Randomized clinical trial: the effects of pregabalin for centrally mediated abdominal pain syndrome

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Abstract

Background: Pregabalin is worldwidely licensed for the treatment of a variety of pain syndromes and supposed to be a potential candidate for the centrally mediated abdominal pain syndrome (CAPS).

Objectives: To investigate the efficacy of pregabalin on nociceptive and emotional symptoms in CAPS patients.

Design: This is an open-label randomized controlled trial.

Methods: CAPS patients were randomized to receive pregabalin 75 mg (P group), pinaverium bromide 50 mg (PB group), or pregabalin combined pinaverium bromide regimen (P + PB group) three times daily for 4 weeks. Questionnaires were completed biweekly. The primary outcomes were defined as the average abdominal pain scores of severity and frequency at weeks 2 and 4. Secondary outcomes included the reduction in abdominal pain scores, Somatic Self-rating Scale (SSS), Patient Health Questionnaire-15 (PHQ-15), and Generalized Anxiety Disorder Scale 7 (GAD-7) scales obtained at the end of trial to the baseline.

Results: Totally, 102 eligible patients were recruited and randomized. The mean severity scores of abdominal pain were 1.39 ± 1.28, 0.97 ± 1.43 *versus* 2.91 ± 1.44 ($p < 0.0001$) in P or PB + P group *versus* PB group at week 2 and were 0.90 ± 1.21, 1.28 ± 1.87 *versus* 2.74 ± 1.75 ($p < 0.0001$) at week 4. The mean frequency scores were 2.55 ± 2.55, 2.03 ± 2.80 *versus* 5.12 ± 2.09($p < 0.0001$) in P or PB + P group *versus* PB group at week 2 and were 1.72 ± 2.46, 2.00 ± 2.90 *versus* 4.55 ± 2.55 ($p < 0.0001$) at week 4. When comparing the changes in SSS, PHQ-15, and GAD-7 scores, patients accepting pregabalin or pregabalin combination regimen reported a more decrease than pinaverium bromide recipients ($p = 0.0002$, $p = 0.0002$, and $p = 0.0033$).

Conclusion: This trial suggests that pregabalin may be beneficial for CAPS abdominal pain and concomitant somatic or anxiety symptoms.

Registration: www.chictr.org.cn (ChiCTR1900028026)

Keywords: centrally mediated abdominal pain syndrome, pregabalin

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Introduction

Centrally mediated abdominal pain syndrome (CAPS), formerly known as functional abdominal pain syndrome, is characterized by continuous, nearly continuous, or frequently recurrent abdominal pain that is often severe and only rarely related to gut function.[1] It has a reported population prevalence of between 0.5% and 1.7%, with a female preponderance.[2] The germane hypothesis for the genesis and maintenance of chronic abdominal pain is the concept of visceral hypersensitivity.[3] Unlike other painful functional gastrointestinal disorders (FGIDs), such as irritable bowel syndrome (IBS) and functional

dyspepsia (FD), CAPS is distinguished by poor relationship of pain with food intake or defecation, and it seems cognitive and emotional features play a larger role in the pain experienced.[1] Prospectively followed up, patients with higher anxiety scores more frequently developed FGID.[4] Antispasmodics and antidepressants are utilized for CAPS, but these therapies are not effective for all patients.[1,5] Patients are often prescribed opiates as they are desperate for relief, and clinicians struggle to control their symptoms.[6] Unfortunately, opiates are considered to be contraindicated due to a risk of opiate-related bowel disruption, painful constipation, or even narcotic bowel syndrome.[7]

Pregabalin, an alkylated analog of γ-aminobutyric acid, binding to the α2δ type 1 protein of the P/Q voltage-dependent calcium channel and reducing the central release of excitatory molecules, acts like an inhibitory neurotransmitter.[8,9] Pregabalin has been worldwidely licensed for a variety of indications, including the treatment of pain syndromes such as neuralgia, fibromyalgia; as adjunctive treatment for partial onset seizures; and for generalized anxiety disorder (GAD).[10] It has been evaluated to alleviate some chronic abdominal pain syndrome, such as IBS or chronic pancreatitis, but has not been studied for CAPS.[11,12] Based on the reported experiences, we hypothesized that pregabalin may play an important role in the therapy of CAPS and undertook a randomized trial to evaluate its efficacy in pain and emotion modulation. We selected an antispasmodic, pinaverium bromide as the control drug.

