Brief Pain Inventory (BPI) at baseline, and post-treatment 2 and 4 weeks. Secondary measures included anxiety and depression (Hospital Anxiety and Depression Scale [HADS] and Generalized Anxiety Disorder 7 [GAD-7] scale), quality of life (Karnofsky Performance Status [KPS] and Quality of Life [QOL] scale), and adverse reactions. Results: The observation group had higher rates of significant pain relief (42.9% vs 18.4%) and overall pain relief efficiency (81.0% vs 53.1%; $P < 0.001$ for both) compared with the control group. At post-treatment 2 and 4 weeks, the observation group demonstrated greater reductions in NRS, VAS, and BPI pain scores, lower anxiety and depression scores, and higher KPS and quality-of-life scores (all $P < 0.001$). Adverse events were comparable between the two groups ($P > 0.05$). Conclusion: Compared with verapamil alone, combined therapy of verapamil and venlafaxine significantly relieves pain, improves psychological outcomes, and enhance patients' quality of life without increasing adverse events. These findings support its potential as an effective and well-tolerated adjunctive strategy for cancer pain management.

Keywords: Verapamil, venlafaxine, cancer pain, combined therapy, pain management

Introduction

Among patients with malignancies, cancer-related pain represents a major factor affecting their quality of life and overall well-being. Approximately 30-50% of cancer patients experience pain, and this proportion may increase to 70-90% in those with advanced disease [1]. Nociceptive pain caused by tissue injury and neuropathic pain caused by nerve injury due to tumor invasion or the process of cancer treatment and other complications, are the two major types of pain [2, 3]. Despite different modes of treatment of cancer pain such as opioids, non-opioid pain killers, and adjuvants, a substantial proportion of patients still experience poor pain control. Opioids remain the cornerstone of cancer pain therapy; however, their long-term administration is often limited by tolerance, dependence, and complications such as constipation, vomiting and sleepiness [4]. Additionally, the opioids are less effective in managing neuropathic pain [5]. Thus, there is an urgent need for novel adjunctive treatments that target alternative pain pathways and reduce the dependence on opioids.

Like other adjuvant treatments for cancer pain, calcium channel blockers and antidepressants have shown promise in pain control in cancer patients by targeting the multidimensional nature of pain. Verapamil is one of the most common calcium channel blockers and is mainly used in management of hypertension and arrhythmia. Evidence has emerged to support its application in pain management [6]. The central action of verapamil involves blocking calcium influx, which reduces neuronal excitability

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and modulates neurotransmitter release [7, 8], thereby alleviating neuropathic pain. Studies have shown that verapamil may serve as a valuable adjunct to existing analgesics to enhance pain management and reduce opioid dose, offering an alternative to conventional pain management strategies [9-11]. In addition, the antidepressant, venlafaxine, a representative of serotonin-norepinephrine re-uptake inhibitors (SNRI), has demonstrated efficacy in managing neuropathic pain [12]. Venlafaxine exerts its analgesic effect by augmenting the signaling of serotonin and norepinephrine within the brain and spinal cord, thereby affecting the pain pathways and enhancing pain tolerance [13]. Clinical trials have confirmed its effectiveness in relieving various neuropathic pain, including cancer-related pain [14]. Besides its analgesic properties, venlafaxine is also used in the treatment of depression, a common comorbidity in cancer patients [15]. Its dual action on both mood and pain perception makes it particularly advantageous for cancer patients who experience both physical and psychological pain.

Given their complementary mechanisms of action, the combination of verapamil and venlafaxine may serve as a new modality in the treatment of cancer pain, especially in patients with both nociceptive and neuropathic pain symptoms. Verapamil, with its calcium-channel-blocking effect, may reduce neuronal excitability and thereby alleviate pain. Venlafaxine, by modulating serotonin and norepinephrine pathways, further enhances analgesia while simultaneously improving mood and psychological well-being. Combing these two drugs may offer synergistic effects by addressing multiple dimensions of cancer-related pain. Although each drug individually has demonstrated benefits in pain management, evidence supporting their concurrent use remains limited. Hence, it is of great importance to investigate the therapeutic benefits and potential risks of this combined regimen, especially in cancer patients with advanced or complex pain syndromes.

