Randomized Control Trial

The Efficacy and Safety of Pregabalin Combined with Venlafaxine in Fibromyalgia Patients: Protocol for a Prospective, Randomized, Open-Label, Blinded-Endpoint Trial

Minying Liu, MD[1], Ruilin He, MD[2], Likui Wang, MD[3], Jian Cui, MD[4], Daying Zhang, MD[5], Bifa Fan, MD[6], Fang Luo, MD, PhD[1], and Shuiqing Li, MD, PhD[7]

From: [1]Department of Pain Management, Beijing Tiantan Hospital, Capital Medical University, Beijing, PR China; [2]Department of Pain Management, Second Affiliated Hospital of Guangxi Medical University, Nanning, Guangxi, PR China; [3]Department of Pain Management, First Affiliated Hospital of Anhui Medical University, Hefei, PR China; [4]Department of Pain Management, First Affiliated Hospital of Army Medical University, Chongqing, PR China; [5]Department of Pain Management, First Affiliated Hospital of Nanchang University, Nanchang, PR China; [6]Department of Pain Management, China-Japan Friendship Hospital, Beijing, PR China; [7]Department of Pain Management, Peking University Third Hospital, Beijing, PR China

Address Correspondence:
Fang Luo, MD, PhD
Department of Pain Management, Beijing Tiantan Hospital, Capital Medical University, PR China
No.119, Nansihuan Xilu, Fengtai District, Beijing, PR China 100070
E-mail: 13611326978@163.com

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Background: Fibromyalgia (FM) is a chronic condition characterized by widespread pain and a range of somatic and psychological symptoms that impose a substantial burden on patients. While pregabalin is an approved and effective monotherapy for many individuals with FM, the efficacy of this medication is often incomplete, particularly for symptoms like fatigue and anxiety. Combination therapy incorporating selective serotonin and norepinephrine reuptake inhibitors (SNRIs), such as duloxetine, has shown promise for enhancing therapeutic outcomes. Venlafaxine, an SNRI with demonstrated efficacy as an FM treatment, has a distinct pharmacological mechanism from pregabalin. However, the synergistic potential of pregabalin and venlafaxine in combination has not been formally evaluated.

Objectives: This study protocol describes a trial designed to test the hypothesis that the combination of pregabalin and venlafaxine is superior to pregabalin monotherapy in providing pain relief to patients with FM.

Study Design: This is a multicenter, prospective, randomized, open-label, blinded-endpoint study.

Setting: This study will be conducted at 7 different hospitals.

Methods: We will recruit 750 adults with a diagnosis of FM and moderate-to-severe pain. Patients will be randomly assigned in a one-to-one ratio to receive either pregabalin monotherapy or combination therapy consisting of pregabalin and venlafaxine for 12 weeks. Both groups will follow a flexible, forced-titration schedule to achieve the maximum tolerated dose. While the patients and treating physicians will be aware of the treatment allocation, the outcome assessors will remain blinded.

Results: The primary outcome is the mean daily pain intensity at week 4, measured on an 11-point numeric rating scale. Secondary outcomes will be evaluated at baseline and at weeks one, 2, 4, 8, and 12 after the treatment initiation. Secondary outcomes include the worst pain intensity, the responder rates (≥ 30% and ≥ 50% pain reduction), the dose of pregabalin and/or venlafaxine, the Revised FM Impact Questionnaire, the Brief Pain Inventory severity and interference subscales, the 36-Item Short Form Survey (SF-36), the Medical Outcomes Study Sleep Scale, the Beck Depression Inventory-II, and adverse events (AEs) occuring throughout the study. Statistical analyses will be performed on the modified intention-to-treat population.

Limitations: An open-label design will be employed, with patient follow-up limited to 12 weeks.

Conclusion: If the combination of pregabalin and venlafaxine proves to be more effective and better tolerated than pregabalin monotherapy, the combination therapy could establish a new standard of care for FM patients who struggle to achieve sufficient pain relief through nonpharmacological therapies.

