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STUDY PROTOCOL

Efficacy and Safety of Pregabalin-Tizanidine vs Pregabalin in Patients with Fibromyalgia: Study Protocol for a Multicenter, Prospective, Randomized, Controlled, Open-Label, Blinded Endpoint Trial

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Background: The global prevalence of fibromyalgia (FM) in the general population is estimated to range from 2% to 4%. Pregabalin, a gamma-aminobutyric acid (GABA) analogue, is one of the most widely prescribed medications for FM. However, at therapeutic doses, its limited efficacy and/or unacceptable side effects mean that many patients derive only partial benefit, often leading to treatment discontinuation. Cyclobenzaprine is a centrally acting muscle relaxant. In August 2025, the United States Food and Drug Administration approved a sublingual formulation of cyclobenzaprine hydrochloride for treating FM in adults. However, its availability is largely confined to North America. Tizanidine, like cyclobenzaprine, is also a muscle relaxant with a central mechanism; however, there is no codified posology for FM treatment with tizanidine.

Methods: This study aims to recruit 164 adult patients diagnosed with FM. Participants will be randomly assigned in a 1:1 ratio to either the intervention group (pregabalin plus tizanidine) or the control group (pregabalin monotherapy). The primary outcome is the change from baseline to week 12 in average pain intensity (during the last 7 days) assessed using the first item of the symptom domain of the Revised Fibromyalgia Impact Questionnaire (FIQR). Secondary outcomes, assessed at weeks 4, 8, 12, 16, 20, and 24, will include: widespread pain, symptom severity, functional performance, balance, muscle strength and power, psychological functioning, sleep quality, self-efficacy, treatment durability, and health-related quality of life.

Ethics and Trial Registration: This study was approved by the Institutional Review Board of Beijing Tiantan Hospital (KY2025-217-03-08) and was registered with ClinicalTrials.gov (NCT07382921). All study procedures will be conducted in accordance with the Declaration of Helsinki (1964) and its subsequent amendments (7th revision, Fortaleza, Brazil, 2013).

Conclusion: This trial will provide evidence for the efficacy and safety of pregabalin combined with tizanidine in the treatment of FM.

Keywords: fibromyalgia, pregabalin, tizanidine

Introduction

Fibromyalgia (FM) is a chronic condition characterized by persistent, widespread musculoskeletal pain and tenderness, often accompanied by a constellation of non-pain symptoms.[1,2] These include sleep disturbances, debilitating fatigue, depression, cognitive dysfunction, impaired physical function, and psychological distress.[3] The global prevalence of FM in the general population is estimated to range from 2% to 4%.[1] Compared to other chronic diseases, FM is associated with a higher symptom

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burden, greater healthcare resource utilization, increased work disability, and poorer health-related quality of life. Therefore, effective and safe therapeutic options are urgently needed for this patient population.[4,5]

When non-pharmacological interventions for FM prove insufficient, pharmacological treatment becomes essential. To date, the United States Food and Drug Administration has approved only three drugs specifically for FM: the gabapentinoid pregabalin, and the serotonin-norepinephrine reuptake inhibitors (SNRIs) duloxetine and milnacipran.[6,7] Among these, pregabalin is the most widely prescribed for FM. It exerts its analgesic effects by binding to voltage-gated calcium channels, reducing calcium influx and subsequently inhibiting the release of excitatory neurotransmitters in the central nervous system.[8,9] However, at therapeutic doses, pregabalin often provides only partial relief due to limited efficacy and/or unacceptable side effects (eg, dizziness, somnolence, weight gain and peripheral edema), which frequently lead to treatment discontinuation.[8,10] The joint guidelines from the Canadian Pain Society and the Canadian Rheumatology Association state that "an ideal pharmacological strategy may address multiple symptoms simultaneously and may necessitate a combination of medications." For newly diagnosed patients with FM who do not respond to non-pharmacological interventions and have not yet received guideline-recommended pharmacotherapy, combining pregabalin with non-antidepressant agents may enhance its analgesic effect.[11–13] This hypothesis has prompted clinical trials comparing pregabalin combination therapy with pregabalin monotherapy.

Cyclobenzaprine is a centrally acting muscle relaxant that primarily exerts its effects on specific brain regions, particularly the brainstem. It functions as an antagonist at multiple receptors, including the 5-hydroxytryptamine 2A (5-HT2A), adrenoceptor alpha-2A (ADRA2A), and histamine H1 receptors.[14] This antagonism reduces the excitability of motor neurons and skeletal muscle tone. Additionally, it may help alleviate anxiety, pain, and inflammation. In August 2025, the United States Food and Drug Administration approved a sublingual formulation of cyclobenzaprine hydrochloride for the treatment of FM in adults.[15] A meta-analysis demonstrated that once-nightly sublingual cyclobenzaprine consistently improved pain response and global impression versus placebo. However, Cyclobenzaprine is characterized by anticholinergic effects (dry mouth, constipation, blurred vision), pronounced somnolence, and potential concerns regarding tachycardia and QTc interval prolongation.[16] Given that cyclobenzaprine is currently unavailable outside North America, investigating the efficacy of other muscle relaxants with similar mechanisms of action in FM is of considerable clinical interest.[16,17]

