Ann Med Res

Current issue list available at Ann Med Res

Annals of Medical Research

journal page: annalsmedres.org

An increase in neuropathic complaints corresponds to the severity of central sensitization-related symptoms in women with fibromyalgia: A cross-sectional study

Feyza Nur Yücel [a,*], Sefa Kurt [b]

[a]University of Health Sciences, Sultan Abdulhamid Han Training and Research Hospital, Department of Physical Medicine and Rehabilitation, Istanbul, Türkiye

[b]Erenköy Physical Therapy and Rehabilitation Hospital, Clinic of Physical Medicine and Rehabilitation, Istanbul, Türkiye

*Corresponding author: dr.fny28@gmail.com (Feyza Nur Yucel)

MAIN POINTS

- CS symptoms, reflected by higher CSI scores, were closely associated with the intensity of neuropathic complaints.
- The strong overlap between CSI and S-LANSS supports the interaction of central sensitization (CS) and neuropathic mechanisms in FM.
- These findings underline the clinical utility of combining CSI and S-LANSS to better phenotype FM-related pain and guide treatment.

Cite this article as: Yucel FN, Kurt S. An increase in neuropathic complaints corresponds to the severity of central sensitization-related symptoms in women with fibromyalgia: A cross-sectional study. *Ann Med Res*. 2025;32(8):335–343. doi: 10.5455/annalsmedres.2025.04.085.

ABSTRACT

Aim: This study aimed to investigate the relationship between central sensitization (CS)-related symptoms and neuropathic complaints in female patients with fibromyalgia (FM).

Materials and Methods: Demographic and clinical variables, including disease duration, current medication, severity of pain, and the FM survey questionnaire, were all recorded. The Fibromyalgia Impact Questionnaire (FIQ) was used to assess the severity of the FM. Neuropathic complaints were investigated by the Self-Leeds Assessment of Neuropathic Symptoms and Sign (S-LANSS) and CS-related symptoms by the Central Sensitization Inventory (CSI), and patient data were compared according to the CSI severity levels. Patients with CSI scores that are at least moderate (CSI≥40) were considered to have central sensitization syndrome (CSS).

Results: One hundred and forty female FM patients were included in the study. The mean (SD) S-LANSS score was calculated as 15.06 (5.61) for all patients. A total of 135 patients (96.4%) had CSS; the mean (SD) CSI-A score for all patients was 61.39 (13.03). Of them, 81.4% (n = 114) were in the very severe CSS group. There was an increase in pain intensity, FIQ, and S-LANSS scores in parallel with the severity of CS-related symptoms (p<0.001). CS-related symptoms and disease severity were shown to have significant effects on S-LANSS variation in hierarchical regression analysis (β:0.34, CI:0.08-0.26, p<0.001; β:0.25, CI:0.01-0.20, p=0.035, respectively).

Conclusion: Neuropathic complaints become evident in tandem with the severity of CS-related symptoms in female FM patients. Clarifying its potential association to CS-related symptoms may help clinicians to understand neuropathic complaints in FM patients in more detail.

Keywords: Central nervous system, Central nervous system sensitization, Chronic pain, Fibromyalgia

Received: Apr 11, 2025 **Accepted:** May 22, 2025 **Available Online:** Aug 25, 2025

INTRODUCTION

Fibromyalgia (FM) is a disorder characterized by the presence of chronic, widespread musculoskeletal pain, fatigue, sleep disturbances, and other cognitive symptoms such as memory, concentration, and mood issues. With a prevalence of around 2% in the global general population, FM is a prevalent syndrome that typically occurs in women [1]. This wide range of FM symptoms typically includes neuropathic complaints, the pathophysiology of which is still poorly understood. The available evidence suggests that certain pathologies, such as central pain dysregulation and small fiber polyneuropathy (SFN), are the source neuropathic complaints of these patients [2].

Central sensitization (CS) is a maladaptive response of the central nervous system characterized by an increased response to normal and/or subthreshold stimuli. Several mechanisms, including the hyperexcitability of the spinal and supraspinal centers and the dysfunction of inhibitory modulatory systems, are potentially involved in the mechanisms of CS that result in an enhanced pain state [3]. Recently, the pathophysiological basis of pain perception in FM has been reshaped within the framework of the concept of nociplastic

pain (NocP). NocP describes a type of chronic pain that occurs due to changes in pain processing mechanisms at the central nervous system level, without obvious tissue damage or a structural lesion in the somatosensory system. FM is one of the syndromes most frequently associated with this type of pain, and CS forms the basis of this pathophysiological process [4]. However, sensory complaints similar to neuropathic pain (NeuP)—such as burning, tingling, allodynia, and hyperalgesia—are frequently reported in FM patients, suggesting a clinical overlap between NocP and NeuP [5]. Apart from pivotal role of CS in FM and NocP, its involvement with the pathophysiology of NeuP implies a possible association between neuropathic complaints and CS in these individuals [6].

Although a direct approach to establishing CS in humans does not yet exist, using quantitative sensory testing (QST) to identify heightened pain sensitization gives clinicians important diagnostic information [7]. Cost, time, and experience requirements restrict the utility of QST in clinical practice, and its associations with patient-reported outcome measures differ according to the patient cohort and the procedure performed. The implementation of self-report questionnaires, which investigate the clinical relevance of CS through sensitization-related symptoms, has increased as a result of these disadvantages [8]. The Central Sensitization Inventory (CSI) stands out as a tool that is frequently preferred for this purpose and has been shown to be valid and reliable in FM patients [9]. In addition, CSI's considerable correlation with various QST modalities is an additional attribute that enhances its significance in clinical practice [10]. Based on a score system that measures the intensity of symptoms related to CS, CSI assists in understanding the negative impact of CS on the individual. FM patients with more severe CS-related symptoms (higher CSI score) also reported longer and more intense pain, according to a recent study [11].

