Original Article

Chronic nonspecific multiple-sites pain [CNMSP] of unknown etiology: Biopsychosocial method of evaluation for the primary care level

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Abstract

Background: Understanding and dealing with chronic nonspecific pain (CNP) is the important entity at primary care hospital. Chronic nonspecific multiple-site pain [CNMSP] of unknown etiology creates diagnostic and therapeutic challenges for primary care physicians due to lack of guidance regarding evaluation and treatment. **Aims and Objectives:** To classify and formulate the evaluation, treatment strategies, and prediction of prognosis of patients with CNMSP of unknown etiology. **Methods:** Patients present with CNMSP of more than 3-month duration without any obvious medical cause. The biopsychosocial [BPS] model with 3P model was applied to see the biological, psychological, and social factors behind persistence. Finally, patients were classified into four groups for evaluation response to treatment and relapse rates in 12-month follow-up. **Results:** Of the total 243 patients of CNMSP, 243 [96.3%] were females. Sixty [24.7%] patients had short duration, and 183 [75.3%] had long duration. Headache was in 115 [47%], low back pain ± leg pain in 96 [39.4%], cervical pain ± shoulder/arm pain in 83 [34.1%], and diffuse body pain in 50 [20.5%] in various combinations. A total of 155 [63.8%] patients had high somatization–sensitization index (SSI), and 144 [59.3%] had low ferritin level. Group 1 [high SSI and low ferritin] had 37.9% of patients, group 2 [high SSI and normal ferritin] had 25.9% of patients, group 3 [low to medium SSI with low ferritin] had 21.4% of patients, and group 4 [low to medium SSI with normal ferritin] had 14.8% of patients. Response to pain symptoms was better in group 1, and relapse rate was higher in group 2. **Conclusion:** CNMSP of unknown etiology itself is a heterogeneous entity, and assessment based on the BPS model can be very useful to understand the treatment plan and outcome of these patients.

Keywords: Non-neuropathic pain, non-nociceptive pain, third dimension of pain

Introduction

Chronic pain [>3-month duration] is a very common presenting symptom at the primary care level, and it is a big challenge for clinicians to distinguish the different types of chronic pain and management of these patients.[1] After many years, chronic pain is now an established clinical entity as it was included in the International Classification of Diseases 11th Revision (ICD-11) classification.[2] At the primary care level, chronic pain can be cancer-related and non-cancer-related. Globally, around 30% of patients are suffering from chronic non-cancer pain resulting in high economic burden.[3,4]

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Two recognizable dimensions of chronic pain are as follows: [a] neuropathic component due to direct injury or damage of nerve tissue, and [b] nociceptive component, which is due to overstimulation of pain receptors by neurochemical agents or inflammatory cytokines.[5] There is another [third] less recognized dimension of chronic pain without any obvious tissue insult and that is called non-neuropathic/non-nociceptive pain. This third dimension of pain has been named in the literature as chronic nonspecific pain [CNP], chronic nonspecific musculoskeletal pain [CNSMSP], and chronic myofascial pain syndrome [MPS].[6-8]

Central neurogenic hypersensitization [CNH] is supposed to be the leading mechanism to explain the third dimension [non-neuropathic/non-nociceptive] of pain in the absence of any recognizable medical cause.[9,10] CNH works through increased signals and low threshold of descending periaqueductal gray matter [PAG]–rostral ventromedial medulla [RVM] pathway.[11] PAG is the primary control for descending pain modulation and it contains enkephalin-producing cells for suppressing the pain, and RVM sends descending inhibitory and excitatory fibers to the dorsal horn of the spinal cord through three categories of cells: on-cells, off-cells, and neutral-cells. In CNH, the "on-cells" can persistently fire even without any nociceptive stimuli and result in chronic pain.[11]

Patients having this third dimension of pain at the primary care level are large in number and respond poorly to the treatment. In an article published on patients of chronic low back pain, it is shown that about 70% of patients were categorized under this nonspecific etiology and a special approach of evaluation was recommended for such patients.[6,12]