This study aims to assess the effectiveness of combining verapamil and venlafaxine in the management of cancer-related pain, with a focus on pain intensity, opioid consumption, quality of life, and adverse events. Specifically, this study investigated whether the addition of verapamil to venlafaxine therapy could provide superior analgesic benefits compared with verapamil alone, and whether such combination therapy could help reduce opioid dependence among cancer patients.

Methods

Case selection

This retrospective analysis included 203 patients with cancer pain who sought treatment at our institution between March 2022 and March 2025. Patients were divided into two groups based on their treatment regimen: the control group (n = 98), which received verapamil alone, and the observation group (n = 105), which received a combination of verapamil and venlafaxine. The flowchart of patient inclusion is shown in **Figure 1**. Ethical approval for this study was granted by the institutional review board of West China School of Public Health and West China Fourth Hospital.

Inclusion criteria: (1) a confirmed diagnosis of malignancy with cancer-related pain [16], (2) at least one month of cancer pain management, (3) age ≥ 18 years, and (4) availability of complete clinical records. Exclusion criteria: (1) severe hepatic or renal dysfunction (e.g., liver cirrhosis or renal failure), (2) uncontrolled psychiatric disorders (e.g., schizophrenia or severe mood disorders), (3) patients with a life expectancy of less than three months due to advanced cancer, (4) prior history of significant allergic reactions to verapamil or venlafaxine, (5) active substance abuse or addiction, or (6) patients who were pregnant or breastfeeding.

Interventions

Patients in the control group were administered verapamil (Isoptin SR, Novartis, Switzerland; product code: 025A101) at a standard dosage of 80 mg twice daily. This regimen was selected based on its established safety profile and clinical evidence of potential analgesic effects through calcium channel blockade. In the observation group, patients received the same verapamil regimen (80 mg twice daily) in combination with venlafaxine (Effexor XR, Pfizer, USA; product code: 215340) at a dose of 75 mg once daily. Venlafaxine, a SNRI, was chosen