Methods

Design and setting

In this randomized open-label clinical trial, the subjects were assigned to pinaverium bromide, pregabalin, or a combination of both for 4 weeks, at the Department of Gastroenterology, Qilu Hospital of Shandong University, from January 2020 to December 2021. Written informed consent was obtained from all patients and if necessary, from their caregivers. Participants were able to withdraw from the study at any time, and they were clearly informed that their relationship with the healthcare provider would not be affected. It was reported according to the CONSORT guidelines and the checklist is available as Supplemental Material.

Subjects

Patients were eligible for inclusion if they were diagnosed for CAPS based on the Rome IV criteria; had negative endoscopy examinations the year prior to enrolment and were willing to participate in the study. The diagnostic criteria for CAPS must include all of the following: continuous or nearly continuous abdominal pain; no or only occasional relationship of pain with physiological events (e.g. eating, defecation, or menses); pain limits some aspect of daily functioning; the pain is not feigned; and pain is not explained by another structural gastrointestinal disorder, FGID, or other medical condition.[1] Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis.

The exclusion criteria were using pregabalin within 30 days or having a known pregabalin allergy; pregnancy or lactation; concurrent organic gastrointestinal diseases or severe systematic disease; concurrent neurological or psychiatric disorders except anxiety/depression; and overlapped with other FGIDs such as IBS or FD.

Interventions

The randomization sequence in a 1:1:1 ratio was generated by a computer. The sequence was concealed in an opaque envelope and kept by an independent research assistant until intervention was assigned. All investigators were blind to the randomization sequence. The subjects were randomized to three groups: (1) PB group: the patients received pinaverium bromide 50 mg three times daily for 4 weeks; (2) P group: the patients received pregabalin 75 mg three times daily for 4 weeks; and (3) PB + P group: the patients received pinaverium bromide 50 mg and pregabalin 75 mg three times daily for 4 weeks.

Questionnaires

All subjects were examined at baseline, week 2, and week 4, to complete a CAPS symptom questionnaire about abdominal pain. The pain severity was scored on a seven-point Likert scale (0 = no pain; 1 = very little; 2 = slight; 3 = moderate; 4 = relatively severe; 5 = severe; and 6 = as severe as it could be, insufferable pain) and the frequency was shown as pain onset days per week.[13]

Common mental disorder questionnaires comprising Somatic Self-rating Scale (SSS), Patient

Health Questionnaire-15 (PHQ-15), and seven-item Generalized Anxiety Disorder Scale (GAD-7) were also administered at baseline and week 4. SSS is a highly valid and reliable self-report questionnaire that is primarily used to evaluate emotional responses and somatic symptoms, consisting of 20 items divided into four domains.[14] PHQ-15 is a self-administered somatic symptoms subscale derived from the full PHQ, including 15 prevalent somatic symptoms.[15] The seven-item GAD-7 was developed to identify and assess GAD yielding a score range of 0–21.[16]

Study outcomes

The primary outcome was to evaluate the difference of mean CAPS symptom scores including abdominal pain severity and frequency among three groups at weeks 2 and 4. The secondary outcome was to evaluate the changes in symptom sores, SSS, PHQ-15, and GAD-7 scales obtained at the end of trial to the baseline.

Statistical methods

As we estimated a 1.5-point more decrease in average pain scores in pregabalin groups than the control group with an expected standard deviation (SD) of 1.8 based on our pilot data, the sample size was calculated as 29 participants in each group with a power of 90% and an α of 0.05. Considering a 15% dropout, this study needed at least 34 participants in each arm. Continuous values are expressed as mean or median (depending on the distribution of the variables) and SD values. For parametric distribution variables, we used one-way analysis of variance with multiple comparisons. For nonparametric distribution variables, Kruskal–Wallis and Dunn's post-test of multiple comparisons were used. We used chi-square test with Fisher's exact test for sex among groups. For all statistical analysis, significance was set at $p < 0.05$. Statistical analysis was performed in GraphPad Prism (v8.0.1).

Results

Recruitment

A three-arm, randomized, open-label preliminary clinical trial was carried out from January 2020 to December 2021. In total, 185 patients were assessed for eligibility and 102 subjects were enrolled and randomized. In all, 34 recipients were assigned to each group. Ten subjects dropped out during the study: five were lost to follow-up, two discontinued due to lack of efficacy, two due to adverse events, and one for non-compliance (Figure 1).