At the primary care level, patients of CNP can have focal/segmental pain such as low back pain or cervicobrachial pain but more commonly they can present with diffuse or multiple-site body pain. Evaluation and management of patients presenting with diffuse or chronic nonspecific multiple-site pain [CNMSP] is challenging when all relevant investigations are within normal range.[13-17] Patients with CNP undergo repeated testing such as magnetic resonance imaging/computed tomography (MRI/CT) scan and blood test without any positive results and then labelled as psychogenic pain syndrome.[18] Person with CNMSP of unknown etiology can be termed as fibromyalgia syndrome [FMS], somatic symptom disorder [SSD], chronic fatigue syndrome [CFS], MPS, or systemic exercise intolerance disorder [SEID], which are associated with many overlapping diagnostic criteria, thus creating high confusion for the primary care doctors.[15-20]

The evaluation of a patient presenting with CNMSP without obvious medical cause needs the biopsychosocial [BPS] model for further management.[6,20] The BPS model has three components: biological, psychological, and social. Therefore, through this study, we are going to describe method of the BPS model for the evaluation of patients with CNMSP of unknown etiology so that the classification and treatment of these patients can be easy at the primary care level.

Method

Target were patients presenting with whole body pain or ≥ four sites of body pain for >3-month duration without any obvious medical cause to explain symptoms [labeled as CNMSP of unknown etiology]. The hospital-based observational cohort study was cleared by the Institutional Ethical Committee, and the patient's consent was obtained before inclusion in the study.

Included patients with CNMSP of unknown etiology should have normal neurological examination [no objective sensory loss, wasting, or weakness] and should have no metabolic, traumatic, degenerative, compressive, neoplastic, inflammatory, or rheumatological cause to explain chronic pain. Patients should not have any definitive abnormality on radiological scan of the concern area. Patients having background of chronic illnesses such as diabetes, cancer, tuberculosis, psoriasis, autoimmune diseases, radiation exposure, psychiatric illness, or systemic failure were excluded. Patients having history of dengue, chikungunya, genitourinary infection, gastrointestinal infection, or other viral infections in the past 3 months were also excluded. To summarize, patients having CNMSP of more than 3 months that cannot be explained by common neurological, rheumatologic, orthopedic, traumatic, or other medical causes were included. All patients were then subjected to chronic pain grade scale [CGPS, Annexure 1], and patients having score ≥50 were included in the study.[21] Short-duration illness was labeled if the duration of symptoms was 3–12 months, and long-duration illness was labeled, if pain symptoms persisted for more than 12-month duration.

Application of the BPS Model with 3P Model:

Biological factor assessment was conducted for estimation only for nutritional deficiency serum ferritin level along with hemoglobin [HB] and mean corpuscular volume [MCV] was conducted for iron deficiency, and patients who had serum ferritin <15 ng/ml ± low HB/MCV were labeled as low ferritin group. Serum level of vitamin D below 50 nanomoles/L or below 20 nanogram/ml was taken as low, while B12 levels below 200 picogram/ml were taken as low.

Psychosocial assessment of all patients was conducted with the help of a questionnaire for the diagnosis of SSI and central sensitization index. This 25-point questionnaire [Annexure 2] was based on validated somatization symptom scale [SSS-8] for SSI and central sensitization inventory [CSI] for central sensitization index as described in the previous study.[22] Patients who scored >50 were labeled as having high SSI. 3P-Disease model [Annexure 3] was applied in follow-up for knowing the predisposing, precipitating, and perpetuating factors for chronic pain.[23]

Grouping of all patients

After the biological and psychosocial assessment, patients were finally kept in the following four clinical groups depending on the findings of SSI [high or low] and serum ferritin level [high or low];

1. Group 1: high SSI with ferritin below 15 ng/ml or 15 μg/L
2. Group 2: high SSI with ferritin above 16 ng/ml or 16 μg/L
3. Group 3: low SSI with ferritin below 15 ng/ml or 15 μg/L
4. Group 4: low SSI with ferritin above 16 ng/ml or 16 μg/L.

Medical treatment given

After classification, patients were subjected to standard medical treatment with initial short-duration non-steroidal anti-inflammatory or opioid analgesics and long-term maintenance therapy with pain modification drugs [antiepileptic and/or antidepressant]. Along with pain modification drugs, the ferritin correction was conducted with iron supplementation and other deficiencies were corrected with vitamin D and B12 supplementation.