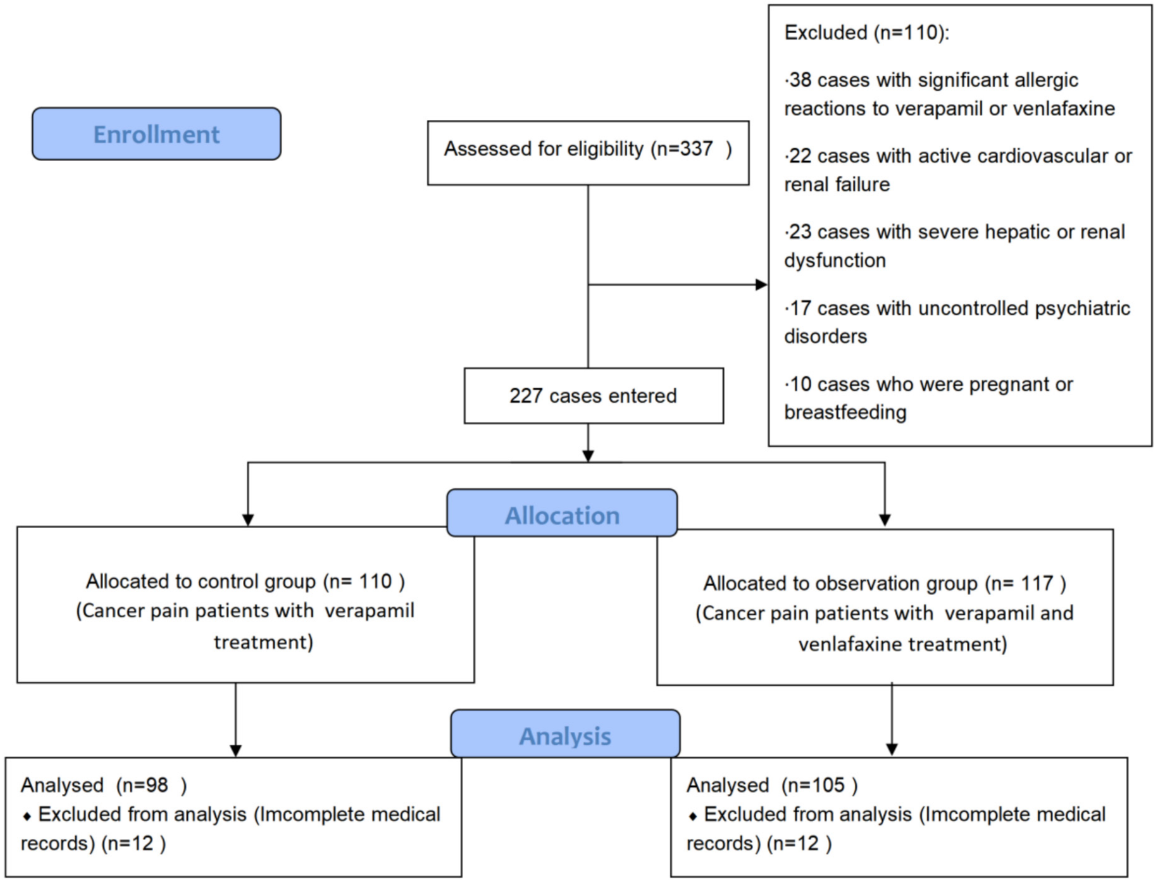

Figure 1. Flow diagram detailing patient selection in this study.

for its dual efficacy in alleviating neuropathic pain and improving psychological symptoms such as anxiety and depression, which frequently coexist in patients with cancer pain.

Both groups continued their assigned treatment regimen for a total of 4 weeks, which was chosen to ensure adequate therapeutic exposure while minimizing the risk of disease progression or treatment intolerance. All patients received routine supportive care according to institutional protocols, including opioid or non-opioid rescue analgesics when clinically indicated. Concomitant medications unrelated to pain or psychological management (e.g., antihypertensives, antiemetics) were permitted, provided they did not interfere with the study drugs. Medication adherence was monitored through inpatient records or outpatient prescription tracking, and any dose adjustments or discontinuations were documented with the reasons specified (e.g., adverse events, patient preference, or clinical judgment). The safety profile of both regimens was assessed by recording treatment-emergent adverse reactions, such as nausea, vomiting, dizziness, fatigue, constipation, dry mouth, headache, and insomnia, at each follow-up visit.

Data collection

The primary outcome of this study was pain relief efficiency at the end of treatment, evaluated using three validated pain assessment instruments: the Numeric Rating Scale (NRS), the Visual Analogue Scale (VAS), and the Brief Pain Inventory (BPI). The NRS is a self-reported 0-10 scale where 0 represents no pain and 10 indicates the worst imaginable pain. The VAS consists of a 10 cm continuous scale with the same anchors. Both scales are widely applied in routine oncology practice to quantify pain intensity within a short timeframe [17, 18]. The BPI measures both pain severity and its interference with daily functioning across domains including mood, mobility, work, and social activity [19]. To capture both short-and medium-term outcomes, all scales were administered at baseline, 2 weeks, and 4 weeks after treatment initiation.

Secondary outcomes included psychological and functional assessments using the Hospital Anxiety and Depression Scale (HADS), the Generalized Anxiety Disorder 7 (GAD-7) scale, the Karnofsky Performance Status (KPS), and the Quality of Life (QOL) scale [20-23]. Higher scores on KPS and QOL reflected better functional and overall well-being, while higher HADS and GAD-7 scores indicated greater psychological distress. Adverse events-including nausea, vomiting, dizziness, fatigue, constipation, dry mouth, headache, and insomnia-were monitored and documented at each assessment point.

Due to the retrospective nature, all scale data were extracted from the hospital's electronic medical record (EMR) system, which routinely records standardized pain and psychological evaluations for cancer patients under the institutional palliative care protocol. These assessments were systematically performed by trained oncology nurses and clinical psychologists at each follow-up visit. Data extraction was conducted independently by two researchers following a double-entry verification process, and any discrepancies were resolved through cross-checking the original patient charts. Cases with missing data across all three timepoints were excluded. This standardized and audited extraction process ensured that the dataset was complete, accurate, and reliable, thereby maintaining the authenticity and scientific rigor of the study findings.