Screening questionnaires are often the first step in identifying the neuropathic component of pain, especially in complex medical settings [12]. The Self-Leeds Assessment of Neuropathic Symptoms and Signs (S-LANSS), for example, is recognized as an easy-to-use and reliable tool for distinguishing neuropathic from nociceptive pain [13]. In fact, for FM patients, S-LANSS scores have been shown to correlate with pressure-pain threshold values, a key indicator of pain sensitization [14].

The connection between neuropathic complaints and CS-related symptoms has been established through the correlation of S-LANSS and CSI scores in various conditions like cervical dystonia and knee osteoarthritis [15, 16]. Given CS's pivotal role in both FM and neuropathic pain, we anticipated an even stronger relationship in FM patients. Therefore, this study aimed to investigate the relationship between CS-related symptoms and neuropathic complaints in female FM patients. We hypothesized that neuropathic complaints are directly linked to the CS-related symptoms experienced by these patients.

MATERIALS AND METHODS

This cross-sectional study was conducted with patients admitted to the physical medicine and rehabilitation outpatient clinic in a tertiary center between October 2022 and 2023. The inclusion criteria for this study were the following: women patients diagnosed with FM according to American College of Rheumatology (ACR 2016) criteria aged between 18 to 65 years, being literate, and agreeing to participate in the study. Only female patients were included in the study due to the relatively small number of male FM patients. Patients with concomitant active infection, malignancy, or central or peripheral nervous system diseases (multiple sclerosis, stroke, radiculopathy, etc.) were excluded. To preserve clinical representativeness, patients using medications commonly prescribed for FM were not excluded. Their medication use was systematically documented and considered during data interpretation. All patients underwent a standard clinical evaluation by a physical medicine and rehabilitation specialist to exclude conditions such as carpal tunnel syndrome (CTS) and cervical disc herniation, which have the potential for symptomatic overlap with FM. Phalen and Tinel tests were performed for CTS, and the Spurling test and a detailed neurological examination were performed for cervical radiculopathy. In cases where clinical findings were suspicious, advanced diagnostic methods such as electromyography or cervical magnetic resonance imaging were used. In this way, peripheral or central nervous system diseases that could accompany or mimic a FM diagnosis were systematically excluded. Initially, a total of 178 patients diagnosed with FM according to the 2016 ACR criteria were screened for inclusion in the study. During the evaluation process, 38 patients with central or peripheral nervous system diseases were excluded from the study. These diseases were determined by a detailed neurological examination performed by a specialist physician, examination of the patients' medical history, and neuroimaging or electrophysiological tests when deemed necessary. As a result, 140 patients who did not have neurological comorbidities and met all inclusion criteria were included in the study.

Verbal and written consent was obtained from all participants with the approval of the local ethics committee for the study (protocol number: 22/640, approval date: 30.12.2022). This study protocol was registered with ClinicalTrials.gov (ClinicalTrials.gov identifier: NCT05701696) and performed following the STROBE Statement [17].

Clinical variables

Demographic and clinical data of all participants were collected through interviews and clinical scales. The duration of the disease and current medical treatments were recorded. The pain intensity was assessed on an 11-point visual analog scale (VAS) (0: no pain, 10: most severe pain imaginable).

https://doi.org/10.5455/annalsmedres.2025.04.085

Primary outcome measurements

Central Sensitization Inventory (CSI)

The CSI, which is divided into two parts, A and B, has been developed primarily to identify CS findings in individuals with chronic pain. Twenty-five items in Part A include somatic and psychosocial health-related symptoms, which are often present in conditions associated with CS. Respondents rate each item on a 5-point Likert scale, ranging from 'never' (0) to 'always' (4), resulting in a maximum possible score of 100. Patients with 40 points and above are considered to have central sensitization syndrome (CSS), and greater scores correspond to more severe CSS [18]. The suggested CSI cut-off values for FM patients in this study were used to classify the patients into four groups: 21 between remission and mild severity, 30 between mild and moderate severity, 37 between moderate and severe disease, and 51 between severe and very severe disease [9]. The patient is questioned in Part B about any medical conditions that fall within the category of CSS diagnoses [19]. The Turkish adaptation of the CSI has been established as valid and reliable [20] (Appendix A).

The Self-Leeds Assessment of Neuropathic Symptoms and Sign (S-LANSS)

The S-LANSS pain scale has been developed to detect individuals with chronic pain that is primarily driven by neuropathic processes. A score of 12 or above out of 24 points on the scale consisting of 7 items is considered in favor of NeuP [13]. It has been demonstrated that the Turkish version of S-LANSS is valid and reliable for identifying neuropathic components in chronic pain patients [21] (Appendix B).

Secondary outcome measurements

Fibromyalgia Severity Scale (FSS)

Widespread Pain Index (WPI)

Five regions total—the axial region, the lower right and left regions, and the upper right and left regions—are noted on this scale with the locations of pain experienced during the prior seven days. The total score ranges from 0 to 19, with a WPI of 7 or more considered essential for the diagnosis of FM.

Symptom Severity Scale (SSS)

In Part A of this scale, fatigue, waking unrefreshed, and cognitive symptoms in the last week are questioned, and each question is scored between 0 and 3 (maximum score of 9). In Part B, the presence of headache, pain, or cramps in the lower abdomen and depression in the last 6 months is evaluated (maximum score of 3). The final SSS is between 0 and 12.

The FSS is the sum of the WPI and SSS. WPI $\geq$ 7 and SSS $\geq$ 5, or WPI = 4-6 and SSS $\geq$ 9, is in favor of FM (Appendix C) [22].

Fibromyalgia Impact Questionnaire (FIQ)

This questionnaire was developed by Burckhardt et al. to determine the degree of disease impact on the current health status of women with FM [23]. The FIQ is composed of 10 items in total, with the initial item being structured as an 11-item Likert scale. The total value ranges from 0 to 100, and higher scores indicate more severe effects on daily activities. Its reliability and validity have been established for assessing functional disability among Turkish women with FM [24] (Appendix D).