Follow-up

Drug titration and tolerability assessment were conducted in the first 2 weeks and then monthly follow-up visits till next 6 months. Patients having low serum ferritin, B12, and vitamin D were reviewed after 3 months to see the rise in the ferritin level of >50ng/dl, vitamin D >50 nanomoles/L, and B12 level >300 picogram/ml. At the end of 3 months, patients having CGPS grades of <25 were labeled as "good responders" and patients with CGPS score of >25 were labeled as "poor responders." In the good responder group, pain modification drug treatment was gradually stopped in the next 3 months and further follow-up continued for 6 months more without medicine to look for any relapses [maximum follow-up time was 12 months]. Patients in the poor responder group were subjected to other adjunctive treatments with pain modification drugs.

Final outcome analysis was conducted at the end of 1 year, and depending on response and relapses, patients were categorized into three groups:

1] Good responder without relapses: when patients had low intensity of pain or no pain persistent CGPS <25 and had no relapse within 3 months of stopping pain modification drugs,
2] Good responder with relapses: when patients had low intensity of pain or no pain and persistent CGPS <25 but had relapse of symptoms within 3 months of stopping pain modification drugs,
3] Poor responder: persistent GGPS above 25 with frequent high intensity of pain.

Statistical analysis

Data analysis was conducted for frequency and association parameters with the help of the Statistical Package for the Social Sciences (SPSS) IBM version 25 [USA]. The frequency of nutritional deficiency and the level of SSI were calculated among patients with CNMSP. Finally, the association of outcome was correlated with ferritin deficiency and SSI with cross-tab analysis. The association of deficient ferritin value [<15 ng/ml] with hemoglobin values was also calculated. A *P* value of > 0.05 on the Chi-square test was taken as significant in association analysis.

Results

Among 280 registered patients, 243 [86.8%] patients of CNMSP of unknown etiology with the mean age of 38.5 years completed the 12-month follow-up, of which >90% were female. A total of 60 [24.7%] patients had short duration and 183 [75.3%] had long duration. Distribution of pain was as follows: headache in 115 [47%] patients, low back pain ± leg pain in 96 [39.4%], cervical pain ± shoulder/arm pain in 83 [34.1%], and diffuse body pain in 50 [20.5%] with various combinations. Among patients of CNMSP of unknown etiology, high SSI was found in 155 [63.8%] patients. Low level of ferritin [<15 ng/ml] was detected in 59.3% of patients, and low vitamin D and B12 level was found in 42.8% of patients [Table 1].

The relationship of low ferritin level with hemoglobin level had shown that among 144 patients with low ferritin, 81 [56.25%] had normal hemoglobin level [Table 2].

The distribution of patients in different clinical groups is shown in Table 3. The most common was group 1 [high SSI and low ferritin <15] with 37.9% of patients. Group 2 [high SSI and ferritin >16] had 25.9% of patients, group 3 [low SSI with low ferritin <15] had 21.4% of patients, and group 4 [low SSI with low ferritin >16] had 14.8% of patients.

The response and relapse rates of pain symptoms in all patients are shown in Table 4. Early improvement and response to treatment were significantly better in group 1 [86.6%] and group 3 [88.6%] as compared to 51.9% in group 2 and 60% in group 4 patients [*P* value = 0.00001].

Relapses were significantly higher in group 1 and group 2 patients [patients with high SSI] with the rate of

Table 1: General characteristics of patients with chronic pain syndrome (*n*=243)

Parameters	Findings
Age	13–72 years (mean age of 38.5 years)
Gender	Male=9 (3.7%) and female 234 (96.3%)
Duration of symptoms	Short (< 12 months)=60 (24.7%) with mean duration of 6.4 months Long (> 12 months)=183 (75.3%) with mean duration of 54 months
Symptoms	Headache=57 (23.5%) Cervicobrachial and hemibody pain=33 (13.6%) Lumbago-sciatica pain=46 (18.9%) Multiple-site pain (four or more sites)=57 (23.5%) Whole body pain=50 (20.5%)
Somatization and sensitization index (SSI)	High (if SSS-8 >12 and/or CSI >50)=155 (63.8%) Low or medium (if SSS-8 <12 and/or CSI <50)=88 (36.2%)
Ferritin level	Low (<15 ng/ml or 15 μg/L)=144 (59.3%) Normal (>15 ng/ml or 15 μg/L)=99 (40.7%)
Other deficiencies of vitamin D and B12	Yes=104 (42.8%) No=139 (57.2%)
Hemoglobin level	Low (<11 gm)=68 (28%) Normal (11 gm and above)=175 (72%)