Statistical analysis

Statistical analyses were conducted using SPSS 26.0. Continuous variables were presented as means ± standard deviations. For comparisons involving continuous data collected at multiple time points (such as pain, psychological, and quality-of-life scores at baseline, week 2, and week 4), repeated measures ANOVA followed by the LSD post-hoc test was used. For other continuous variables, independent t-tests or Mann-Whitney U tests were applied, as appropriate. Categorical variables were expressed as frequencies and percentages, and comparisons were performed using the chi-square test. A p-value of < 0.05 was considered statistically significant. All statistical tests were two-sided, and 95% confidence intervals (CIs) were calculated for the odds ratios (OR).

Results

Baseline characteristics

The distributions of age (P = 0.984), sex (P = 0.984), and BMI (P = 0.518) were comparable between the two groups, indicating balanced baseline demographic characteristics. In addition, clinical profiles, including baseline pain severity (P = 0.058) and duration (P = 0.303), cancer type (solid vs. hematologic; P = 0.794), cancer stage (P = 0.658), and educational background (P = 0.752) did not differ between groups. Comorbid conditions (P = 0.682), use of opioids (P = 0.881), patterns of opioid type (P = 0.831) and dose category (P = 0.976), as well as functional status assessed by the KPS (P = 0.719), were likewise statistically insignificant (**Table 1**). These results confirm that the two groups were comparable at baseline, thereby minimizing potential confounding factors and ensuring the reliability of subsequent efficacy analyses.

Clinical efficacy

The observation group exhibited a markedly higher proportion of patients achieving significant pain relief (42.9% vs. 18.4%, P < 0.001). In contrast, ineffective pain relief was significantly more common in the control group (45.9% vs. 19.0%, P < 0.001). Although the rates of effective pain relief were comparable between the two groups (38.1% vs. 35.7%, P = 0.725), the overall pain relief efficiency was substantially higher in the observation group, reaching 81.0% compared with 53.1% in the control group (P < 0.001) (**Table 2**).

Cancer-related pain evaluations

At baseline, there were no significant differences in pain scores between the two groups. However, after 2 weeks and 4 weeks of treatment, the observation group showed a superior reduction in pain, with the NRS, VAS and BPI scores dropping more significantly than in the control group (P < 0.001) (**Figure 2**).

Table 1. Comparison of baseline characteristics between the two groups of patients

Characteristic	Control Group (n = 98)	Observation Group (n = 105)	t/X^2	*P*-value
Age (years, Mean ± SD)	58.56 ± 11.35	58.59 ± 9.70	0.020	0.984
Sex			0.002	0.984
Male	54	58		
Female	44	47		
BMI (kg/m^2)	23.79 ± 3.21	24.09 ± 3.28	0.648	0.518
Pain Score (VAS)	6.55 ± 1.24	6.89 ± 1.27	1.904	0.058
Duration of Pain (months)	9.87 ± 2.45	10.25 ± 2.77	1.033	0.303
Cancer Type			0.068	0.794
Solid	78	82		
Hematologic	20	23		
Education			0.100	0.752
≤ High school	60	62		
> High school	38	43		
Cancer Stage (Stage III/IV)			0.196	0.658
Stage III	39	45		
Stage IV	59	60		
Comorbidities			0.168	0.682
Yes	42	48		
No	56	57		
Use of Opioids			0.022	0.881
Yes	70	74		
No	28	31		
Type of Opioid Used			0.371	0.831
Morphine (%)	35 (35.7%)	38 (36.2%)		
Oxycodone (%)	22 (22.4%)	25 (23.8%)		
Fentanyl (%)	13 (13.3%)	11 (10.5%)		
Average Daily Morphine Equivalent (MME, mg/day, Mean ± SD)	43.51 ± 15.55	40.66 ± 16.90	1.248	0.214
Opioid Dose Category			0.048	0.976
Mild (< 30 mg/day)	24 (24.5%)	25 (23.8%)		
Moderate (30-60 mg/day)	31 (31.6%)	34 (32.4%)		
High (> 60 mg/day)	15 (15.3%)	15 (14.3%)		
Karnofsky Performance Score (KPS)	75.00 ± 6.44	74.63 ± 7.72	0.361	0.719

Table 2. Comparison of clinical efficacy at four weeks post-treatment between the two groups

Parameter	Control Group (n = 98)	Observation Group (n = 105)	X^2	*P*-value
Significant Relief (n, %)	18 (18.4%)	45 (42.9%)	14.204	< 0.001
Effective Relief (n, %)	35 (35.7%)	40 (38.1%)	0.123	0.725
Ineffective Relief (n, %)	45 (45.9%)	20 (19.0%)	16.814	< 0.001
Pain Relief Efficiency (%)	53.1%	81.0%	17.917	< 0.001

Anxiety and depression status

At baseline, there were no significant differences in anxiety or depression scores between the two groups, indicating comparable initial conditions. However, after 2 weeks and 4 weeks of treatment, the observation group demonstrated significantly lower anxiety and depression scores compared to the control group ($P < 0.001$) (**Figure 3**).