Baseline characteristics

Baseline characteristics for enrolled subjects are outlined in Table 1. In PB group, the mean age was 46.5 ± 14.72, 55.9% female; mean abdominal pain scores of severity and frequency were 3.50 ± 1.26 and 5.82 ± 1.57; mean SSS, PHQ-15, and GAD-7 scores were 41.12 ± 7.01, 10.15 ± 4.30, and 9.32 ± 5.30, respectively. In P group, the mean age was 49.2 ± 13.69, 50% female; mean abdominal pain scores of severity and frequency were 3.68 ± 1.36 and 6.09 ± 1.49; mean SSS, PHQ-15, and GAD-7 scores were 42.50 ± 7.69, 11.24 ± 4.56, and 9.27 ± 5.80. In PB + P group, the mean age was 45.1 ± 15.12, 64.7% female; mean abdominal pain scores of severity and frequency were 3.85 ± 1.18 and 5.79 ± 1.86; mean SSS, PHQ-15, and GAD-7 scores were 43.15 ± 9.00, 11.21 ± 4.39, and 10.56 ± 6.36, respectively. No significant differences were found in each items among three groups.

Study outcomes

Primary outcomes defined as mean abdominal pain scores at weeks 2 and 4 are shown in Table 2. In comparing the severity of abdominal pain at week 2, patients in the P group and PB + P group reported lower scores than those in the PB group (1.39 ± 1.28, 0.97 ± 1.43 *versus* 2.91 ± 1.44, overall Kruskal–Wallis test; $p < 0.0001$). When comparing the pain frequency, patients receiving pregabalin or pregabalin combination regimen suffered less pain attacks than pinaverium bromide recipients (2.55 ± 2.55, 2.03 ± 2.80 *versus* 5.12 ± 2.09, overall Kruskal–Wallis test; $p < 0.0001$). Findings were similar between the week 2 data compared with the end of treatment, week 4 symptom scores. In comparing the severity of abdominal pain at week 4, patients in the P group and PB + P group reported lower scores than those in the PB group (0.90 ± 1.21, 1.28 ± 1.87 *versus* 2.74 ± 1.75, overall Kruskal–Wallis test; $p < 0.0001$). When comparing the pain frequency, patients in two pregabalin groups suffered less pain attacks than pinaverium bromide recipients (1.72 ± 2.46, 2.00 ± 2.90 *versus*