Table 2: Correlation of ferritin level and hemoglobin level. Iron deficiency can occur with normal HB as 56.25% of patients with ferritin <15 ng/ml had normal HB

Hemoglobin (HB) Level	Normal ferritin	Low ferritin	Total	*P*
Normal hemoglobin	94 (98%)	81 (56.25%)	175 (72%)	
Low hemoglobin	5 (2%)	63 (43.75%)	68 (28%)	0.00001
Total	99 (40.7%)	144 (59.3%)	243 (100%)	

Table 3: Distribution of patients in four different groups according to SSI and serum ferritin levels (*n*=243)

Groups	Low ferritin (<15 ng/ml)	Normal ferritin (>15 ng/ml)	*P*
High SSI	92 (Group 1)=37.9%	63 (Group 2)=25.9%	0.97
Normal SSI	52 (Group 3)=21.4%	36 (Group 4)=14.8%	
Total	144=59.3%	99=40.3%	

SSI=Somatization and sensitization index

Table 4: Response and relapse rates in different groups

Groups	Response in the first 6 months	Follow-up after 6 months in patients with good response	*P*
Group 1 (*n*=75)	Good=65 (86.6%) Poor=10 (13.4%)	Relapsed=44 (67.7%) No relapse=21 (32.3%)	0.00001
Group 2 (*n*=79)	Good=38 (48.1%) Poor=41 (51.9%)	Relapsed=28 (73.7%) No relapse=10 (26.3%)	
Group 3 (*n*=44)	Good=39 (88.6%) Poor=5 (11.4%)	Relapsed=15 (38.5%) No relapse=24 (61.5%)	
Group 4 (*n*=45)	Good=27 (60%) Poor=18 (40%)	Relapsed=10 (37%) No relapsed=17 (63%)	

67.7% [group 1] and 73.7% [group 2] as compared to groups 3 and 4 [$P = 0.00001$].

Discussion

Chronic multiple-site pain of unknown etiology is a common presenting complaint in busy primary care and specialty outpatient department. Global prevalence of chronic pain is estimated to be 19.2% that included mixed etiology of all three causes [neuropathic, nociceptive, and nonspecific].[24] Clinical syndromes of neuropathic pain due to neuropathy, neuralgia, and central pain are well-recognized at the primary care level as the diagnosis is based on objective neurological signs and positive correlation with investigations.[25,26] Complex regional pain syndrome type 1 is the only neuropathic pain condition that needs special attention to recognize and treat.[27] Nociceptive pain syndrome, however, is due to various inflammatory and post-traumatic conditions, and its diagnosis can be confirmed with the help of local examination and inflammatory markers.[5] One point of attention for primary care level clinicians that they should be careful in the interpretation of various inflammatory makers as good number of normal people can have false-positive rheumatological biomarkers such as rheumatoid factor, anti-nuclear antibody [ANA], human leukocyte antigen B27 (HLA B-27) and Uric acid therefore, over-diagnosed or miss-diagnosed of rheumatological is possible.[28]

Many patients with diffuse or multiple-site musculoskeletal pain without definitive evidences of neuropathic and inflammatory pain are initially seen by general and primary care physicians, and then to a rheumatologist or orthopedic doctor, and when no definite diagnosis is reached, then they finally come to either psychiatrists or neurologists at final step.[24] McBeth and Jones[29] showed that chronic musculoskeletal pain in adolescents and adults has three common patterns: neck–shoulder–brachial pain, low back–leg pain, and widespread chronic pain. The author also concluded that the prevalence of these types of pain is high in society with unclear mechanisms to explain the symptoms and felt that there is a need for further investigation.[29] Therefore, the term CNSMSP was used by Sullivan PO *et al.*,[6] and he recommended for multidimensional BPS method of evaluation for such patients. The results of this study showed the usefulness of a practical and clinically applicable approach for the evaluation of patients with chronic undiagnosed pain with a BPS model.