Hospital Anxiety and Depression Scale (HADS)

This scale was developed by Zigmond and Snaith in 1983 to screen for anxiety and depression in individuals with physical illness [25]. The HADS comprises a total of 14 questions, with 7 focusing on anxiety and 7 on depression. Participants respond to these questions using a four-point Likert scale (0–3). The Turkish validity and reliability of the scale have been demonstrated, and a score above 10 for anxiety and above 7 for depression is considered significant [26] (Appendix E).

Data analysis

This study was completed with 140 patients overall, and the minimal sample size determined based on the previous study was 111 to achieve an error alpha of 0.05 for a 95% confidence interval (CI) and a power of 0.95 [14]. G*power (v3.1.9.4; University of Dusseldorf, Dusseldorf, Germany) was used for the computation of sample size.

Statistical analysis

Statistical model selection was based on normality tests, and Shapiro-Wilk tests, skewness-kurtosis, and histogram graphs were used to assess data distribution. Data having an absolute skew value less than two and an absolute kurtosis (proper) value less than seven was considered to have a normal distribution [27]. Due to the parametric distribution of the data, continuous variables were presented using the mean and standard deviation (SD). Using the independent t-test for continuous data, Pearson's chi-square, and Fisher's exact test for categorical variables, patient variables were compared based on the presence of NeuP. A one-way ANOVA was used to compare the following clinical variables at three levels of CSI: symptom duration, WPI, VAS, SSS, FIQ, S-LANSS, and HADS. Post-hoc multigroup comparisons were applied with the Tukey test.

To investigate the linear association between S-LANSS and CSI scores and selected clinical parameters, bivariate correlation analysis was applied. Finally, hierarchical regression models were constructed, and the variables included in the model and the order of inclusion were determined by taking into account the results of univariate regression analysis and previous similar studies [14, 28]. Before the regression model was

https://doi.org/10.5455/annalsmedres.2025.04.085

fitted to a dataset, assumptions were tested, including linearity, independence, multicollinearity, and normality. To assess the potential for multicollinearity across all of the explanatory factors, we used the variance inflation factor (VIF). No significant multicollinearity was found, as indicated by a VIF < 5 [29]. The effect of medical treatment on the S-LANSS score was examined by regression analysis, whereby the subcategories were coded as dummy variables. Four (n-1) dummy codes representing the treatment categorical variable were included in the regression analysis. The patient group that did not receive medical treatment was selected as the reference category and was not included in the regression model as a predictor. With a 95% CI, a value of $p<0.05$ was considered statistically significant in all analyses conducted using SPSS version 26.0 (IBM Corporation, Armonk, NY, USA).

RESULTS

The mean (SD) age of 140 female patients participating in the study was 44.38 (10.77) years, and the mean (SD) BMI value was 27.58 (5.13) kg/m^2. Patients' mean (SD) pain intensity was 7.55 (SD: 1.52) on a 0–10 scale, and the mean (SD) pain duration was 55.57 (SD: 43.82) months. Out of the total patients, 102 were on duloxetine (72.9%), 8 were on pregabalin (5.7%), 5 were on amitriptyline (3.6%), and 8 were on a combination of pregabalin and duloxetine (5.7%). The mean daily dose was 40.91 mg (SD = 14.50) in 110 patients using duloxetine, 285.00 mg (SD = 50.71) in 15 patients using pregabalin, and 25.00 mg (SD = 0) in 5 patients using amitriptyline. Of the patients, 12.1% were not receiving any medical treatment (Table 1). The mean (SD) values of patients for WPI, SSS, and FSS were calculated as 11.88 (3.55), 8.66 (2.15), and 20.48 (4.73), respectively.

Table 1. Comparison of patients' characteristics according to the presence of neuropathic pain (values are presented as mean ± standard deviation or n (%), as appropriate).

	FM patients (n=140)		P-value
	NeuP- (n=25)	NeuP+ (n=115)	
Age (year), mean (SD)	47.60 (12.49)	43.68 (10.29)	0.153
Marital status			
Married	18 (72)	96 (83.5	0.181
Single	7 (28)	19 (16.5)	
Education level			
Primary school	12 (48)	2 (33)	0.277
Middle school	2 (8)	20 (17.4)	
High school	5 (20)	36 (31.3)	
University	6 (24)	21 (18.3)	
Job			
Housewife	12 (48)	61 (53)	0.148
Student	2 (8)	13 (11.3)	
Laborer	0 (0)	6 (5.2)	
Servant	2 (8)	12 (10.4)	
Retired	5 (20)	5 (4.3)	
Self-employment	4 (16)	18 (15.7)	
BMI (kg/m^2)	28.93 (5.11)	27.27 (5.10)	0.151
Symptom duration (months)	61.68 (45.81)	54.22 (43.46)	0.462
VAS	6.68 (1.77)	7.75 (1.39)	0.008*
Medical treatment			
Duloxetine	18 (72)	84 (73)	0.738
Pregabalin	1 (4)	7 (6.1)	
Amitriptyline	1 (4)	4 (3.5)	
Duloxetine+ Pregabalin	1 (4)	7 (6.1)	
None	4 (16)	13 (11.3)	

BMI: Body mass index, VAS: Visual analog scale. *statistically significance.

A total of 135 patients (96.4%) had a CSS, and the mean (SD) CSI score for all patients was found to be 61.39 (13.03). When the patients were categorized according to the severity levels of CSI, the percentages were calculated as mild 2.1% (n = 3), moderate 0.7% (n = 1), severe 15.7% (n = 22), and very severe 81.4% (n = 114), respectively.

The mean (SD) S-LANSS score of the participants was 15.06 (5.61), and there were 115 patients (82.1%) with NeuP. There was no CSS and NeuP in 5 patients (3.6%); 20 patients (14.3%) had CSS but no NeuP; and 115 patients (82.1%) had both CSS and NeuP. Table 2 presents a comparison of clinical scales based on the presence of NeuP.