Tizanidine, like cyclobenzaprine, is a centrally acting muscle relaxant. As a centrally acting alpha-2 adrenergic receptor agonist, tizanidine inhibits the release and downstream effects of norepinephrine in the brainstem (eg, the locus coeruleus) and spinal cord.[18,19] It also inhibits the release of excitatory amino acids, such as glutamate and aspartate, from spinal interneurons. Consequently, tizanidine enhances presynaptic inhibition of motor neurons, resulting in skeletal muscle relaxation, as well as sedative and anxiolytic effects.[6,20] A previous open-label, uncontrolled study reported that tizanidine is a useful medication for the treatment of fibromyalgia, with improvements in pain, global assessment, fatigue, and Fibromyalgia Impact Questionnaire (FIQ) scores. However, previous study was limited by methodological shortcomings, including the absence of a control group and short follow-up durations.[21]

Based on this rationale, we will conduct a RCT clinical trial to evaluate the efficacy and safety of pregabalin and tizanidine combination therapy versus pregabalin monotherapy for pain control in patients with FM.

Methods

Objectives

This study aims to evaluate the efficacy and safety of pregabalin-tizanidine combination therapy versus pregabalin monotherapy for pain management and other core symptom domains (eg, depressive symptoms, sleep quality, fatigue, anxiety) in patients with FM. The primary hypothesis is that combination therapy with pregabalin and tizanidine provides superior analgesic efficacy compared to pregabalin monotherapy in patients with FM.

Study Design

This is a multicenter, prospective, randomized, open-label, parallel-group trial with blinded endpoint evaluation (PROBE design) comparing pregabalin-tizanidine combination therapy with pregabalin monotherapy in adults with FM (Figure 1). The trial protocol adheres to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT)