Chronic pain conditions are more prevalent in the female population as shown in our previous studies.[24-29] There is no obvious explanation for the gender difference in chronic pain, and genetic, anatomic, biological, hormonal, and psychosocial factors were evaluated for high prevalence of chronic persistent pain in women.[30] Low level of ferritin is one specific factor related to pain in females as only women are at higher risk for having low ferritin levels specially if they have history of menorrhagia or polymenorrhagia. Thus, we explained high incidence of chronic pain in females on the basis of low serum ferritin level and it can act as a specific biomarker of CNP in female. About two-thirds of females in our cohort had ferritin below 15 micrograms/L. If we also take account of mild-to-moderate deficiency of ferritin [between 16 and 40 micrograms/L], then this number will be higher.

Low ferritin, an indicator of chronic iron deficiency anemia [IDA], is a good biomarker for chronically persistent painful conditions.[31] Various chronic pain conditions that had already been linked with low ferritin are migraine and FMS.[22,31-36] Mechanism of chronic pain with low ferritin cannot be fully explained on the basis of poor oxygenation due to IDA.[35] In our study, 56% of patients with low ferritin had normal hemoglobin, and if patients of chronic pain had been evaluated with hemoglobin level, only then diagnosis of IDA can be missed due to normal hemogram report.[35] Now, it is known that ferritin not only acts as a storehouse for heme synthesis but also helps in the production of serotonin and dopamine; therefore, severe deficiency of ferritin can still continue to produce heme but these neurochemicals get disturbed at this point.[36] Ferritin is important co-factor for the enzymes such as tyrosine hydroxylase and tryptophan hydroxylase, which are required for serotonin and dopamine synthesis, respectively.[36]

Iron supplementation in patients with chronic migraine and fibromyalgia with low ferritin had been shown to be associated with good clinical response in pain management.[31-36] Recommended sustained level of ferritin for adequate prevention and control of chronic pain is at or around 100 μg/l.[35] Although we found that sustained level of ferritin above 50 is good enough for remission of pain, some time, we found a dramatic response in pain after iron supplementation among the patients with low ferritin [groups 1 and 3]. Some of the patients in groups 1 and 3 had relapses when they were not able to maintain adequate ferritin level in follow-up, and to prevent future relapse, we have to get repeated monitoring of serum ferritin at least once in 6 months in menstruating females.

The most challenging groups in our cohort were those with associated high SSI which means groups 1 and 2, and group 2 was called "group of death" as it was the most difficult-to-treat group. We combined somatic and sensitization index together as both are associated with high anxiety, and it had been documented that both of these factors may lead to common neurophysiological process to induce and maintain painful symptoms.[37]

After initial response to treatment, these patients can have relapses in follow-up. In group 1, patients after initial good response were seen with correction of ferritin but these relapses can be due to either recurrent IDA or physical/mental stressors as shown in 3P model assessment. As mentioned earlier, treatment of patients in group 2 was the most difficult as there was high risk of relapses even with trivial environmental stressors. In group 2, day-to-day life stressors make pain miserable so that medical treatment is usually insufficient and these patients need other adjuvant therapies such as cognitive behavior therapy [CBT] that can be very helpful.[38,39]

Other deficiencies with low ferritin, such as low vitamin D and B12, can also contribute to maintain chronic pain signals.[40-42] Thus, we should not miss these reversible factors in groups 2 and 4 as iron therapy is not helpful in these patients. Finally, after our study and previous reports, it is clear that multimodal strategies are required for patients with chronic pain with high central SSI.[38-42]

The limitation of this study is that we had selected only the extreme ends SSI and ferritin level of chronic pain, means those patients had severely high level of SSI and very low level of ferritin level. The picture is not black and white; we also have gray areas in between which means those patients had mild-to-moderate SSI [25–50 score] and moderately low ferritin [16 to 49 ng/ml]. These moderate groups of patients are still unexplored and need further elaboration. Patients of Group 4 needs further exploration as no specific mechanism found to explain their persistent pain. Another area for future exploration is to plan specific strategy for central neural sensitization and somatization differently as central sensitization is better explained on the basis of neurobiology, while somatization is related to psycho-pathology.