Key words: Fibromyalgia, pregabalin, blinded-endpoint, venlafaxine

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Building and Continuing Education Center Cancer Pain Management (No. PMT1001-1). The trial registration was done at ClinicalTrials.gov (NCT07186751) in September 2025. This study was approved by the Institutional Review Board of Beijing Tiantan Hospital, Capital Medical University (KY2025-217-03) and other center's local institutional review board. All patients provided written informed consent prior to enrollment. This study was conducted in accordance with the criteria set by the Declaration of Helsinki. Findings from this study will be disseminated through peer-reviewed journals and presentations at scientific conferences.

Conflict of interest: Each author certifies that he or she, or a member of his or her immediate family, has no commercial association (i.e., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted article.

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Fibromyalgia (FM) is a chronic condition characterized by a multifaceted symptom profile, including widespread pain, fatigue, sleep disturbance, cognitive impairment, and somatic symptoms (1). The condition is a common cause of chronic widespread pain, affecting approximately 1.2% to 5.4% of the general population, and the prevalence increases with age (2). FM places a substantial burden on individuals, manifesting in elevated health care costs, reduced productivity, and even significant disability (3).

The management of FM involves a multimodal approach, as recommended by the European League Against Rheumatism (4). Initial treatment emphasizes patient education and physical therapy, often supplemented by nonpharmacological interventions such as cognitive behavioral therapy and mindfulness-based approaches. Exercise is highlighted consistently as a central element of care, encompassing graded aerobic and strengthening activities (e.g., walking), as well as low-impact mind-body modalities such as yoga, Pilates, and tai chi. When these measures fail to provide sufficient symptom relief, management is often escalated to include psychotherapy and pharmacological treatment. Current pharmacological options for managing FM include antidepressants (5,6), anticonvulsants (7,8), and muscle relaxants (9,10), among others. The United States Food and Drug Administration has currently approved 4 pharmacological agents for the management of FM: pregabalin, duloxetine, milnacipran, and sublingual cyclobenzaprine (11,12).

Pregabalin, an anticonvulsant that serves as a ligand for the $\alpha 2\delta$ subunit of voltage-gated calcium channels, exerts its analgesic effect by reducing presynaptic neurotransmitter release and postsynaptic excitability (13). This medication is the only anticonvulsant approved by the United States Food and Drug Administration for the treatment of FM (14). Clinical studies have demonstrated the efficacy of pregabalin in alleviating pain intensity for approximately 40% of patients with FM and in improving sleep disturbance (15-17). Furthermore, the effects of pregabalin on fatigue, anxiety, and overall quality of life remain limited (7), highlighting the need for exploring strategies to enhance comprehensive symptom relief, such as combination medication therapy.

Meanwhile, duloxetine is a well-established FM treatment (6) that has received approval from the United States Food and Drug Administration and been studied extensively (18,19), including in combination with pregabalin (20). A randomized controlled trial reported that combining pregabalin with duloxetine reduced pain intensity scores by 35.1%, compared to a reduction of only 12.3% seen in association with pregabalin monotherapy (20). However, up to 35.1% of the patients experienced drowsiness during the titration of combination medication (20). These findings underscore the need to explore the practice of combining pregabalin with alternative medications to enhance treatment efficacy.

Venlafaxine, like duloxetine, is a selective serotonin and norepinephrine reuptake inhibitor (SNRI). Both agents are thought to modulate FM-caused pain by enhancing serotonin and norepinephrine signaling in descending pain pathways, thereby influencing central pain processing (6). Beyond FM, SNRIs, particularly duloxetine, have also shown analgesic benefits in patients with chronic musculoskeletal conditions such as chronic low back pain and osteoarthritis-related knee pain, supporting a broader role for these medications in centrally mediated pain modulation (21-23). Despite their shared classification, however, duloxetine and venlafaxine differ in monoamine transporter engagement. Venlafaxine exhibits dose-dependent monoamine transporter selectivity, acting predominantly as a selective serotonin reuptake inhibitor at its minimal effective dose (75 mg/d), and showing dual inhibition of serotonin and norepinephrine reuptake at higher doses (approximately $\geq$ 150 mg/d) (24-26). In contrast,