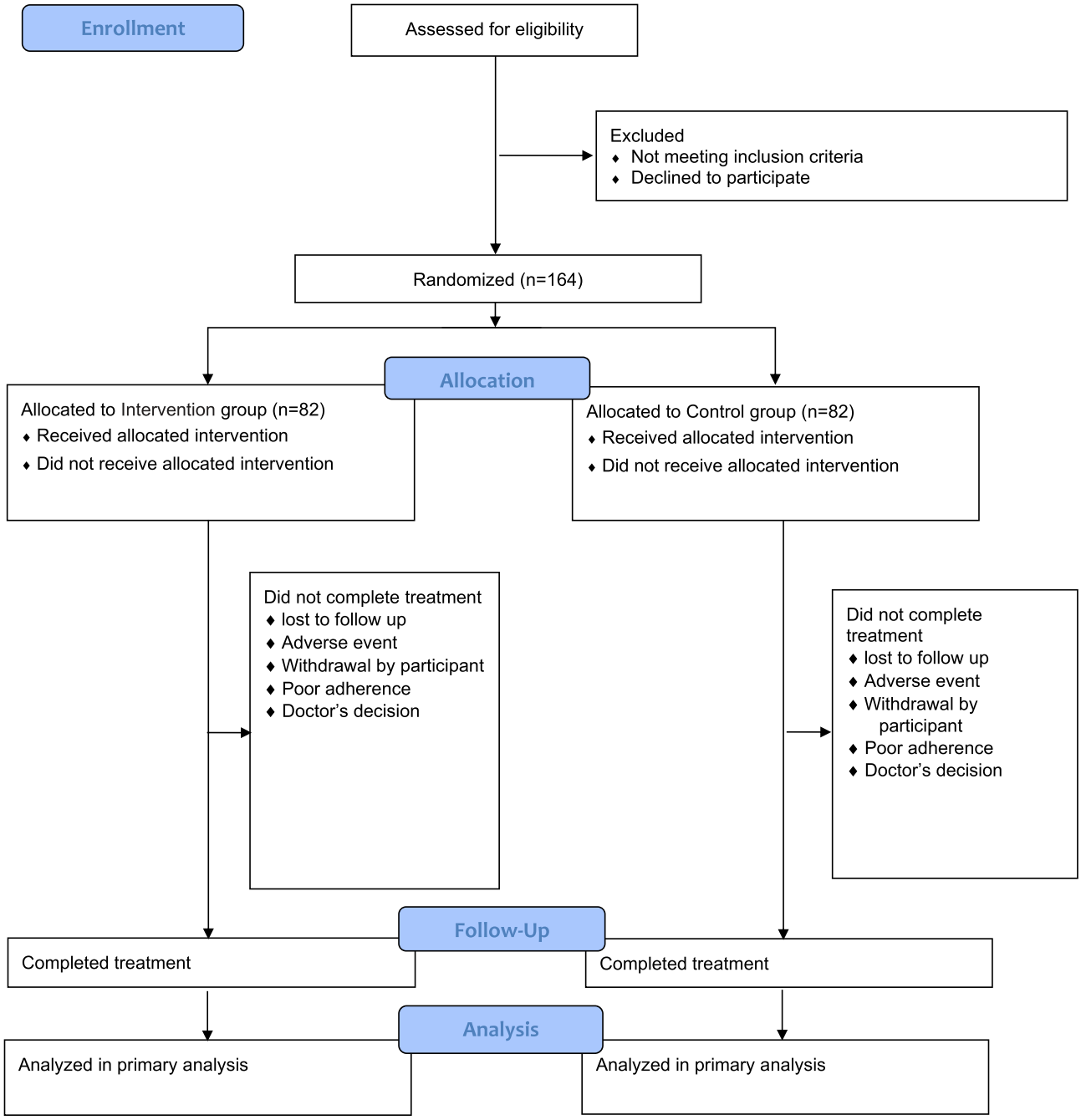

Figure 1 Flowchart of enrollment, allocation, intervention, and assessment.

guidelines.[22] A flexible dose titration will be employed to reach each participant's maximal tolerated dose (MTD). The effects of the two treatments will then be compared using the prespecified primary and secondary outcome measures. The study will be conducted in accordance with the principles of the Declaration of Helsinki. The reporting of this trial will adhere to the Consolidated Standards of Reporting Trials (CONSORT) guidelines and the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement. An overview of the trial procedures is provided in Table 1.

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Table 1 The Schedule of Enrollment, Interventions, and Assessments

	Study Period									
	Enrolment	**Allocation**	**Intervention Period & Follow-Up**							
Time (Week)	−1	0	4	8	12	16	20	24	36	48
Enrollment										
Eligibility screen	✓									
Informed consent	✓									
Demographic data	✓									
Medication history	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Allocation		✓								
Interventions										
Intervention group Tizanidine plus Pregabalin										
Control group Pregabalin										
Assessments										
Baseline data	✓	✓						✓		
Vital tests: blood pressure, weight, height, heart rate		✓	✓	✓	✓	✓	✓	✓		
Safety tests: creatinine, GFR, thrombocyte count, bilirubin, ALT, AST, EKG	✓			✓		✓		✓		
Average pain intensity[a]		✓			✓					
Secondary Outcomes										
Fibromyalgia Impact Questionnaire Revised[b]		✓	✓	✓	✓	✓	✓	✓	✓	✓
Short Form 36 Health Survey		✓	✓	✓	✓	✓	✓	✓	✓	✓
The Patient's Global Assessment		✓	✓	✓	✓	✓	✓	✓	✓	✓
The Beck II Depression Inventory		✓	✓	✓	✓	✓	✓	✓	✓	✓
The Pittsburgh Sleep Quality Index		✓	✓	✓	✓	✓	✓	✓	✓	✓
The Hospital Anxiety and Depression Scale		✓	✓	✓	✓	✓	✓	✓	✓	✓
The Perceived Stress Scale		✓	✓	✓	✓	✓	✓	✓	✓	✓
Widespread Pain Index		✓	✓	✓	✓	✓	✓	✓	✓	✓
Adverse events		✓	✓	✓	✓	✓	✓	✓	✓	✓

Notes: [a]Primary outcome. [b]Weekly assessment. ✓ indicates the scheduled performance of the procedure or assessment at the corresponding visit.
Abbreviation: GFR, Glomerular Filtration Rate.

Study Setting

The trial will be conducted at the Pain Clinic, Beijing Tiantan Hospital, People's Hospital of Xinjiang Uygur Autonomous Region and Sichuan Provincial People's Hospital. For transparency and analytical reproducibility purposes, the dataset and data coding will be deposited in the Open Science Framework.

Recruitment and Informed Consent

Patients diagnosed with FM who have an appointment at the Pain Clinics of Beijing Tiantan Hospital, People's Hospital of Xinjiang Uygur Autonomous Region and Sichuan Provincial People's Hospital will be invited to participate in the study. They will receive written information about the trial from their attending nurse or physician. All eligible candidates will be provided with detailed information regarding the study, including its purpose, the interventions involved, potential benefits, possible risks, and the management of such risks. Given the potential for additive central nervous system depression when pregabalin is co-administered with tizanidine—specifically increased risks of dizziness, somnolence, and orthostatic hypotension—all participants will receive standardized verbal and written counselling regarding these interactions. They will be advised to avoid driving, operating heavy machinery, or activities requiring mental alertness until individual tolerance is established, and to rise slowly from seated or supine positions to reduce the risk of falls from hypotension. Candidates will be given at least one hour to consider their participation. After obtaining written informed consent, the clinician will review the study's eligibility criteria to confirm the participant's suitability. It will be emphasized that participation is entirely voluntary and that consent may be withdrawn at any time without consequence.