At different CSI levels, the S-LANSS score had a significant difference in the one-way analysis of variance ($p<.001$) (Table 3). Pearson correlation coefficients between CSI and S-LANSS scores and the VAS, SSS, FIQ, and HADS anxiety subscore were statistically significant ($p<.05$), indicating a significant linear relationship for both scales with these clinical parameters. Only the CSI score was statistically significantly correlated with the WPI and HADS depression subscores ($p = .011$ for WPI, $<.001$ for HADS). Age, BMI, and the duration of symptoms did not significantly correlate with CSI and S-LANSS ($p>.05$). The correlation analysis of S-LANSS and clinical parameters is represented in the scatter plots in Figure 1. The analysis revealed no statistically significant correlation between the administered drug dosages and S-LANSS scores ($p>.05$).

In univariate linear regression analysis, CSI, VAS, FIQ, SSS, FSS, and HADS-anxiety were significantly associated with S-LANSS ($p\leq.001$). Four variable blocks were implemented in a hierarchical multiple regression analysis to examine the variables' efficacy in predicting variations in S-LANSS scores. The results of hierarchical regression showed that patients' disease-related factors, including VAS, SSS, FSS, and FIQ, tested in block 1, explained 20% of the variance in their S-LANSS score ($F(4,131) = 8.32$, $p<.001$, $R^2 = 0.20$). Only the FIQ score ($p = .001$) was associated with the S-LANSS increase; other disease-related factors were not statistically significant ($p>.05$). In block 2, medical treatment variables were included in the model, but no significant effect of treatment on the variance of the S-LANSS score was found ($F(4,127) = 4.75$, $p = .341$, $R^2 = 0.23$, $\Delta R^2 = 0.03$). The third block ($F(2,125) = 3.75$, $p = .954$, $R^2 = 0.23$), which included HADS

https://doi.org/10.5455/annalsmedres.2025.04.085

Table 2. Comparison of clinical scales according to the presence of neuropathic pain (values are presented as mean ± standard deviation or n (%), as appropriate).

	FM patients (n=140)		P-value
	NeuP- (n=25)	NeuP+ (n=115)	
WPI	11.56 (3.04)	11.93 (3.62)	0.597
SSS	8.00 (2.47)	8.79 (2.04)	0.144
FSS	19.56 (4.29)	20.64 (4.76)	0.269
FIQ	59.64 (17.05)	70.14 (12.03)	0.007*
CSI-A	52.40 (16.80)	63.35 (11.22)	<0.001*
CS severity			
Moderate	7 (28)	13 (11.3)	
Severe	3 (12)	32 (27.8)	<0.001*
Extreme	10 (40)	70 (60.9)	
CSI-B			
Restless leg syndrome	3 (12)	12 (10.4)	0.732
Chronic fatigue syndome	3 (12)	10 (8.7)	0.703
Temporomandibular joint disorder	1 (4)	3 (2.6)	0.549
Tension headaches/migraines	7 (28)	42 (36.5)	0.418
Anxiety or panic attacks	7 (28)	37 (32.2)	0.684
Depression	10 (40)	47 (40.9)	0.936
HADS-Anxiety	10.92 (4.04)	11.48 (3.63)	0.529
HADS-Depression	9.04 (3.06)	9.08 (3.61)	0.955
S-LANSS	5.36 (3.78)	17.17 (3.19)	<0.001*

WPI: Widespread pain index, SSS: Symptom severity scale, FSS: Fibromyalgia severity scale, FIQ: Fibromyalgia Impact Questionnaire, CS: Central sensitization, CSI: Central sensitization inventory, HADS: Hospital Anxiety Depression Scale, S-LANSS: Self-leeds assessment of neuropathic symptoms and sign, NeuP: Neuropathic pain. *statistically significance.

Table 3. Clinical features and post-hoc results of patients according to the Central Sensitization Inventory severity levels (values are presented as mean ± standard deviation).

	CS+			P-value	Post-hoc
	Moderate (I) (n=20)	Severe (II) (n=35)	Extreme (III) (n=80)		
Symptom duration	58.80 (41.37)	46.09 (32.73)	58.56 (48.53)	0.352	-
VAS	6.95 (1.54)	7.15 (1.56)	7.99 (1.23)	0.001*	I vs III, II vs III
WPI	10.95 (3.41)	11.40 (2.77)	12.30 (3.86)	0.212	-
SSS	6.30 (1.81)	8.20 (1.80)	9.59 (1.69)	<0.001*	I vs II, II vs III, I vs III
FIQ	57.54 (11.29)	64.92 (13.61)	73.64 (10.10)	<0.001*	I vs III, II vs III
HADS-Anxiety	7.85 (2.80)	10.29 (3.29)	12.89 (3.17)	<0.001*	I vs II, II vs III, I vs III
HADS-Depression	6.80 (3.05)	8.35 (3.31)	9.99 (3.40)	<0.001*	I vs III, II vs III
S-LANSS	11.45 (5.36)	16.11 (3.84)	16.29 (5.14)	<0.001*	I vs II, I vs III

BMI: Body mass index, VAS: Visual analog scale, WPI: Widespread pain index, SSS: Symptom severity scale, FIQ: Fibromyalgia Impact Questionnaire, CS: Central sensitization, CSI: Central sensitization inventory, HADS: Hospital Anxiety Depression Scale, S-LANSS: Self-leeds assessment of neuropathic symptoms and sign. *statistically significance.

anxiety and depression subscores, did not yield a significant change in variation compared to the second block. Overall, the final model, including all variables, explained 30.5% of the S-LANSS variance ($F(1,124) = 3.75$, $p<.001$, $R^2 = 0.30$), while the CSI explained an additional 7.4% of the variance when included in the model. The results of the hierarchical regression analysis indicated that FIQ and CSI were independently associated with S-LANSS variation ($p = .036$ and $< .001$, respectively) and that the models constructed were statistically significant ($p<.01$). The regression analysis results are detailed in Table 4.