duloxetine generally demonstrates a comparatively more balanced dual-reuptake profile across therapeutic doses. Consistent with this finding, in vitro binding data indicate that duloxetine binds the serotonin transporter and norepinephrine transporter with a norepinephrine-to-serotonin inhibition constant ratio of approximately 9, whereas venlafaxine shows a norepinephrine-to-serotonin inhibition constant ratio of approximately 30, indicating a relatively greater serotonin transporter preference for venlafaxine (27). In clinical practice, the labeling for special populations also differs between the 2 agents. Clinicians are recommended to avoid administering duloxetine in cases of chronic liver disease/cirrhosis or those of severe renal impairment (GFR/CrCl < 30 mL/min), whereas venlafaxine provides dose-adjustment guidance in hepatic or renal impairment (28,29).

Several clinical studies have investigated the effects of venlafaxine on patients with FM, reporting improvements in pain intensity (6,30,31). A previous trial reported that patients receiving venlafaxine experienced significantly reduced (approximately 36.4%) pain intensity and improvements in their total scores on the FM Impact Questionnaire (32). Additionally, an open-label clinical trial of 11 FM patients suggested that venlafaxine could enhance sleep quality, fatigue, and overall quality of life (31). However, there are currently no trials investigating the combination of pregabalin and venlafaxine in FM patients.

Given the distinct pharmacological mechanisms of pregabalin and venlafaxine, we will conduct a multicenter, prospective, randomized, pregabalin-controlled, open-label, blinded-endpoint study to test the hypothesis that the combination of pregabalin and venlafaxine may offer greater pain relief than pregabalin monotherapy for FM patients.

Methods and Analysis

Objective

The aim of this study is to compare the efficacy of combining pregabalin with venlafaxine to that of pregabalin monotherapy as a form of treatment for FM.

Setting

Patients will be recruited from the departments of pain management of 7 different hospitals. All researchers will be trained using the same training protocol. This study is scheduled to start in September 2025 and is expected to conclude after a duration of 3 years.

Trial Design

This trial is a multicentric, prospective, randomized, open-label, blinded-endpoint (PROBE) study, designed to evaluate whether the combination of pregabalin and venlafaxine may offer greater pain relief than pregabalin monotherapy for FM patients. In total, 750 patients will be recruited from 7 different hospitals all over China. The study protocol was approved by the Institutional Review Board of Beijing Tiantan Hospital, Capital Medical University (KY2025-217-03) and the local ethics committee at all participating centers. This trial will be conducted in full accordance with the principles of the Declaration of Helsinki. The study was prospectively registered at ClinicalTrials.gov (NCT07186751) on September 2025 (www.clinicaltrials.gov/study/NCT07186751?term=NCT07186751&rank=1). The timeline and detailed schedule of the study are summarized in Table 1.

Recruitment and Informed Consent

Patients will be prospectively recruited from the pain management departments of participating centers. Attending physicians will identify potential candidates diagnosed with FM and screen them for eligibility based on the predefined inclusion and exclusion criteria.

Prior to randomization, the investigators will obtain written informed consent from all eligible patients. The consent form will describe the study objectives, procedures, and potential benefits and risks. The investigators will provide a clear explanation of the study and allow adequate time for the patients to review the information and ask questions. Consent will be signed voluntarily, with the assurance that patients may withdraw at any time without consequences for their ongoing medical care.