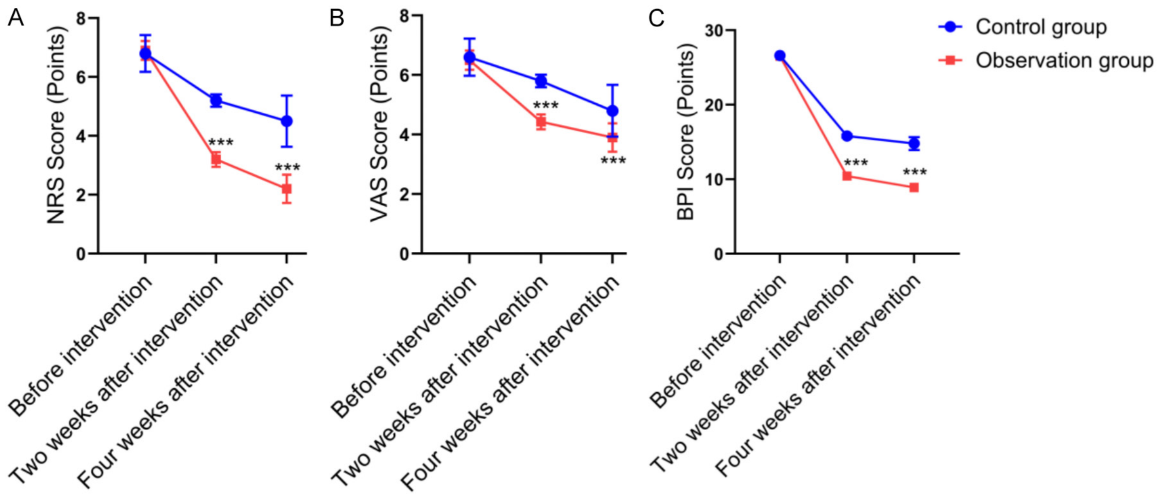

Figure 2. Comparison of pain between the two groups. (A) NRS, (B) VAS, (C) BPI. Compared to the control group, ***P < 0.001. Notes: NRS: Numeric Rating Scale; VAS: Visual Analogue Scale; BPI: Brief Pain Inventory.