Participants

Inclusion Criteria

Patients must meet all of the following criteria before they will be considered for recruitment:

1. Aged 18–65 years.
2. Fulfill the 2016 updated American College of Rheumatology (ACR) diagnostic criteria for FM who have experienced insufficient symptom relief with non-pharmacological treatments and have not previously received guideline-recommended pharmacological treatment for FM.[3,23] Specifically, the diagnosis will be confirmed by the presence of: (1) a Widespread Pain Index (WPI) score ≥7 and a Symptom Severity Scale (SSS) score ≥5, or a WPI of 4–6 and an SSS score ≥9; (2) generalised pain, defined as pain in at least 4 of 5 regions; and (3) symptoms that have been present at a similar level for at least 3 months.
3. Sufficient cognitive function, visual acuity and language skills to complete questionnaires and pain diaries and to participate in telephone communication with study nurses to permit titration of the study drugs.
4. Experienced daily pain (≥4/10 on a numerical rating scale) for at least 3 months.

Exclusion Criteria

Patients will be excluded if they meet any of the following criteria:

1. Presence of a painful condition, including inflammatory rheumatic disease, more than 50% as severe as but distinct from FM.
2. Women who are pregnant or lactating.
3. Women of childbearing potential not using adequate contraceptives.
4. Known mild, moderate or severe hepatic impairment; baseline alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 times the upper limit of normal (ULN); estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m^2 (ie, chronic kidney disease Stage 3 or greater); or any history of drug-induced liver injury.
5. Unstable cardiovascular disease (myocardial infarction within the preceding year, unstable angina, or congestive heart failure) or clinically relevant abnormal 12-lead electrocardiogram.
6. Any poorly controlled medical condition that, in the opinion of the investigator, would interfere with proper conduct of the trial.
7. Severe depression, as determined by a Beck Depression Inventory–II score of 29 or more suicidal ideation, as determined by a Beck Depression Inventory–II item 9 score of 2 or more any current major psychiatric disorder (eg, schizophrenia, bipolar disorder) that is not well controlled.
8. Hypersensitivity to any of the study medications.
9. Any current alcohol or drug abuse or dependence (except nicotine and caffeine).

10. Those taking more than 90 mg morphine equivalents per day.
11. Prior Pharmacotherapy Exclusion: Defined as (i) documented treatment failure (<30% pain reduction or intolerable adverse effects) with ≥2 of the following classes recommended in FM guidelines (pregabalin/gabapentin, serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants) within the past 12 months; (ii) current use of excluded concomitant medications (eg, strong CYP1A2 inhibitors, systemic corticosteroids) that cannot be washed out; or (iii) patient refusal to discontinue current pharmacotherapy.
12. Psychiatric Comorbidity Exclusion: Defined as the presence of an exclusionary psychiatric condition as per protocol criteria (eg, current severe major depressive episode with suicidal ideation, bipolar I disorder, psychotic disorder, substance use disorder within the preceding 6 months) based on medical record review and the Mini-International Neuropsychiatric Interview (MINI) at screening.

Withdrawal Criteria

1. Failure to follow the research protocol.
2. Severe adverse events (AEs) that occurred during the treatment period.

Prior to their inclusion in the study, all subjects undergo a physical examination, as well as laboratory tests consisting of a complete blood count, an electrocardiogram, liver enzymes (including serum ALT, AST, total bilirubin, alkaline phosphatase), and urea and creatinine levels. Hepatic function will be monitored at baseline and at weeks 8, 16, and 24 to detect subclinical hepatocellular injury. Study drug (tizanidine and/or pregabalin) will be permanently discontinued for (i) ALT or AST > 5 × ULN, (ii) ALT or AST > 3 × ULN with associated symptoms (eg, fatigue, nausea, right upper quadrant pain, jaundice) or total bilirubin > 2 × ULN, or (iii) any sign of acute liver failure (eg, coagulopathy); these events will be reported as Serious Adverse Events and followed until resolution. Study drug will be withheld or dose-reduced if symptomatic hypotension occurs (systolic blood pressure <90 mmHg with dizziness or presyncope).

Randomization and Blinding

After completing the baseline examination, eligible participants who meet the inclusion and exclusion criteria will be randomly assigned in a 1:1 ratio to either the intervention group (pregabalin plus tizanidine) or the control group (pregabalin monotherapy). Randomization will be performed using a centralized, web-based randomization service (Sealed Envelope Ltd, London, UK). To ensure balanced allocation across study sites, randomization will be stratified by center using a computer-generated permuted block design with varying block sizes. The allocation sequence will be generated and securely held by the online randomization system. Upon enrolling an eligible participant, the site investigator will log into the secure platform to obtain the unique treatment assignment. This procedure ensures robust allocation concealment, as the treatment assignment remains unknown until the moment of participant registration. Given the distinct pharmacological profiles and dosing regimens of the two interventions (combination therapy vs monotherapy), it was not feasible to blind participants or treating clinicians to treatment assignment. However, to minimize assessment bias, all outcome assessors and research personnel responsible for collecting primary and secondary efficacy endpoints were kept masked to group allocation. The integrity of assessor masking was monitored throughout the trial. A separate unblinded research nurse, who had no contact with outcome assessors, conducted weekly telephone calls to monitor medication adherence, manage protocol-specified dose adjustments, and AEs, vital signs, including seated and standing blood pressure and heart rate, were recorded at every study visit. Sedation was assessed using the Stanford Sleepiness Scale at each visit. In addition, participants completed a weekly electronic diary capturing self-reported episodes of dizziness, severe drowsiness, or falls. Masking of outcome assessors and data analysts was maintained until the completion of all endpoint assessments and the database was locked for the final analysis.