Eligibility Criteria

Inclusion Criteria

1. Diagnosed with FM in line with the 2016 revisions to the 2010/2011 FM diagnostic criteria (1);
2. Aged more than 18 years;
3. Suffering from moderate to severe FM, with 11-point numeric rating scale (NRS) score of more than 4 at baseline, that has not been effectively alleviated by nonpharmacological treatments or treated with the currently recommended pharmacological method for managing FM;
4. Agreed to sign the informed consent form.

Table 1. *The schedule of enrollment, interventions, and assessments.*

	-1 day	0 day	1 week	2 weeks	4 weeks	8 weeks	12 weeks
Enrollment							
Eligibility screening	✓						
Informed consent	✓						
Allocation		✓					
Intervention							
Pregabalin monotherapy		✓					
Combination therapy		✓					
Assessment							
Baseline data	✓						
Mean daily pain intensity*					✓		
Worst pain intensity			✓	✓	✓	✓	✓
Proportion of responders achieving ≥ 30% and ≥ 50% reduction from baseline in average pain intensity			✓	✓	✓	✓	✓
Dose of pregabalin and/or venlafaxine			✓	✓	✓	✓	✓
Revised FM Impact Questionnaire			✓	✓	✓	✓	✓
Brief Pain Inventory severity			✓	✓	✓	✓	✓
Brief Pain Inventory interference			✓	✓	✓	✓	✓
Short-Form 36 Health Survey			✓	✓	✓	✓	✓
Medical Outcomes Study Sleep Scale			✓	✓	✓	✓	✓
Beck Depression Inventory-II			✓	✓	✓	✓	✓
Adverse events			✓	✓	✓	✓	✓

*Primary outcome. FM, fibromyalgia.

Exclusion Criteria

1. A history of psychiatric disease;
2. Hypersensitivity or contraindications to pregabalin or venlafaxine;
3. Pregnancy or breastfeeding;
4. Presence of serious systemic diseases, including uncontrolled hypertension, uncontrolled diabetes, significant cardiac dysfunction, or chronic hepatic or renal dysfunction;
5. Acute or chronic pain conditions other than FM.

Withdrawal Criteria

1. Failure to follow the research protocol;
2. Experiencing severe adverse events (AEs) during the treatment period.

Randomization and Blinding

Eligible and consenting patients will be randomly assigned in a one-to-one ratio to receive either the pregabalin monotherapy or the combination therapy (pregabalin with venlafaxine). We will use a computer-generated, stratified block randomization sequence (block size of 4), created via a secure online platform (Sealed Envelope Ltd). To account for potential center-related variability, randomization will be stratified by trial site.

The allocation sequence will be concealed using sequentially numbered, sealed envelopes, prepared by a research assistant independent of the clinical team. The designated envelope will be opened only after eligibility confirmation and consent. This study will employ an open-label, blinded-endpoint design. Consequently, while patients and treating investigators will be aware of the treatment assignments, the outcome assessors will remain blinded to group allocation throughout data collection to ensure unbiased assessments of the endpoints.

Intervention

Patients will record their daily pain in pain diaries for the duration of the trial. Baseline daily NRS pain will be recorded in paper diaries for one week.

To minimize confounding variables and isolate the effects of the study interventions, the patients are prohibited from using certain concomitant treatments throughout the 12-week trial period. These include all

analgesic medications (e.g., nonsteroidal anti-inflammatory drugs, acetaminophen, opioids), procedural interventions (e.g., nerve blocks, acupuncture), and any newly initiated programs such as cognitive behavioral therapy or formal exercise regimens.

Eligible patients will be randomized to one of 2 open-label treatment arms: pregabalin monotherapy or combination therapy. Both groups will follow a flexible forced-titration schedule designed to achieve the maximum tolerated dose (MTD) that balances therapeutic efficacy with patient tolerability. Dose titration will be guided by regular weekly calls from research personnel. Generally, in the pregabalin (Lyrica®, Pfizer) monotherapy group, treatment will be initiated at 150 mg/day, administered in 2 divided doses. After 7 days, the dose will be increased to 300 mg/day. Thereafter, based on individual response and tolerability, the dose may be further increased to a maximum of 450 mg/day (33). In the combination therapy group, patients will receive both pregabalin and venlafaxine (Effexor® XR capsules, Pfizer). The dose titration for the pregabalin will be identical to that of the monotherapy group. Concurrently, venlafaxine will be initiated at 75 mg/day. If well-tolerated, the dose may be increased in 75 mg/day increments at weekly intervals, guided by the patient's clinical response and side effects profile, to a maximum dose of 225 mg/day.