DISCUSSION

This study investigated the association between neuropathic complaints and CS-related symptoms in female FM patients. This study offers a novel perspective by revealing a graded association between CS symptom severity and neuropathic complaints in female FM patients, using validated tools. Our results indicate that higher CSI and S-LANSS scores are associated with greater disease activity, as reflected by increased SSS and FIQ scores, highlighting their relevance in assessing overall symptom burden in FM.

Using S-LANSS, the prevalence of NeuP was found to be 82.1%, and the severity of neuropathic complaints increased

https://doi.org/10.5455/annalsmedres.2025.04.085

Table 4. Hierarchical regression analysis results examining the relationship between the Self-Leeds Assessment of Neuropathic Symptoms and Sign and selected clinical parameters.

Predictors	S-LANSS						
	B	SE B	β	R^2	p	95% CI for B	
						Lower	Upper
Step 1				0.20	<0.001*		
VAS	0.46	0.37	0.12		0.222	-0.28	1.20
SSS	0.22	0.30	0.08		0.467	-0.37	0.81
FSS	-0.10	0.13	-0.08		0.453	-0.35	0.16
FIQ	0.15	0.04	0.35		0.001*	0.06	0.23
Step 2¨				0.23	0.300		
Duloxetine	2.64	1.40	0.21		0.062	-0.01	5.24
Pregabalin	1.80	2.21	0.08		0.545	-2.24	6.19
Amitriptyline	4.56	2.64	0.15		0.121	-0.64	9.50
Duloxetine+ Pregabalin	3.43	2.23	0.14		0.188	-0.65	7.87
Step 3~				0.23	0.751		
HADS-Anxiety	-0.45	0.14	-0.03		0.751	-0.33	0.24
HADS-Depression	-0.01	0.16	-0.01		0.940	-0.34	0.31
Step 4				0.30	<0.001*		
VAS	0.51	0.36	0.14		0.161	-0.21	1.24
SSS	-0.11	0.26	-0.04		0.483	-0.70	0.33
FSS	-0.06	0.13	-0.05		0.650	-0.30	0.19
FIQ	0.10	0.05	0.25		0.036*	0.01	0.20
Duloxetine	2.85	1.33	0.21		0.058	0.20	5.50
Pregabalin	2.22	2.13	0.08		0.369	-2.01	6.44
Amitriptyline	5.06	2.54	0.16		0.068	0.03	10.09
Duloxetine+ Pregabalin	4.14	2.15	0.17		0.071	-0.34	8.27
HADS-Anxiety	-0.19	0.14	-0.13		0.402	-0.47	0.19
HADS-Depression	-0.10	0.16	-0.06		0.524	-0.42	0.21
CSI	0.15	0.04	0.34		<0.001*	0.08	0.26

S-LANSS: Self-leeds assessment of neuropathic symptoms and sign , VAS: Visual analog scale, WPI: Widespread pain index, SSS: Symptom severity scale, FIQ: Fibromyalgia Impact Questionnaire, HADS: Hospital Anxiety Depression Scale, CSI: Central Sensitization Inventory, CI: Confidence interval, ¨Step 2 includes variables in step 1, ~Step 3 includes variables in step 2, *Statistically significant.

in parallel with CS-related symptoms. In research including 78 FM patients, NeuP was detected in 92.1% of the patients based on LANSS and 82.9% of the patients based on DN4 [30]. The prevalence of NeuP in FM patients as assessed using different questionnaires appears to be in line with this study's findings. However, it is emphasized that these questionnaires should be used to identify patients who deserve further clinical evaluation for NeuP rather than to make a definitive diagnosis [12]. Current guidelines state that a comprehensive clinical evaluation, including QST, should be the cornerstone of NeuP diagnosis. The findings of the examination should be bolstered by imaging, neurophysiology, biopsies, and laboratory testing [31]. Although it is not difficult to meet these requirements of NeuP in certain disease groups, this is not the case for FM.

The processes behind the development of NeuP, one of the primary clinical features of FM, are still not fully understood. Although there is not enough evidence to draw a definitive conclusion in these patients, there are opinions supporting the idea that NeuP is of peripheral or central origin. Small fiber neuropathy (SFN) is the most commonly postulated peripheral pathophysiological cause of NeuP, and the presence of SFN is supported by QST, skin biopsy, and confocal microscopy in these patients [32]. On the other hand, structural and functional neuroimaging studies support the hypothesis that FM and neuropathic complaints in these patients arise from dysfunction in the central pain processing [2]. A third possibility refers to a combination of peripheral and central involvement; in FM patients with SFN, alterations have been documented in the structural and functional connections of the encephalon that favor CS [33]. Furthermore, given the central role that CS plays in NeuP, some viewpoints suggest that it is not clinically possible to differentiate between CS pain and NeuP [34]. This hypothesis is supported not only by the involvement of CS in the pathophysiology of NeuP but also by the similarities between the QST findings, which are characterized by hyperalgesia and allodynia, and the medications used to treat NeuP and CS. By raising membrane excitability and synaptic effectiveness and lowering inhibition in nociceptive pathways, CS is hypothesized to have a key role in NeuP. While numerous molecules are known to play a part in the CS-NeuP relationship, animal models offer sufficient proof that Brain-Derived Neurotrophic Factor (BDNF) acts as a crucial function in regulating this association [35]. It has also been reported that serum BDNF levels are increased in FM patients and correlate with QST parameters [36]. These findings may make the relationship between neuropathic complaints and CS-related symp-