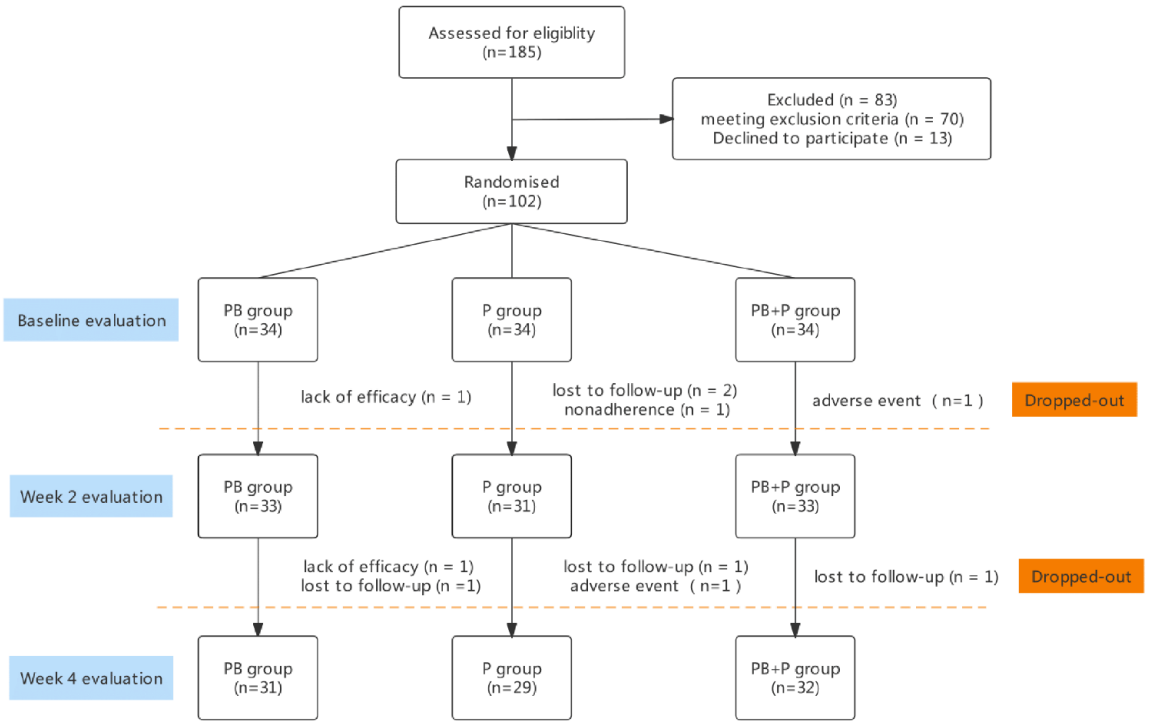

Figure 1. The flow chart of the exploratory trial.

Table 1. Baseline demographics of enrolled patients.

Group		PB	*P* Value	PB + P	*p* Value
Age, mean ± SD		46.5 ± 14.72	49.2 ± 13.69	45.1 ± 15.12	0.4540
Sex (female), *n*%		19 (55.9%)	17 (50%)	22 (64.7%)	0.4679
Abdominal pain score, mean ± SD	Severity*	3.50 ± 1.26	3.68 ± 1.36	3.85 ± 1.18	0.4889
	Frequency$	5.82 ± 1.57	6.09 ± 1.49	5.79 ± 1.86	0.8405
SSS score, mean ± SD		41.12 ± 7.01	42.50 ± 7.69	43.15 ± 9.00	0.7250
PHQ-15 score, mean ± SD		10.15 ± 4.30	11.24 ± 4.56	11.21 ± 4.39	0.6486
GAD-7 score, mean ± SD		9.32 ± 5.30	9.27 ± 5.80	10.56 ± 6.36	0.5496

Kruskal–Wallis test was used to compared continuous variable, and Fisher's test was used to compared discrete variables.
*Shown as the Likert scores.
$Shown as pain onset days per week.
GAD-7, Generalized Anxiety Disorder Scale 7; PHQ-15, Patient Health Questionnaire-15; SD, standard deviation; SSS, Somatic Self-rating Scale.

4.55 ± 2.55, overall Kruskal–Wallis test; $p < 0.0001$). Pregabalin only or combination treatment was superior to pinaverium bromide in reducing the pain scores during the 4 weeks.

The changes in CAPS symptom scores defined as the values corresponding to the scores acquired at the end of weeks 2 and 4 minus the baseline scores were assessed. During preceding 2-week

Table 2. Mean abdominal pain scores at weeks 2 and 4.

Group	PB	*p* Value	PB + P	p_1 Value	p_2 Value	p_3 Value
Week 2						
Severity, mean ± SD	2.91 ± 1.44	1.39 ± 1.28	0.97 ± 1.43	0.0008	<0.0001	0.4595
Frequency, mean ± SD	5.12 ± 2.09	2.55 ± 2.55	2.03 ± 2.80	0.0009	<0.0001	>0.9999
Week 4						
Severity, mean ± SD	2.74 ± 1.75	0.90 ± 1.21	1.28 ± 1.87	0.0003	0.0015	>0.9999
Frequency, mean ± SD	4.55 ± 2.55	1.72 ± 2.46	2.00 ± 2.90	0.0003	0.0005	>0.9999

Dunn's post-test of multiple comparisons *p* value is indicated in the table. p_1 Value was calculated between PB group and P group; p_2 value was between PB group and PB + P group; p_3 value was between P group and PB + P group.
SD, standard deviation.

intervention, patients in the P group and PB + P group experienced the most pronounced relief compared to those in the PB group for severity and frequency of abdominal pain (Figure 2(a)–(b), overall Kruskal–Wallis test; $p < 0.0001$). Similarly, the changes during whole 4 weeks of the trial indicated that the reduction in abdominal pain scores was more significant in P group and PB + P group than that in control arm (Figure 2(c)–(d), overall Kruskal–Wallis test; $p < 0.0001$ and $p < 0.0004$).

The changes in mental disorder scores including SSS, PHQ-15, and GAD-7 during the 4 weeks were evaluated as well. When comparing the changes in SSS scores, patients accepting pregabalin or pregabalin combination regimen reported a more decrease than pinaverium bromide recipients (Figure 3(a), overall Kruskal–Wallis test; $p = 0.0002$). The changes in PHQ-15 and GAD-7 scores in this two pregabalin groups were also pronounced than the control group ((Figure 3(b)–(c)), overall Kruskal–Wallis test; $p = 0.0002$ and $p = 0.0033$).