Study Interventions

Participants are not required to discontinue or wash out their existing analgesic medications prior to enrollment. However, during the screening period, participants are not permitted to initiate any new analgesic medications (eg, non-steroidal anti-inflammatory drugs, acetaminophen), and the introduction of any new drugs during the study period is prohibited. Acetaminophen will be permitted as rescue medication for FM-related pain, at a single dose of up to 1000 mg, not exceeding

a total daily dose of 3000 mg. If a participant reports consuming >2000 mg of acetaminophen per day for ≥3 consecutive days: An unscheduled liver enzyme panel (ALT, AST, total bilirubin, alkaline phosphatase) will be performed within 48 hours. All rescue medication use, including dose and frequency, will be prospectively recorded in the case report forms (CRFs).

Study medication will be initiated at a low dose and flexibly titrated to each participant's MTD to optimize the balance between pain relief and tolerability. Titration will be guided by weekly follow-up calls conducted by an unblinded research nurse who is not involved in outcome assessment. Dose escalation will cease if either of the following occurs: (a) intolerable AEs emerge at a higher dose, or (b) the participant reports achieving "a lot" or "complete" pain relief. If intolerable AEs occur, the dose will be reduced to the last well-tolerated level. During the maintenance phase, the dose will remain fixed at the last well-tolerated level (ie, the participant's established MTD). Dose adjustments during the maintenance phase are permitted only for compelling safety reasons and will be documented as protocol deviations.

All patients will receive their assigned treatment for 24 weeks following randomization.

Participants in the intervention group will receive open-label tizanidine orally (Tizanidine Hydrochloride tablets; Sichuan Credit Pharmaceutical Co., Ltd., China). The tizanidine dose will be gradually titrated over approximately three weeks according to the following schedule[21,24–28]

Initial dose: 2 mg/day, administered at bedtime.

The dose will be increased by 2 mg every two days (with two or three divided doses maintained) from week 1 through week 3 until a maximum of 16 mg/day is achieved, depending on therapeutic response, tolerability, sedation and blood pressure.

If a participant cannot tolerate a scheduled dose increment due to AEs, the dose will be maintained at the last well-tolerated level. Forced titration to the maximum dose of 16 mg/day will not be required; the final dose will be individualized based on tolerability and efficacy. Hepatic function will be systematically monitored throughout the study period and dose adjustment for renal impairment. Participants in the intervention group will also receive open-label pregabalin (Viatris Pharmaceutical Co., Ltd., Canonsburg, PA, USA), following a flexible titration schedule.[29,30]

Week 1: Initiate at 150 mg/day (75 mg twice daily).

Subsequent weeks: Based on efficacy and tolerability, the dose may be increased by 150 mg/day at weekly intervals, up to a maximum of 450 mg/day (225 mg twice daily). As this is a flexible titration, the final dose achieved during the titration phase may be lower than the maximum of 450 mg/day, based on individual tolerability and response. If a participant cannot tolerate a dose increase, the dose will be reduced to the previously well-tolerated level. Thus, forced titration to 450 mg/day will not be required; the final dose will be individualized.

Participants in the control group will receive pregabalin monotherapy following the same flexible titration schedule described for the intervention group.

Participants retain the right to withdraw their consent at any time during the trial without providing a reason. In the event of withdrawal, the primary reason(s) will be documented in the case report form whenever possible. The allocated intervention will not be modified, and the dose will not be increased above the protocol-defined maximum under any circumstances. If a participant's clinical condition necessitates a treatment strategy outside the protocol—for instance, requiring a dose above the maximum for adequate pain relief, management of intolerable side effects, or initiation of more potent medications (eg, antidepressants)—the study medication will be discontinued. The participant will then be withdrawn from the trial to receive appropriate clinical management. The demographic and clinical characteristics of participants who withdraw, along with their reasons for withdrawal, will be summarized descriptively.

Study Outcomes

Primary Outcome

The primary outcome is the change from baseline to week 12 in average pain intensity, assessed using the first item of the symptom domain of the Revised Fibromyalgia Impact Questionnaire (FIQR). The FIQR is a well-validated, multidimensional

instrument that assesses participant-reported severity of FM across multiple domains. These include pain intensity, physical function, fatigue, morning tiredness, depression, anxiety, job difficulty, and overall well-being. Each item is scored on an 11-point numerical rating scale from 0 to 10, with higher scores indicating greater severity or impact of symptoms. This item asks participants to rate their average pain over the preceding 7 days on an 11-point numerical rating scale ranging from 0 ("no pain") to 10 ("unbearable pain").