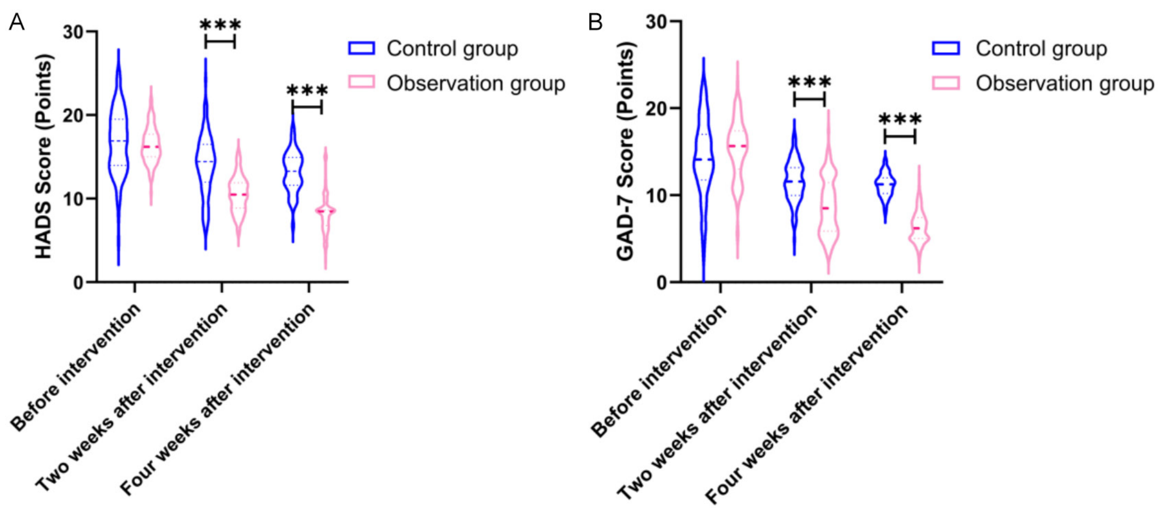

Figure 3. Comparison of anxiety and depression status between the two groups. A. HADS; B. GAD-7. Compared to the control group, ***P < 0.001. Notes: HADS: Hospital Anxiety and Depression Scale; GAD-7: Generalized Anxiety Disorder 7.

Quality of life scores

As shown in **Figure 4**, after 2 weeks and 4 weeks of treatment, the observation group demonstrated significantly higher KPS and QOL scores compared to the control group (P < 0.001).

Adverse reactions

The incidence of side effects, such as nausea, vomiting, dizziness, fatigue, demonstrated no significant differences between the two groups (P > 0.05) (**Table 3**).

Discussion

In this retrospective study, the combination of venlafaxine (an SNRI) and verapamil (a calcium channel blocker) demonstrated superior overall outcomes in cancer pain management compared with verapamil monotherapy. Patients receiving the combined regimen experienced higher rates of pain relief, greater reductions in pain intensity, and significant improvements in psychological well-being and quality of life, without an increase in adverse effects. These results highlight the synergistic potential of targeting both nociceptive and neuropathic mech-

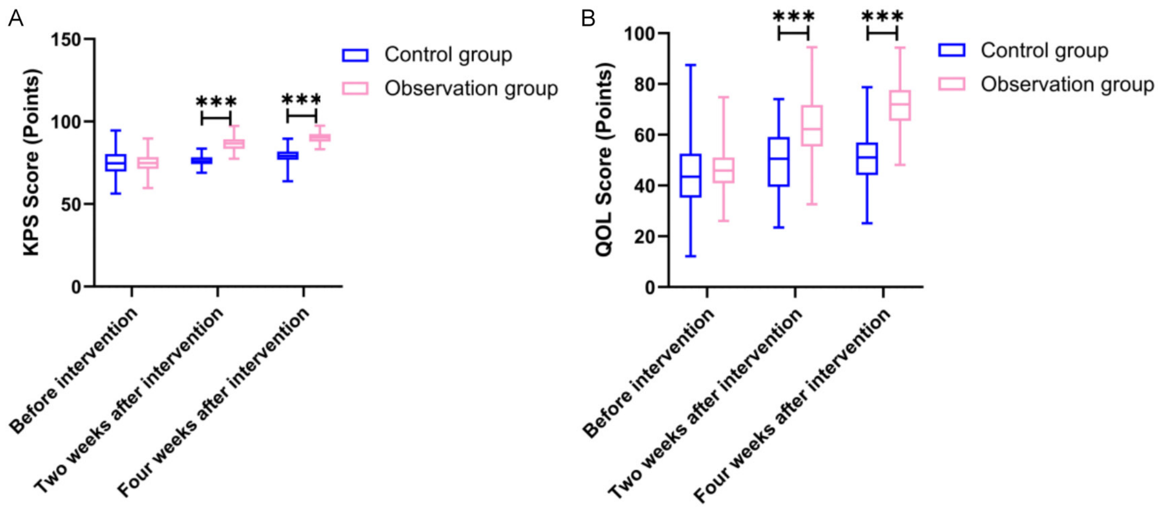

Figure 4. Comparison of quality of life between the two groups. (A) KPS, (B) QOL. Compared to the control group, ***P < 0.001. Notes: KPS: Karnofsky Performance Status; QOL: Quality of Life.