Conclusions

Our study showed that CNMSP is not a single entity and it is complex and associated with third dimension of pain mechanisms. CNH is the main mechanism behind it. Now, we can say that this entity is not called "nonspecific," and various BPS factors are responsible for predisposition, precipitation, and perpetuation of pain symptoms. Through this article, we tried to decode the entity of CNMSP of unknown etiology, which can be managed with few important biomarkers and predictable model of classification. This BPS mode of analysis and its guidance for a multimodal treatment strategy can further explore the mysteries of CNP. Future researches are required to confirm these findings, and more elaborative research is required for the gray zone areas among the clinical group.

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Conflicts of interest

There are no conflicts of interest.

References

1. Mills S, Torrance N, Smith BH. Identification and management of chronic pain in primary care: A review. Curr Psychiatry Rep 2016;18:22-30.
2. Barke A, Korwisi B, Jacob R, Konstanjsek N, Rief W, Treede RD. Classification of chronic pain for the international classification of disease [ICD 11]: Results of the 2017 international World Health Organization field testing. Pain 2022;163:e310-8.
3. Hestmann R, Bratas O, Gronning K. Chronic pain self-management interventions in primary care – dose it makes any difference? A qualitative study. BMC Health Serv Res 2023;23:537.
4. Teng W, Boo AYY, Lim ZW. Management of chronic non-cancer pain in primary care. Singapore Med J 2023;64:115-20.
5. Nicholson B. Differential diagnosis: Nociceptive and neuropathic pain. Am J Manag Care 2006;12:s256-62.
6. Sullivan PO, Beales D, Jensen L, Murray K, Myers T. Characteristics of chronic non-specific musculoskeletal pain in children and adolescents attending a rheumatology outpatients clinic: A cross-sectional study. Pediatr Rheumatol 2011;9:2-9.
7. Deyo RA. Low back pain. N Engl J Med 2001;344:363-70.
8. Jahre H, Grotle M, Smedbraten K, Dunn KM, Oiested BE. Risk factors for nonspecific neck pain in young adults. A systematic review. BMC Musculoskelet Disord 2020;21:366-77.
9. Kinder LL, Bennett MD, Jones KD. Central sensitivity syndromes: Mounting pathophysiologic evidence to link fibromyalgia with other common chronic pain disorders. Pain Manag Nurs 2011;12:15-24.
10. Nijs J, Meeus M, Oosterwijck JV, Roussel N, Kooning MD, Ickmans K, *et al.* Treatment of central sensitization in patients with unexplained chronic pain: what options do we have. Expert Opin Pharmacother 2011;12:1087-98.