Secondary Outcomes

1. The FIQR will be administered weekly throughout the 24-week intervention period for all participants.

For the following secondary outcomes, the between-group change at baseline compared to 4, 8, 12, 16, 20, and 24 weeks of treatment will be assessed:

2. Health-related Quality of Life assessments are made using the Medical Outcome Study Short Form 36 Health Survey (SF-36). The SF-36 is a self-administered, 36-item questionnaire that assesses the concepts of physical functioning, role limitations due to physical problems, social function, bodily pain, general mental health, role limitations due to emotional problems, vitality, and general health perceptions. Summary scores include physical function, mental function, and combined total function. Scores range from 0 to 100, with higher scores indicating better health status.
3. The Patient's Global Assessment (Global Visual Analogue Scale) is a visual analogue scale that measures the level of FM severity on a 10-point scale with 10 reflecting the most extreme severity and 0 reflecting no severity.
4. The Beck II Depression Inventory (BDI) is a 21-question, validated, self-report instrument that measures the severity of depressive symptoms (each scored 0–3, sum=0–63). Higher scores reflect a greater degree of symptom severity. The total questionnaire score ranges from 0 to 63 points. The result is interpreted by the usual classifications as follows: no depression (0–9 points), mild depression (10–18 points), moderate depression (19–29 points) and severe depression (>30 points).
5. The Pittsburgh Sleep Quality Index is an 11-item, validated, self-report questionnaire that measures sleep quality. Lower scores are associated with better sleep quality. This questionnaire has 7 dimensions: subjective quality, sleep latency, sleep duration, habitual sleep efficacy, sleep perturbations, use of hypnotic medication, and daily dysfunction. Each dimension is scored from 0 (no problems) to 3 (severe problems), where the total score varies in a range from 0 to 21 points.
6. The Hospital Anxiety and Depression Scale is a 14-item, validated, self-report questionnaire that assesses levels of depression and anxiety. Higher scores reflect greater levels of anxiety and depression.
7. The Perceived Stress Scale is the most widely used psychological instrument for measuring the perception of stress. The 10-item scale also includes a number of direct queries about current levels of experienced stress. For this instrument, higher scores reflect a greater degree of symptom severity.
8. Pain distribution: assessed by the Widespread Pain Index (WPI) from the 2016 diagnostic criteria for FM. The WPI measures the number of painful areas (score range = 0–19) on the patient's body over the last week prior to the assessment. Higher scores reflect a greater degree of symptom severity.
9. Frequency and severity of AEs, Patient safety will be ensured by vigilant AE assessment and judicious drug titration. Any occurrences of major AEs will be tracked as secondary outcomes and also reported to the Ethics Board. Assessment and reporting of AEs will adhere to Consolidated Standards for Reporting Trials recommendations.

Follow-Up

Participants will be contacted by telephone on a weekly basis and will attend in-clinic visits every four weeks throughout the study period. During these scheduled contacts, the investigator or research nurse will assess and document medication adherence, inquire about potential AEs, and address any study-related concerns. Participants will be specifically asked about common AEs associated with the study medications. These may include dry mouth, drowsiness, dizziness, blurred vision,

dysgeusia, increased appetite, hypotension, bradycardia, weight gain, and gastrointestinal symptoms (eg, constipation, heartburn). Participants may also contact the investigator by telephone at any time to discuss any emergent concerns between scheduled visits. A detailed schedule of outcome assessments is provided in Table 1. Participant safety will be ensured through ongoing AE monitoring and protocol-guided dose titration. All serious AEs will be recorded as secondary outcomes and reported to the independent ethics committee at Beijing Tiantan Hospital, Capital Medical University, Beijing, China. The assessment and reporting of AEs will adhere to the CONSORT guidelines for harm reporting.

All participants who complete the 24-week interventional period will be offered the opportunity to enroll in a separate, optional post-trial observational follow-up lasting an additional 24 weeks (for a total of 48 weeks from baseline). During this phase, participants will be managed according to standard clinical care; continuation, discontinuation, or switching of pharmacotherapy (including tizanidine, pregabalin, or other analgesics) will be at the discretion of the treating physician and will not be dictated by the protocol. The following data will be collected at Weeks 36 and 48: FIQR total and domain scores, BDI-II, Current medication use (including any tizanidine or pregabalin, and any use of other centrally acting agents), AEs, with a specific focus on features suggestive of physical dependence (eg, withdrawal symptoms upon discontinuation or dose reduction, cravings, difficulty reducing dose) recorded using a structured checklist.