Adverse events

No serious adverse events were reported during the whole study. Dizziness and lethargy were the most common side effects observed in two pregabalin groups with the incidence of 14/68(20.6%) and 9/68(13.2%) contrast to none reported in the pinaverium bromide arm ($p = 0.0044$ and $p = 0.0263$). However, the side effects were well tolerated by majority of the patients with no need of further treatment and would disappear as days pass by. Only two subjects discontinued the study due to side effects.

Discussion

Pharmacotherapeutic options of CAPS include antispasmodics or antidepressants. Antispasmodics are frequently utilized for functional chronic abdominal pain, but are not always effective.[5] The use of antidepressants is usually restricted at gastroenterology department, since patients may be reluctant to use 'antidepressants' for gastrointestinal symptoms on account of its stigmatizing features and gastroenterologists not well trained for its application may prescribe wrongly.[17] Clinicians struggle to improve abdominal pain without resorting to opiates, which should almost never be prescribed for CAPS pain. In this research, we conducted an open-label, randomized clinical trial to examine the efficacy of pregabalin in CAPS subjects and chose pinaverium bromide as the positive controlled drug due to its common use and good compliance compared to antidepressants. We found that pregabalin only or pregabalin combination intervention was superior to pinaverium bromide only for the relief of abdominal pain. Pregabalin could attenuate the nociceptive and emotional manifestations of enrolled patients.

Pregabalin are α2δ ligands that generally bind potently to an auxiliary protein associated with voltage-gated calcium channels, reducing depolarization-induced calcium influx at nerve terminals, which reduces the release of several excitatory neurotransmitters including glutamate,