https://doi.org/10.5455/annalsmedres.2025.04.085

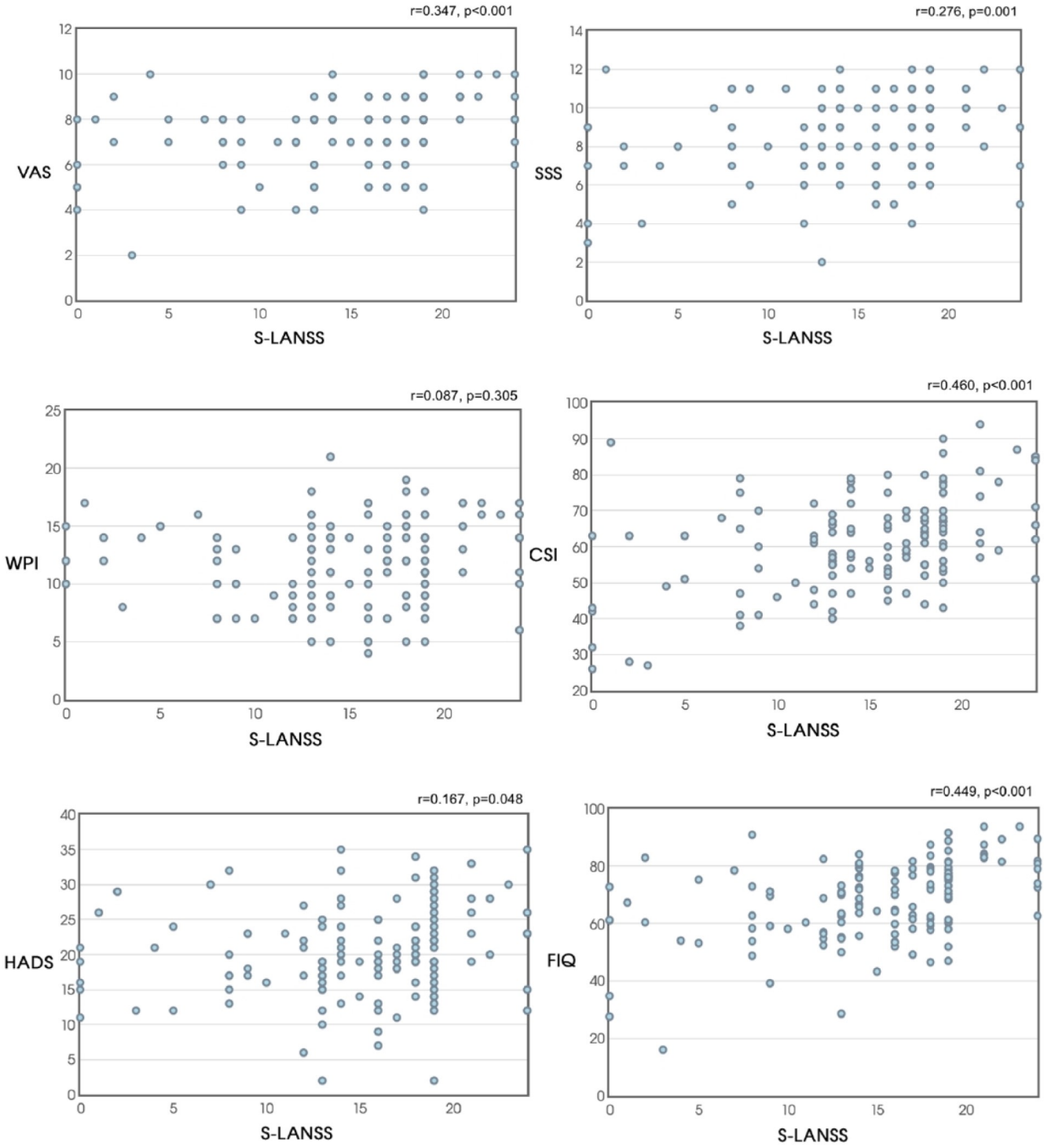

Figure 1. Scatter plots show the relationship between the Self-Leeds Assessment of Neuropathic Symptoms and Sign and other clinical scales.

toms more understandable in FM.

When evaluating the results, it is important to recognize the constraints of questionnaire utilization, even though these associations make sense given the role of CS in FM. The initial step in assessing the patient's symptom burden from CS is frequently to use CSI as a helpful tool. Comparably, in clinical practice, the initial step in evaluating NeuP frequently involves an array of questionnaires. However, it is unclear how well these NeuP scales work in the context of nociplastic pain because they were designed to differentiate between nociceptive and NeuP. A study involving patients with lumbar stenosis further implies that the correlation between PainDETECT and CSI might be brought about by factors that overlap, including widespread pain [37]. Yet although they may appear similar at first glance, NeuP and CS-related symptoms have fundamental differences. Unlike typical neuropathic com-

https://doi.org/10.5455/annalsmedres.2025.04.085

plaints limited to nervous system involvement, CS-related symptoms arise from hypersensitivity in multiple physiological systems. In addition to pain hypersensitivity, CS-related symptoms are linked to a more extensive hypersensitivity impacting several organs and systems across all sensory modalities, including light, sound, smell, and taste [38].

The diversity of the patients' medical treatments is another factor that could have an impact on the study's findings. Regression analysis revealed, however, that the treatment administered had no noticeable effect on the S-LANSS score. Only 10 to 25 percent of FM patients who are taking medication report being able to reduce their symptoms, including NeuP, and research indicates that a multimodal therapeutic approach may be helpful [2]. Consequently, it is not unexpected that the S-LANSS score is unaffected by the patients' drug use.

The clinical importance of CS-related symptoms in FM patients stems from their close relationship with disease severity and comorbidities [9]. This study result confirms that, in tandem with the severity of CS-related symptoms, there is an increase in pain intensity, disability, and psychological issues in FM. Despite the fact that FM is the prototype for central sensitivity syndromes, the clinical assessment of patients with FM does not usually include CS-related symptoms. It has been noted that because FM is a complex and clinically changeable condition, it is inappropriate to use a single symptom, such as pain severity, as a clinical outcome measure [39]. Similar to the findings of this study, Neblett et al. reported that the CSI score in FM patients tends to be at very severe levels and correlates with disease parameters [40]. An impression of the disease activity in FM may be obtained by combining CS-related symptoms with other clinical indicators such as pain and symptom severity, as well as neuropathic complaints.