Data Collection

All study personnel will undergo systematic training based on the finalized research protocol prior to the start of the trial. Prior to participant enrollment, a pilot run will be conducted to ensure that all staff are familiar with the study procedures and CRFs. Study data will be recorded in either paper-based or electronic CRFs by the investigators and research coordinators responsible for participant enrollment and follow-up. The CRFs and study-specific standard operating procedures (SOPs) will be developed directly from this protocol. An independent Data and Safety Monitoring Committee (DSMC) will review accumulating safety and efficacy data at six-month intervals throughout the trial. Based on its review, the DSMC will provide recommendations regarding the continuation, modification, or early termination of the study. The final study database will be locked for analysis only after all data queries have been resolved and a formal lock procedure has been completed under the supervision of the data manager and the principal investigator. Data entry accuracy will be ensured through the use of EpiData 4.6 (EpiData Association, Denmark), employing double-entry and validation procedures.

Sample Size

In the absence of prior RCTs evaluating tizanidine for FM, we estimated the sample size based on data from previous pregabalin RCTs.[29,31,32] In those studies, baseline self-reported pain intensity on a 0–10 numerical rating scale (NRS) had a mean of 6.7 and a standard deviation (SD) of 1.5 in the target population. According to the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) guidelines, a 15% reduction in pain—equivalent to a 1.0-point decrease on the NRS in this population—is considered a minimal clinically important difference (MCID) at the individual patient level.[33] A 30% reduction (approximately 2.0 points) is regarded as a clinically meaningful change, and a 50% reduction as a substantial improvement. However, the IMMPACT guidelines do not provide a definition for a minimal clinically important difference between treatment groups. To ensure a conservative estimate that accounts for potentially greater variability in our study population and methodology, we increased the assumed SD from 1.5 to 2.0. Using these parameters ($\Delta = 1.0$, SD = 2.0), a two-sided alpha of 0.05, and 80% power, the sample size required per group for an independent two-sample *t*-test was approximately 63 participants. We therefore rounded this up to 65 participants per group. Allowing for a potential attrition rate of 20%, the final target sample size was set at 82 participants per group. Sample size calculation was performed using PASS software (version 15.0; NCSS LLC, Kaysville, UT, USA).

Statistical Analysis

The primary efficacy analysis will be performed on the intention-to-treat (ITT) population, which includes all randomized participants, irrespective of treatment adherence or study completion. Efficacy analyses will also be conducted on the per-protocol (PP) population. The safety population will comprise all randomized participants who received at least one dose of the study medication. Missing data in the ITT analysis will be handled using linear mixed-effects models.

The model will include treatment group, visit time (as a categorical factor), the treatment-by-time interaction, and the baseline score of the primary outcome as fixed effects. A random intercept for each participant will be incorporated to account for the correlation of repeated measures within the same individual. This model provides valid inferences under the missing-at-random (MAR) assumption. Sensitivity analyses will be conducted to assess the robustness of the primary findings under different missing-data assumptions. All hypothesis tests will be two-sided, with the significance level set at 5%. Treatment effect estimates will be reported with their 95% confidence intervals (CIs). All statistical analyses will be performed using SPSS software (version 21.0; SPSS Inc., Chicago, IL, USA).

The primary confirmatory comparison for each secondary outcome is at Week 24. Intermediate time-point estimates will be reported as supportive and exploratory without formal multiplicity adjustment. An independent, blinded biostatistician will finalise the statistical analysis plan before database lock, independently verify primary and secondary endpoint analyses, and ensure adherence to the multiplicity adjustment plan. Secondary analyses will evaluate the change from baseline in the FIQR score at Weeks 4, 8, 12, 16, 20, and 24, in addition to the primary 12-week endpoint. Continuous variables will be summarized as mean (standard deviation, SD) for approximately normally distributed data, or as median (interquartile range, IQR) otherwise. Categorical variables will be reported as frequencies and percentages. Baseline characteristics will be compared between groups using independent *t*-tests (or Mann-Whitney *U*-tests for non-normal data) for continuous variables, and Pearson's chi-square tests (or Fisher's exact tests for small expected counts) for categorical variables. These analyses are purely descriptive and are not intended to test for baseline equivalence. Pre-specified subgroup analyses of the primary outcome will be conducted according to key baseline characteristics, including age, sex, disease duration, baseline pain intensity, and baseline FIQR score. In exploratory analyses, selected baseline variables will also be examined as potential predictors of treatment response. All subgroup and predictor analyses are exploratory and hypothesis-generating; the study is not powered to detect definitive treatment effects within subgroups. A P-value <0.05 for the treatment-by-subgroup interaction term will be considered to indicate a statistically significant subgroup effect.

Discussion

FM remains challenging to manage, as current therapies offer only partial relief and are often associated with disabling AEs. Therefore, there is an urgent need for improved FM treatments that offer greater analgesic efficacy and a more favorable safety and tolerability profile.[2,5,34] No prospective study has formally evaluated the tizanidine–pregabalin combination for pain relief in any chronic pain condition. Preclinical and retrospective observations suggest possible additive analgesic effects when tizanidine is combined with gabapentinoids in neuropathic pain models and refractory headache, but these findings remain preliminary and uncontrolled. Given the distinct AE profiles of tizanidine and pregabalin, we hypothesize that their combination will provide superior analgesic efficacy without exacerbating AEs in patients with FM. This trial aims to generate rigorous evidence to support a potentially improved therapeutic strategy for FM.