AEs will be monitored closely at each study contact. If a patient experiences intolerable AEs at any dose, the dosage of the suspect medication will be reduced to the highest previously tolerated level, which will be defined as the patient's MTD. If AEs are intolerable even at the initial dose, the medication will be discontinued, and the patient will be withdrawn from the trial. In the combination therapy group, any decisions regarding dose modification due to AEs will be made by the treating physician to determine the appropriate adjustment for one or both medications. Patients who achieve satisfactory pain relief will maintain their current effective and tolerable dose.

Follow-up

The study protocol spans 12 weeks and includes a screening visit and 5 subsequent follow-up contacts. Visits are scheduled for the first, second, fourth, eighth, and twelfth weeks. The first-week and second-week visits will be conducted via telephone to monitor the patient for AEs, assess the initial efficacy of the treatment, and guide dose titration. The fourth-, eighth-, and twelfth-week visits will be conducted in an outpatient clinic. These visits will involve a comprehensive clinical evaluation, reassessment of the treatment's efficacy and safety, pill counts to assess the patient's adherence to the regimen, and the administration of all study questionnaires and assessment scales.

Data Management and Quality Assurance

Data will be collected by trained study investigators using standardized case report forms designed specifically for this protocol. To ensure the accuracy and integrity of the data, all information will be entered into a centralized electronic database (EpiData Manager, Version 4.6.0.6, EpiData Association) using an independent double-data entry procedure. Any discrepancies identified during this process will be resolved by referring back to the original source documents.

An independent data- and safety-monitoring committee will be established to oversee the trial. The committee will convene every 6 months to review cumulative safety and validity data, assess the overall conduct of the study, and provide recommendations to the steering committee regarding the continuation, modification, or termination of the trial.

Patient and Public Involvement

There was no patient or public involvement in the development of the research question, study design, or selection of outcome measures. Patients will be recruited by physician referral at the participating clinical sites. The findings of the study will be disseminated to the scientific community through presentations at academic conferences and publication in peer-reviewed journals. A summary of the results will also be made available to patients upon request at the conclusion of the study.

Study Outcomes

Primary Outcome

The primary endpoint for measuring efficacy is the mean daily pain intensity at week 4. This result will be determined by calculating the average pain scores from pain diaries over 7 consecutive days. Patients will rate their average pain intensity using an 11-point NRS, on which 0 indicates no pain and 10 represents the worst imaginable pain.

Secondary Outcomes

All secondary endpoints will be evaluated at baseline and at weeks one, 2, 4, 8, and 12 after the

initiation of the treatment. These outcomes are as follows:

1. Worst pain intensity, which will be derived from the patients' pain diaries collected at the aforementioned follow-up time points.
2. Proportion of responders achieving ≥ 30% and ≥ 50% reduction from baseline in average pain intensity.
3. Dose of pregabalin and/or venlafaxine. At the aforementioned follow-up time points, the researchers will inquire about the current dosages of pregabalin and/or venlafaxine being administered to the patients. Any dose adjustments, interruptions, or discontinuations will be documented in detail, as will the reasons.
4. Revised FM Impact Questionnaire, a 21-item self-reported measure evaluating function, overall impact, and symptoms over the previous week. Scores range from 0 to 100, with higher values indicating greater disease burden.
5. Brief Pain Inventory severity (BPI-S) and interference (BPI-I) scores: The BPI will be used to quantify pain severity (BPI-S subscale) and the extent to which pain interferes with daily function (BPI-I subscale). Both subscales provide a comprehensive assessment of the patient's pain experience beyond a single intensity score.
6. Short-Form 36 Health Survey (SF-36): General health status will be evaluated using the SF-36. This widely used instrument measures 8 domains of physical and mental health, with higher scores representing a better quality of life.
7. Medical Outcomes Study Sleep Scale (MOS-Sleep): Disturbances in sleep, a core symptom of FM, will be evaluated using the MOS-Sleep, a 12-item self-report questionnaire that assesses various aspects of sleep quality and quantity.
8. Beck Depression Inventory-II (BDI-II): The severity of depressive symptoms will be measured with the BDI-II, a 21-item questionnaire on which higher scores correspond to more severe symptomatology.
9. AEs: A treatment-emergent AE is defined as any unfavorable medical occurrence that emerges during treatment and was absent at baseline, or worsens relative to pretreatment status. The onset, severity, and duration of AEs will be recorded in patient diaries and reviewed at each study visit. All reported AEs will be evaluated for severity (mild, moderate, severe, or life-threatening) and causality in relation to study medications.

Statistical Analysis

Sample size calculation was performed using the PASS 11 software (NCSS, LLC). A previous prospective, single-center study compared the respective efficacy of a combination of pregabalin and duloxetine, pregabalin or duloxetine monotherapy, and a placebo in adult patients with FM. The study found that the average pain intensity at the MTD of the pregabalin group was 5.0, while the average pain intensity in the combination pregabalin-and-duloxetine group was 3.7 (20). Based on those results, we assume that the average pain intensity for the pregabalin monotherapy group will be 5.0, and the average pain intensity for the combination therapy group will be 4.5. A sample size of 674 patients (337 per group) is calculated to provide 90% power to detect the between-group difference, with an overall type I error rate of 0.05. To account for a dropout rate of 10%, the total required sample size is 750 patients (375 per group).

SPSS Version 27.0 (IBM Corporation) and R Version 4.6.1 (R Foundation) will be employed to perform the statistical analysis. The conclusion will be determined in line with the intention-to-treat principle, in accordance with the CONSORT guidelines. All analyses will be performed using both the modified intention-to-treat and per-protocol principles. All randomized patients will be included in the efficacy analyses if they have received at least one dose of the study medication and have at least one post-baseline assessment of any efficacy parameter. For the safety population analysis, all randomized patients who receive at least one dose of the study medication will be included.

The primary outcome, along with other continuous variables, will be summarized as the mean (standard deviation) for normally distributed data or median (interquartile range) for skewed data, with normality assessed via the Shapiro-Wilk test. Normally distributed continuous variables will be compared between groups using Student's t-test, while skewed continuous variables will be analyzed with the Mann-Whitney U test. Categorical variables will be presented as counts (percentages) and compared using the Chi-square test or Fisher's exact test. Repeated measurement data will be analyzed using a mixed model for repeated measures, as appropriate. A 2-sided $P < 0.05$ will be considered statistically significant for all analyses.

The primary outcome is the average pain intensity at week 4, calculated as the average diary score during the fourth week. If more than 50% of the daily scores during week 4 are missing, the primary outcome for

that patient will be treated as missing. Missing data for weekly pain intensity will be handled using multiple imputation based on the Markov chain Monte Carlo method.

Additionally, to assess the robustness of the primary outcome to the assumption about missing data, several sensitivity analyses will be performed. In the worst-case scenario, patients in the combination therapy arm who discontinued their participation in the study will be assumed to have unfavorable outcomes, while those in the monotherapy arm who also discontinued their participation in the study will be assumed to have favorable outcomes. The inverse will apply in the best-case scenario.

Furthermore, prespecified subgroup analyses will be performed for the primary outcome based on age, gender, course of FM, baseline pain intensity, and baseline Widespread Pain Index (WPI). A P value < 0.05 for the interaction term will be considered statistically significant to suggest a subgroup effect.