11. Ossipov MH, Morimura K, Porreca F. Descending pain modulation and chronification of pain. Curr Opin Support Palliat Care 2014;8:143-51.
12. Chairotto A, Koes BW. Nonspecific low back pain. N Engl J Med 2022;386:1732-40.
13. Amundsen PA, Evans DW, Rajendran D, Bright P, Bjorkli T, Eldridge S, *et al.* Inclusion and exclusion criteria used in non-specific low back pain trials: A review of randomized controlled trials published between 2006 and 2012. BMC Musculoskelet Disord 2018;19:113-25.
14. Last AR, Hulbert K. Chronic low back pain: Evaluation and management. Am Fam Physician 2009;79:1067-74.
15. Gerwin RD. A review of myofacial pain and fibromyalgia – factors that promote persistence. Acupunct Med 2005;23:121-34.
16. Fukuda K, Straus SE, Hickie I, Sharpe MC, Dobbins JG, Komaroff A. The chronic fatigue syndrome: A comprehensive approach to the definition and study. International Chronic Fatigue Syndrome Study Group. Ann Intern Med 1994;121:953-59.
17. Lahmann C, Henningsen P, Noll-Hussong M. Somatoform pain disorder – overview. Psychiatr Danub 2010;22:453-8.
18. Hendler N. Why chronic pain patients are misdiagnosed 40-80% of the time? J Recent Adv Pain 2016;2:94-8.
19. Galvez-Sanchez CM, Reyes Del Peso GA. Diagnostic criteria for Fibromyalgia: Critical review and future perspective. J Clin Med 2020;9:1219. doi: 10.3390/jcm9041219.
20. Bevers K, Watts L, Kishino ND, Gatchel RJ. The biopsychosocial model of the assessment, prevention, and treatment of chronic pain. US Neurol 2016;12:98-104.
21. Dixon D, Pollard B, Johnston M. What does the chronic pain questionnaire measures? Pain 2007;130:249-53.
22. Goel D, Garg S, Srivastav M, Gupta S, Kaur A. Biomarkers of chronic nonspecific pain syndrome: A cross-sectional hospital-based pilot study. Indian J Pain 2020;34:15-21.
23. Write CD, Tiani AG, Billingsley AL, Steinman SA, Larkin KT, McNeil DW. A framework for understanding the role of psychological processes in disease development, maintenance, and treatment: The 3P-Disease model. Front Psychol 2019;10:2498. doi: 10.3389/fpsyg. 2019.02498.
24. Saxena AK, Jain PN, Bhatnagar S. Prevalence of chronic pain among adults in India. Indian J Paliat Care 2018;24:472-7.
25. Bussa M, Mascaro A, Sbacchi E, Dourandish M, Rindaldi S. Understanding peripheral neuropathic pain in primary care: Diagnosis and management. Eur Rev for Med Pharmacol Sci 2021;25:1990-96.
26. Haanpaa ML, Backonja MM, Bennett MI, Bouhassira D, Cruccu G, Hansson PT, *et al.* Assessment of neuropathic pain in primary care. Am J Med 2009;122:S13-21.
27. Harnik MA, Kesselring P, Ott A, Urman RD, Luedi MM. Complex regional pain syndrome [CRPS] and the value of early detection. Curr Pain Headache Rep 2023;17:417-27.
28. Siva C, Larson EC, Barnett M. Rationale use of blood tests in evaluation of rheumatic diseases. Missouri Med 2002;109:59-63.
29. Mcbeth J, Jones K. Epidemiology of chronic musculoskeletal pain. Best Pract Res Clin Rheumatol 2007;21:403-25.
30. Meisler JG. Chronic pain conditions in women. J Womens Health 1999;8:313-20.
31. Meng SH, Zhou HB, Li X, Wang MX, Kang LX, Fu JM, *et al.* Association between dietary iron intake and serum ferritin and severe headache or migraine. Front Nutr 2021;8:685564. doi: 10.3389/fnut. 2021.685564.
32. Aamodt AH, Borch-Iohnsen B, Hagen K, Stovner LJ, Asberg A, Zwart JA. Headache prevalence related to haemoglobin and ferritin. The HUNT study. Cephalagia 2004;24:758-62.
33. Ortancil O, Sanli A, Eryuksel R, Basaran A, Anakarali H. Association between serum ferritin and fibromyalgia syndrome. Eur J Clin Nutr 2010;64:308-12.
34. Yao W-C, Chen H-J, Leong K-H, Chang K-L, Tina Wang Y-T, Wu L-C, *et al.* The risk of fibromyalgia in patients with iron deficiency anemia: A nationwide population based cohort study. Sci Rep 2021;11:10496. doi: 10.1038/s41598-021-89842-9.
35. Soppi ET. Iron deficiency without anemia – A clinical challenge. Clin Case Rep 2018;6:1082-86.
36. Beard JL, Connor JR, Jones BC. Iron in the brain. Nutr Rev 1993;51:157-70.
37. Bourke JH, Langford RM, White PD. The common link between functional somatic syndromes may be central sensitization. J Psychosom Res 2015;78:228-36.
38. Lim JA, Choi S-H, Lee WJ, Jang JH, Moon GY, Kim YC, *et al.* Cognitive-behavioral therapy for patients with chronic pain. Medicine 2018;97:23.
39. Gupta S, Goel D, Garg S, Tikka SK, Preeti M, Tyagi P. Effect of adjunctive transcranial direct current stimulation and cognitive behavior therapy on headache disability in episodic frequent or chronic tension type headache. Indian J Pain 2022;36:140-6.
40. Ummer K, Noone M. Prevalence of B12 deficiency in patients presenting with non-specific pain and other sensory symptoms: A clinical observational study. Neurology 2015;84:(Supp 14). doi: 10.1212/wnl. 84.14_supplement. p3.307.
41. Prakash S, Kumar M, Belani P, Susvirkar A, Ahuja S. Interrelationships between chronic tension type headache, musculoskeletal pain, and vitamin D deficiency: Is Osteomalacia responsible for both headache and Musculoskeletal pain? Ann Indian Acad Neurol 2013;16:650-8.
42. Fazelian S, Amani R, Paknahad Z, Kheiri S, Khajehali L. Effect of Vitamin D supplement on mood status and inflammation in vitamin D deficient Type 2 diabetic women with anxiety: A randomized clinical trial. Int J Prev Med 2019;10:17-25.