This trial incorporates both pragmatic and exploratory elements. This study will be the first to evaluate the efficacy and safety of the pregabalin-tizanidine combination in patients with FM. For pragmatic reasons, the protocol includes a titration phase that permits the use of lower doses if tolerability issues arise. The primary outcome is the change from baseline to Week 12 in average pain intensity over the previous 7 days, measured using an 11-point numerical rating scale derived from the first item of the FIQR symptom domain. This outcome measure is widely accepted as representing a clinically meaningful improvement for patients. In addition, pre-specified subgroup analyses of the primary outcome will be conducted. Subgroup analyses aim to explore the consistency or heterogeneity of treatment effects across different patient cohorts, thereby identifying subpopulations that may derive greater or lesser benefit from the intervention. This approach facilitates the generation of novel hypotheses, offering direction for subsequent precision medicine research and individualized treatment strategies. It also serves to validate the robustness of the primary findings by assessing whether the observed treatment effect is consistent across key subgroups (eg, age, sex). However, subgroup analyses are inherently exploratory. Therefore, their findings should be interpreted with caution.

Cyclobenzaprine, a tricyclic structurally related to amitriptyline, has modest efficacy in fibromyalgia—particularly for sleep and pain—but its anticholinergic adverse effects, marked sedation, and cardiovascular risks (tachycardia, potential QTc prolongation) lead to high discontinuation rates, especially in older and multimorbid patients. In contrast, tizanidine,

an imidazoline-derived central α2-adrenergic agonist, lacks significant anticholinergic activity and produces muscle relaxant and analgesic effects primarily through presynaptic inhibition of excitatory amino acid release in spinal and supraspinal pathways. Its shorter half-life allows flexible bedtime dosing that minimises daytime sedation, and its reduction of glutamatergic neurotransmission may be particularly relevant to the central sensitisation pathophysiology of fibromyalgia. Therefore, tizanidine was selected as the muscle relaxant for this combination study, with the expectation that its safety and tolerability profile will facilitate longer-term adherence.

This study has several limitations. First, the open-label design is a limitation of this protocol. Although the PROBE framework with centralized randomization and blinded statistical analysis reduces some sources of bias, we cannot exclude the possibility that participants' and clinicians' awareness of treatment assignment may inflate subjective symptom reporting in the active treatment arm. The reliance on patient-reported outcomes amplifies this concern. Accordingly, any positive efficacy findings from this trial should be interpreted as preliminary and will require confirmation in a subsequent double-blind, placebo-controlled trial. Second, the 24-week treatment duration limits our ability to evaluate the long-term efficacy and safety of the intervention. Third, the relatively small sample size limits the generalizability of the findings. In addition, the cost-utility of the combined treatment was not evaluated. Finally, although the titration protocol was designed to reflect real-world clinical practice, it may have introduced variability in dosing and tolerability. The 24-week intervention period, with the primary efficacy endpoint at week 12, was selected to balance the need for rigorous efficacy assessment against participant retention and logistical feasibility. However, we recognise that a 24-week duration does not permit definitive conclusions regarding sustained efficacy beyond six months, nor does it adequately capture the potential for late-emerging adverse events, tolerance, or dependence that have been observed with centrally-acting muscle relaxants in longer clinical series (eg, declining spasticity control and increasing sedation with prolonged tizanidine use).

Despite these limitations, this pragmatic trial provides important preliminary evidence on the efficacy and safety of the pregabalin-tizanidine combination therapy. The findings warrant confirmation in longer-term, double-blind trials with larger sample sizes. To promote transparency and reproducibility, the study protocol was registered with ClinicalTrials.gov (NCT07382921) and is publicly available.

After three decades of intensive research, the clinical benefits of pharmacological treatments for FM remain modest and poorly defined. This trial aims to evaluate the analgesic efficacy and safety of the pregabalin-tizanidine combination in patients with FM using a rigorous, adequately powered design.

Study Status

The study began in February 2026. Estimated trial completion is expected by June 2027.

Abbreviations

AEs, adverse events; BDI, Beck II Depression Inventory; CRFs, case report forms; DSMC, Data and Safety Monitoring Committee; FIQR, Fibromyalgia Impact Questionnaire Revised; FM, Fibromyalgia; GABA, gamma amino butyric acid; ITT, intention-to-treat; MTD, maximal tolerated dose; MAR, Missing at Random; MCID, minimal clinical important difference; PROBE, Prospective; Randomized; Open-label; Blinded Endpoint; PGB, Pregabalin; PGIC, Patient Global Impression of Change; SPIRIT, Standard Protocol Items, Recommendations for Interventional Trials; SF-36, Medical Outcome Study Short Form 36 Health Survey; SOPs, standard operating procedures; WPI, Widespread Pain Index.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agreed to be accountable for all aspects of the work.

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Disclosure

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