The CSI and S-LANSS scores reported in our study reveal both overlapping and divergent aspects of CS and NeuP components in FM. It is reported that these two mechanisms often coexist in FM and may interact in the clinical presentation [5]. Our findings underline the complementary roles of CSI and S-LANSS in evaluating pain mechanisms in FM. While both scales may capture overlapping symptom domains, CSI primarily reflects CS processes, whereas S-LANSS identifies neuropathic features based on patient-reported symptoms and clinical signs. Using these tools together in FM may help identify distinct pain phenotypes and support more personalized treatment strategies in clinical practice.

Limitations

Limitations of this study include its cross-sectional design, inclusion of only female patients, and lack of quantitative methods to assess both CS and NeuP. Since the majority of FM patients in clinical practice are female, we think that this will not have a major impact on the interpretation of the results. However, it is not feasible to generalize the present findings to male FM patients. The fact that the participants were receiving medical treatment is not seen as a limitation; rather, we believe that in cases where patients cannot receive optimal treatment, the results may be misleading. Additionally, in this study, NeuP was assessed only with the S-LANSS scale. The fact that other scales such as PainDETECT or DN4 were not used may limit the comprehensive assessment of NeuP.

CONCLUSION

In this cross-sectional study, the frequency of NeuP investigated with S-LANSS in female FM patients was found to be 82.1%. Concomitant CSS was present in all cases with NeuP, and CSI had a significant effect on S-LANSS variation. Despite being excluded from the diagnosis of NeuP due to the lack of a particular lesion localized in the nervous system, FM patients' pain experiences are not substantially different from those of those who meet the International Association for the Study of Pain (IASP) definition. Whether or not there is disease involvement in the peripheral or central nervous systems, "neuropathic complaints" in FM may be considered one of the manifestations of CS when regarding shared pathophysiological mechanisms and the findings of this study. We hope that elucidating NeuP, which is frequently encountered in FM and still remains a gray zone, and its relationship with CS-related symptoms will be a guide in understanding this issue.

Ethics Committee Approval: Local ethics committee approval was obtained (University of Health Sciences Hamidiye Scientific Researchs Ethics Committee, protocol number: 22/640, approval date: 30.12.2022).

Informed Consent: All participants were informed about the purpose, methods, potential risks, and benefits of the study. Verbal and written informed consent was obtained from all participants prior to their inclusion in the study, in accordance with the Declaration of Helsinki.

Peer-review: Externally peer-reviewed.

Conflict of Interest: No conflict of interest was declared by the authors regarding this article.

Author Contributions: Conception and design of study: FNY; Acquisition of data: FNY, SK; Analysis and/or interpretation of data: FNY, SK; Drafting the manuscript: FNY, SK; Revising the manuscript critically for important intellectual content: FNY.

Financial Disclosure: No financial support was obtained for this study.

REFERENCES

1. Clauw DJ. Fibromyalgia: a clinical review. *JAMA.* 2014;311(15):1547-55. doi: 10.1001/jama.2014.3266.
2. Cheng CW, Wong CS, Hui GK, et al. Fibromyalgia: is it a neuropathic pain? *Pain Manag.* 2018;8(5):377-88. doi: 10.2217/pmt-2018-0024.
3. Latremoliere A, Woolf CJ. Central sensitization: a generator of pain hypersensitivity by central neural plasticity. *J Pain.* 2009;10(9):895-926. doi: 10.1016/j.jpain.2009.06.012.