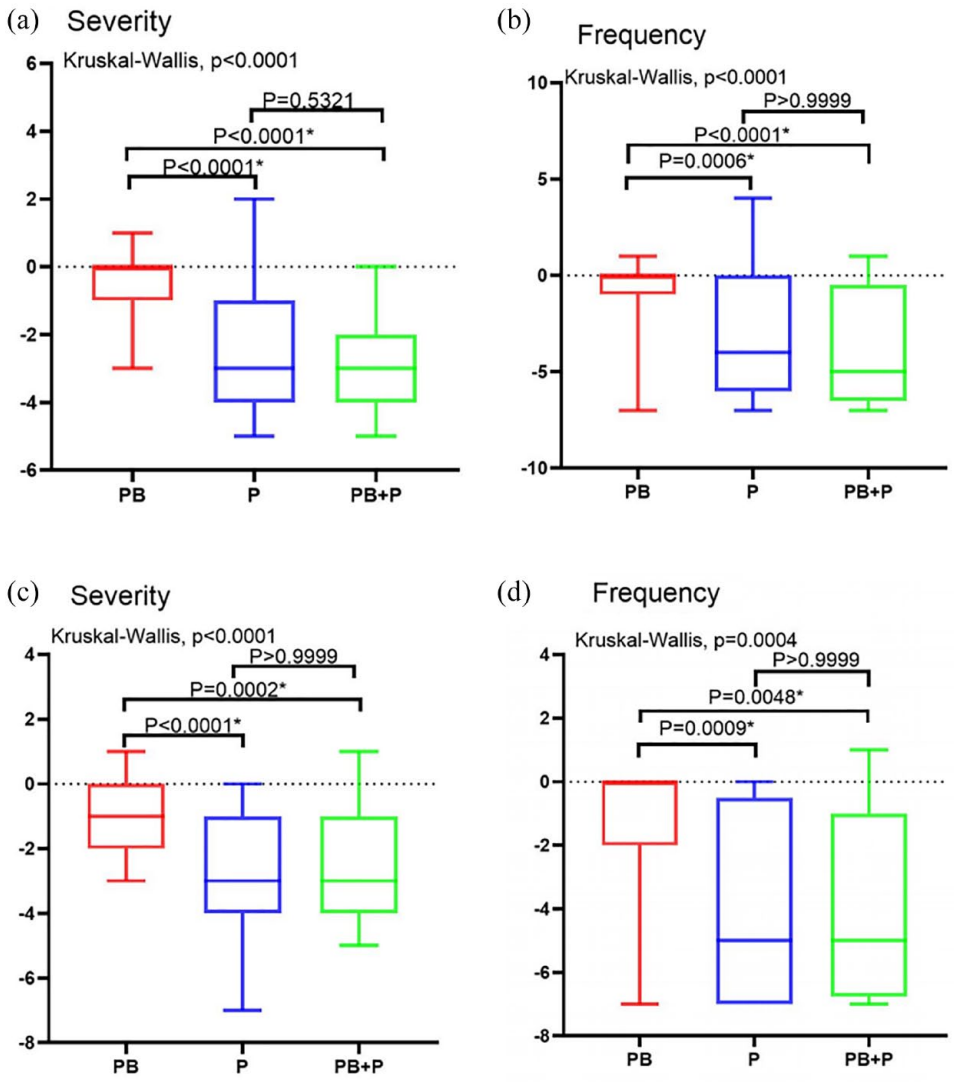

Figure 2. The changes in abdominal pain scores during 2-week and 4-week intervention. (a)–(b), the changes in severity and frequency, respectively, during preceding 2 weeks. (c)–(d), the changes in severity and frequency, respectively, during 4 weeks. The values correspond to the score at the end of weeks 2 and 4 minus the baseline score. Lower score corresponds to better condition of the patients. The Kruskal–Wallis *p* value for overall comparison and the Dunn's post hoc comparison *p* value are indicated in each figure. Dunn's $p < 0.05$ indicates a significant difference between the two groups.

noradrenaline, substance P, and calcitonin gene-related peptide, which are involved in pain mechanisms.[18] Data from animal models provide evidence for the inhibition of visceral nociception by pregabalin in which hypersensitivity has been induced by either an inflammatory stimulus or stress. Pregabalin (200 mg/kg s.c.) suppressed the trinitrobenzene sulfonic acid-induced colonic allodynia but did not modify the colonic threshold in normal conditions of rats.[19] In patients with IBS, pregabalin (titrated from 50 mg tid to 200 mg tid over 3 weeks) increased distension sensory thresholds to normal levels in IBS patients with rectal hypersensitivity and reduced both visceral allodynia and hyperalgesia.[20] In comparison to placebo, pregabalin may be beneficial for IBS symptoms including abdominal pain, bloating, and diarrhea.[11] Pregabalin also has positive effects on FD patients, leading to significant alleviation of dyspeptic symptoms, especially in patients with predominant epigastric pain.[21] The biology of CAPS is likely similar to other chronic visceral pain disorders, such as IBS or FD.[1] However, pregabalin has never been studied for CAPS. Our