Table 3. Comparison of adverse reactions between the two groups

Parameter	Control Group (n = 98)	Observation Group (n = 105)	X^2	*P*-value
Nausea (%)	16 (16.3%)	18 (17.1%)	0.024	0.876
Vomiting (%)	8 (8.2%)	10 (9.5%)	0.116	0.733
Dizziness (%)	12 (12.2%)	13 (12.4%)	0.001	0.976
Fatigue (%)	18 (18.4%)	20 (19.0%)	0.015	0.901
Constipation (%)	10 (10.2%)	11 (10.5%)	0.004	0.949
Dry Mouth (%)	5 (5.1%)	7 (6.7%)	0.223	0.637
Headache (%)	7 (7.1%)	8 (7.6%)	0.017	0.897
Insomnia (%)	12 (12.2%)	14 (13.3%)	0.054	0.817
Rash (%)	6 (6.1%)	5 (4.8%)	0.183	0.669
Appetite Loss (%)	9 (9.2%)	10 (9.5%)	0.007	0.934
Sweating (%)	4 (4.1%)	5 (4.8%)	0.055	0.814
Total Incidence (%)	107.3%	115.2%	-	-
Patients with ≥ 1 Adverse Reaction (%)	60 (61.2%)	65 (61.9%)	0.010	0.921

Footnote: The total incidence is the sum of the percentages of individual adverse reactions. Percentages may exceed 100% because some patients experienced multiple adverse reactions. No *P*-value is provided for the total incidence, as it is a summary statistic.

anisms while addressing the emotional dimensions of cancer pain.

Mechanistically, venlafaxine likely modulates neuropathic pain by enhancing serotonin and norepinephrine transmission [24], while verapamil inhibits calcium-dependent pain signaling pathways [25]. Previous studies have shown that calcium channel blockers can enhance analgesia, such as verapamil potentiating morphine's effects in experimental pain models and nimodipine reducing morphine requirements in cancer pain [26]. These findings highlight the potential of a multi-mechanistic approach targeting both nociceptive and neuropathic pain components, offering a promising strategy for managing complex cancer pain syndromes.

In addition to analgesia, the combination treatment regimen was more effective in reducing psychological complaints. Such findings are not a surprise, given that venlafaxine functions as an antidepressant and an anxiolytic. It highlights the dual advantage of combining an SNRI into cancer pain management: relieving anxiety while reducing pain. This is particularly relevant in cancer pain, where the relationship between pain and psychological well-being is particularly strong, and where the effects of depression and anxiety in increasing pain intensity are well established [27]. By improving mood, venlafaxine may indirectly improve pain coping and reduce the degree of pain experienced through psychological and behavioral mechanisms. Conversely, verapamil has no psychotropic effects; therefore, patients in the monotherapy arm did not experience comparable improvements in anxiety or depression.

Clinical recommendations also support this rationale. For instance, guidelines suggest considering SNRI such as venlafaxine or duloxetine for cancer patients with neuropathic pain and depression/anxiety [28]. However, in an earlier study of venlafaxine for neuropathic pain in breast cancer survivors, no significant improvement in mood was observed, possibly due to a short 10-week follow-up period or insufficient statistical power [29]. Our study showed evident anxiolytic/anti-depressant effects within 4 weeks of combined treatment. This may be attributable to higher baseline anxiety/depression scores in our cohorts or enhanced mood secondary to better pain control. Clinically, the alleviation of anxiety and depression is essential, as psychological improvement often reinforces reductions in pain intensity. Patients with lower psychological distress tend to sleep better, engage more actively in therapies, and report less pain interference. Therefore, the mental health benefits observed with combination therapy represent an important added benefit.

The present study also has some limitations. First, the sample size was small, and follow-up period was short (only 4 weeks), limiting the ability to assess long-term efficacy and safety. Second, the absence of a placebo or a standardized opioid control group prevents direct comparison with conventional cancer pain management methods. Third, patient selection may have impacted the generalizability of the findings; many participants may have neuropathic pain or baseline psychological distress, making them more responsive to SNRIs. Fourth, the study design was not completely blinded, which may have introduced the potential for expectation bias in self-reported results. Fifth, although the mechanistic rationale for verapamil is promising, it is not commonly employed as an analgesic, and its application to pain relief should be further confirmed through pharmacological study.

Conclusion

Verapamil in combination with venlafaxine produces a more favorable therapeutic effect for cancer pain than verapamil alone, as the combination offers greater pain relief, improved mood and anxiety control, and increased quality of life, without conferring additional toxicity. The combination of these two agents is based on their complementary mechanisms of action: one reduces nociceptive pain transmission by blocking calcium channels and the other relieves neuropathic pain and psychological distress due to SNRI action, therefore more effectively addressing the multifactorial nature of cancer pain.

Disclosure of conflict of interest

None.

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