https://doi.org/10.5455/annalsmedres.2025.04.085

4. Kosek E, Cohen M, Baron R, et al. Do we need a third mechanistic descriptor for chronic pain states? *Pain.* 2016;157(7):1382-6. doi: 10.1097/j.pain.0000000000000507.
5. Martinez-Lavin M. Dorsal root ganglia: fibromyalgia pain factory? *Clin Rheumatol.* 2021;40(2):783-7. doi: 10.1007/s10067-020-05528-z.
6. Finnerup NB, Kuner R, Jensen TS. Neuropathic Pain: From Mechanisms to Treatment. *Physiol Rev.* 2021;101(1):259-301. doi: 10.1152/physrev.00045.2019.
7. Arendt-Nielsen L, Yarnitsky D. Experimental and clinical applications of quantitative sensory testing applied to skin, muscles and viscera. *J Pain.* 2009;10(6):556-72. doi: 10.1016/j.jpain.2009.02.002.
8. Coronado RA, George SZ. The Central Sensitization Inventory and Pain Sensitivity Questionnaire: An exploration of construct validity and associations with widespread pain sensitivity among individuals with shoulder pain. *Musculoskelet Sci Pract.* 2018;36:61-7. doi: 10.1016/j.msksp.2018.04.009.
9. Salaffi F, Farah S, Mariani C, et al. Validity of the Central Sensitization Inventory compared with traditional measures of disease severity in fibromyalgia. *Pain Pract.* 2022;22(8):702-10.doi: 10.1111/papr.13162.
10. Neblett R, Sanabria-Mazo JP, Luciano JV, et al. Is the Central Sensitization Inventory (CSI) associated with quantitative sensory testing (QST)? A systematic review and meta-analysis. *Neurosci Biobehav Rev.* 2024;161:105612. doi: 10.1016/j.neubiorev.2024.105612.
11. Scerbo T, Colasurdo J, Dunn S, et al. Measurement Properties of the Central Sensitization Inventory: A Systematic Review. *Pain Pract.* 2018;18(4):544-54. doi: 10.1111/papr.12636.
12. von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet.* 2007;370(9596):1453-7. doi: 10.1016/s0140-6736(07)61602-x.
13. Mayer TG, Neblett R, Cohen H, et al. The development and psychometric validation of the central sensitization inventory. *Pain Pract.* 2012;12(4):276-85. doi: 10.1111/j.1533-2500.2011.00493.x.
14. Neblett R, Cohen H, Choi Y, et al. The Central Sensitization Inventory (CSI): establishing clinically significant values for identifying central sensitivity syndromes in an outpatient chronic pain sample. *J Pain.* 2013;14(5):438-45. doi: 10.1016/j.jpain.2012.11.012.
15. Düzce Keleş E, Birtane M, Ekuklu G, et al. Validity and reliability of the Turkish version of the central sensitization inventory. *Arch Rheumatol.* 2021;36(4):518-26. doi: 10.46497/ArchRheumatol.2022.8665.
16. Bennett MI, Smith BH, Torrance N, Potter J. The S-LANSS score for identifying pain of predominantly neuropathic origin: validation for use in clinical and postal research. *J Pain.* 2005;6(3):149-58. doi: 10.1016/j.jpain.2004.11.007
17. Koc R, Erdemoglu AK. Validity and reliability of the Turkish Self-administered Leeds Assessment of Neuropathic Symptoms and Signs (S-LANSS) questionnaire. *Pain Med.* 2010;11(7):1107-14. doi: 10.1111/j.1526-4637.2010.00837.x
18. Wolfe F, Clauw DJ, Fitzcharles MA, et al. 2016 Revisions to the 2010/2011 fibromyalgia diagnostic criteria. *Semin Arthritis Rheum.* 2016;46(3):319-29. doi: 10.1016/j.semarthrit.2016.08.012.
19. Burckhardt CS, Clark SR, Bennett RM. The fibromyalgia impact questionnaire: development and validation. *J Rheumatol.* 1991;18(5):728-33.
20. Sarmer S, Ergin S, Yavuzer G. The validity and reliability of the Turkish version of the Fibromyalgia Impact Questionnaire. Rheumatol Int. 2000;20(1):9-12.doi: 10.1007/s002960000077
21. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand.* 1983;67(6):361-70. doi: 10.1111/j.1600-0447.1983.tb09716.x.
22. Aydemir O, Güvenir T, Küey L, Kültür S. Validity and Reliability of Turkish Version of Hospital Anxiety and Depression Scale. *Turkish Journal of Psychiatry.* 1997;8(4):280-7.
23. Ubeda-D'Ocasar E, Valera-Calero JA, Gallego-Sendarrubias GM, et al. Association of Neuropathic Pain Symptoms with Sensitization Related Symptomatology in Women with Fibromyalgia. *Biomedicines.* 2022;10(3). doi: 10.3390/biomedicines10030612.
24. Kim HY. Statistical notes for clinical researchers: assessing normal distribution (2) using skewness and kurtosis. *Restor Dent Endod.* 2013;38(1):52-4. doi: 10.5395/rde.2013.38.1.52.
25. Zhang Y, Ma H, Bai Y, et al. Chronic Neuropathic Pain and Comorbid Depression Syndrome: From Neural Circuit Mechanisms to Treatment. *ACS Chem Neurosci.* 2024;15(13):2432-44. doi: 10.1021/acschemneuro.4c00125.
26. Du S, Hu Y, Bai Y, et al. Emotional Distress Correlates Among Patients With Chronic Nonspecific Low Back Pain: A Hierarchical Linear Regression Analysis. *Pain Pract.* 2019;19(5):510-21. doi: 10.1111/papr.12772.
27. Akaltun MS, Altindağ Ö, Akyol A, et al. Neuropathic Pain and Its Relationship with Clinical Findings in Patients with Fibromyalgia. *Noro Psikiyatr Ars.* 2022;59(1):44-7. doi: 10.29399/npa.25092.
28. Attal N, Bouhassira D, Baron R. Diagnosis and assessment of neuropathic pain through questionnaires. *Lancet Neurol.* 2018;17(5):456-66. doi: 10.1016/S1474-4422(18)30071-1.
29. Haanpää M, Attal N, Backonja M, et al. NeuPSIG guidelines on neuropathic pain assessment. *Pain.* 2011;152(1):14-27. doi: 10.1016/j.pain.2010.07.031
30. Oaklander AL, Herzog ZD, Downs HM, Klein MM. Objective evidence that small-fiber polyneuropathy underlies some illnesses currently labeled as fibromyalgia. *Pain.* 2013;154(11):2310-6. doi: 10.1016/j.pain.2013.06.001.
31. Aster HC, Evdokimov D, Braun A, et al. CNS imaging characteristics in fibromyalgia patients with and without peripheral nerve involvement. *Sci Rep.* 2022;12(1):6707. doi: 10.1038/s41598-022-10489-1.
32. Toda K. Central sensitization pain should be included in (central) neuropathic pain. *Pain Physician.* 2014;17(6):E783.
33. Vanelderen P, Rouwette T, Kozicz T, et al. The role of brain-derived neurotrophic factor in different animal models of neuropathic pain. *Eur J Pain.* 2010;14(5):473 e1-9. doi: 10.1016/j.ejpain.2009.09.006.
34. Nijs J, Meeus M, Versijpt J, et al. Brain-derived neurotrophic factor as a driving force behind neuroplasticity in neuropathic and central sensitization pain: a new therapeutic target? *Expert Opin Ther Targets.* 2015;19(4):565-76. doi: 10.1517/14728222.2014.994506.
35. Iwasaki R, Miki T, Miyazaki M, et al. Neuropathic Pain Was Associated with Central Sensitivity Syndrome in Patients with Preoperative Lumbar Spinal Stenosis Using the painDETECT and Central Sensitization Inventory Questionnaires: A Cross-Sectional Study. *Pain Res Manag.* 2023;2023:9963627. doi: 10.1155/2023/9963627.
36. Mezhov V, Guymer E, Littlejohn G. Central sensitivity and fibromyalgia. *Intern Med J.* 2021;51(12):1990-8. doi: 10.1111/imj.15430.
37. Sarzi-Puttini P, Giorgi V, Atzeni F, et al. Fibromyalgia position paper. *Clin Exp Rheumatol.* 2021;39 Suppl 130(3):186-93. doi: 10.55563/clinexprheumatol/i19pig.
38. Neblett R, Hartzell MM, Mayer TG, et al. Establishing Clinically Relevant Severity Levels for the Central Sensitization Inventory. *Pain Pract.* 2017;17(2):166-75. doi: 10.1111/papr.12440.

https://doi.org/10.5455/annalsmedres.2025.04.085