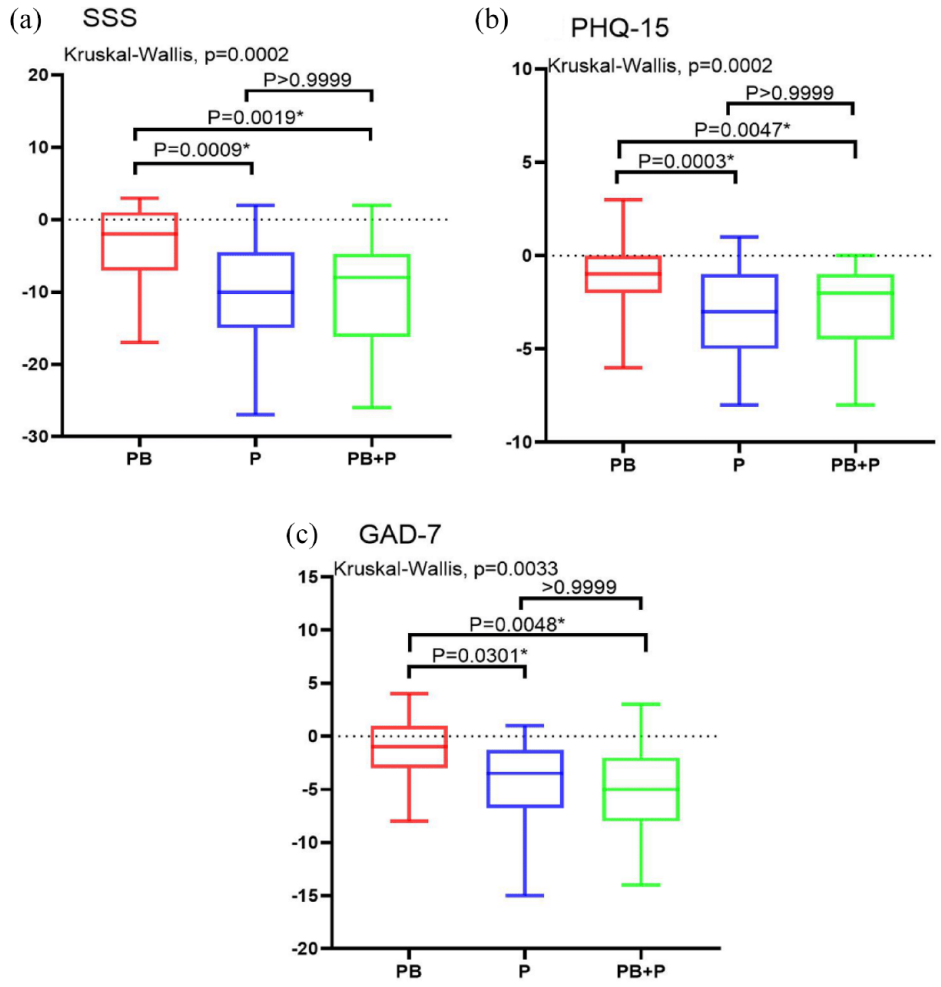

Figure 3. The changes in mental disorder scores during 4-week intervention: (a) the SSS scores change, (b) the PHQ-15 scores change, and (c) the GAD-7 scores change. The values correspond to the score at the week 4 minus the baseline score. Lower score corresponds to better condition of the patients. The Kruskal–Wallis *p* value for overall comparison and the Dunn's post hoc comparison *p* value are indicated in each figure. Dunn's $p < 0.05$ indicates a significant difference between the two groups.
GAD-7, Generalized Anxiety Disorder Scale 7; PHQ-15, Patient Health Questionnaire-15; SSS, Somatic Self-rating Scale.

study demonstrated that pregabalin could significantly reduce CAPS abdominal pain scores compared to other antispasmodic drug, perhaps due to the visceral nociception inhibition similar to IBS.

The psychiatric component in CAPS patients was clear with 88.9% diagnosed with depression, 38.9% with anxiety and panic disorders, 27.8% with post-traumatic stress disorder, and 33.3% having clear social stressors documented in previous study.[6] International guidelines and updated systematic reviews and meta-analysis indicate that pregabalin is efficacious in acute or long-term treatment and relapse prevention in GAD based on its presynaptic modulatory effect over excitatory neurons.[22–24] The results of this study are consistent with the study conducted by Olivares JM *et al.*[25] In Olivares's study, pregabalin might be effective for the treatment of patients with GAD who have shown inadequate response to previous antidepressants and have severe depressive symptoms. In this context, we examined subjects' mental disorders by SSS, PHQ-15, and GAD-7 questionnaires. SSS and PHQ-15 are measures evaluating the severity of somatic symptoms. GAD-7 is a widely used instrument to screen patients for GAD. Our study demonstrated that

the use of pregabalin not only resulted in a pronounced relief for anxiety disorders but somatic symptoms as well related to its psychotropic drug effects. Compared to antidepressants, pregabalin had no indications of mental disorders in its instructions and might be more acceptable by patients.

Several limitations of this study should be considered. The recipients of the study were recruited in a single center and at a small scale, and the 4-week follow-up duration was relatively short. Additionally, the study unlike strictly double-blinded clinical trials was an open-label clinical trial. These two issues might have caused a potential bias. Despite these shortcomings, our study provides important data suggesting a preferable effect of pregabalin than a commonly used therapeutic drug on CAPS symptoms, particularly for chronic abdominal pain and mental disorders. The novel findings of this study warrant further validation, especially in large clinical trials.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Qilu Hospital of Shandong University, Jinan, China [Approval number: 2019 (No. 178)]. Written informed consent was obtained from all patients and if necessary, from their caregivers. This trial was registered at www.chictr.org.cn (ChiCTR1900028026).

Consent for publication

The contents of the paper and the opinions expressed within are those of the authors, and it was the decision of the authors to submit the manuscript for publication. The authors have de-identified the details such that the identity of the patients may not be ascertained in any way.

Author contribution(s)

Ri Xu: Conceptualization; Data curation; Investigation; Project administration; Writing – original draft; Writing – review & editing.

Yanyan Wang: Conceptualization; Project administration; Writing – review & editing.

Wei Han: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Writing – original draft; Writing – review & editing.

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Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supplemental material

Supplemental material for this article is available online.

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