Study Status

The first patient was enrolled in September 2025. As of the submission of this manuscript, the study is in the recruitment phase. Forty patients have been enrolled.

Role of Sponsor

The sponsor had no role in the trial design, trial conduct, data handling, data analysis or writing and publication of the manuscript.

Discussion

This study intends to adopt a designed and implemented randomized controlled method to compare the efficacy and safety of a pregabalin-and-venlafaxine combination to pregabalin monotherapy as a treatment for FM. The aim of this study is to explore a treatment with greater efficacy for FM patients who have found nonpharmacological therapy to be ineffective.

The PROBE study design offers a balance between rigorous methodology and practical feasibility. While blinding is challenging in combination therapy trials due to differences in dosing regimens and side effect profiles, the blinded-endpoint approach helps minimize bias in outcome assessment. By randomizing patients to either combination therapy or pregabalin monotherapy, we aim to generate robust evidence on the incremental benefits of adding venlafaxine to pregabalin, while also exploring potential differences in safety and tolerability.

In this study, the average pain intensity at week 4 as measured on the NRS was selected as the primary outcome because pain remains the hallmark symptom in FM and is central to the burden of disease. The average pain score on the NRS is widely regarded as the gold standard for assessing chronic pain and has been employed in nearly all well-designed FM studies over the past decade (20,34-37).

We also selected the Revised FM Impact Questionnaire as a secondary outcome to capture multidimensional disease burden and treatment-related change in patients with FM, including the categories of function, overall impact, and symptoms. The Revised FM Impact Questionnaire is widely used in FM research and offers practical advantages over the original FM Impact Questionnaire, including updated symptom content, a simplified uniform 0-10 scoring format, and refined wording to enhance usability across diverse populations (38-40). By contrast, the WPI is primarily intended as a diagnostic component to quantify pain distribution and is less commonly applied as a short-term, treatment-responsive outcome measure (41). In keeping with our use of the 2016 revisions to the 2010/2011 American College of Rheumatology FM diagnostic criteria for eligibility and diagnostic characterization, we will collect WPI at baseline and additionally examine WPI in subgroup analyses.

There are several limitations of this prospective study. First, an open-label design, instead of a double-blinded, double-dummy, placebo-controlled, crossover design will be used in this multicenter study due to limited funding. This choice may influence the measurement of outcomes and introduce bias. Second, the follow-up at the twelfth week precludes conclusions about long-term efficacy and safety, particularly regarding cardiovascular risks associated with prolonged SNRIs use. Third, while venlafaxine offers greater dosing flexibility for patients with hepatic or renal impairments than does duloxetine, our study excludes individuals with clinically significant dysfunction in these systems. Consequently, our findings may not be fully generalizable to these special populations. Therefore, future research utilizing larger cohorts, extended observation periods, and alternative SNRI combinations (e.g., desvenlafaxine) is required to refine clinical guidelines and validate the safety of the combined pregabalin and venlafaxine regimen in more diverse, comorbid populations.

Conclusions

Ultimately, the findings from this trial could contribute significantly to the evolving landscape of FM treatment. If the combination of pregabalin and venlafaxine proves to be more effective and better tolerated than pregabalin monotherapy, the former could establish a new standard of care for FM patients who struggle to achieve sufficient pain relief through nonpharmacological therapies. By expanding the pharmacological toolkit for FM management, this trial has the potential to improve the quality of life for patients and reduce the global health burden associated with this chronic pain condition.

Author Contributions

Minying Liu drafted the initial manuscript. Ruilin He, Likui Wang, and Jian Cui were responsible for conceptualizing the trial and revising the initial manuscript. Shuiqing Li and Fang Luo, as the principal investigators, oversaw the study and refined the final manuscript. Daying Zhang and Bifa Fan played a major role in designing the research protocol and will be actively involved in patient follow-up. All authors participated in the critical review and revision of both the study protocol and the manuscript.

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