Annexure 1: Seven-item CPGS scoring [ref 21]

Question asked	Response
How would you rate your pain on a 0-10 scale at the present time, this is right now, where 0 is "no pain" and 10 is "pain as bad as it could be"?	
In the past 6 months, how intense was your worse pain rated on a 0-10 scale [rated as above]?	
In the past 6 months, on average, how intense was your pain rated on a 0-10 scale [rated as above]? [That is your usual pain at times you were experiencing pain.]	
About how many days in the last 6 months have you been kept from your usual activities [work, school, housework] because of this pain?	
In the past 6 months, how much has this pain interfered with your daily activities on a 0-10 scale where 0 is "no interference" and 10 is "extreme change"?	
In the past 6 months, how much has this pain changed your ability to take part in recreational, social, and family activities where 0 is "no change" and 10 is "extreme change"?	
In the past 6 months, how has this pain changed your ability to work [including housework] where 0 is "no change" and 10 is "extreme change"?	

CPGS: Chronic Pain Grading Scale

Annexure 2: Psychosocial evaluation for SSI

Patient's name:	Age/sex		Date		Always
Symptoms	**Never**	**Rarely**	**Sometime**	**Often**	
Low back pain	0	1	2	3	4
Pain in arms, legs, or joints	0	1	2	3	4
Feel pain all over the body	0	1	2	3	4
Having headaches	0	1	2	3	4
Feel pain in pelvic area	0	1	2	3	4
Feel pain in my jaws	0	1	2	3	4
Feeling chest pain or shortness of breath	0	1	2	3	4
Feel muscle tension or pain in my neck and shoulder	0	1	2	3	4
Feels as body muscles are stiff and achy	0	1	2	3	4
Dizziness	0	1	2	3	4
Feel discomfort in bladder or urination or I have high frequency of urine	0	1	2	3	4
Stomach or bowel problem, having diarrhea and/or constipation	0	1	2	3	4
Trouble in getting proper sleep	0	1	2	3	4
Tired and unfresh in morning after sleep	0	1	2	3	4
My legs get uncomfortable sensation and restless feeling while go for sleep	0	1	2	3	4
Feels severe anxiety or anxiety attacks	0	1	2	3	4
Habit of teeth grinding or teeth clenching	0	1	2	3	4
I feel that I have low energy	0	1	2	3	4
Need help for daily routine activities due to pain/fatigue and get tired easily	0	1	2	3	4
Sensitive to bright light or certain smells make me uneasy	0	1	2	3	4
I have sensitive skin, dryness, or itching	0	1	2	3	4
Difficulty in concentration and memory means I have difficulty in remembering things	0	1	2	3	4
I feel sad and depressed with low mood	0	1	2	3	4
Stress makes my physical symptoms worse	0	1	2	3	4
Having bad memories of childhood [physical or mental]	0	1	2	3	4
PHQ 25 total score			=		

SSI SCORE: subclinical: 0 to 29 mild: 30 to 39 moderate: 40 to 49 severe: 50 to 59 extreme: 60 to 100

Annexure 3: BPS-3P model [ref 23]

	Predisposing	Precipitating [triggers]	Perpetuating
Biological factors	Family history positive or genetic risk factors, birth defects, nutrition deficiency, age, gender, and race	Onset of acute illness, onset of severe medical disease, surgery, trauma or substance abuse, nutrition deficiency, menstrual problem	Substance use/abuse, chronic physical illness, and immunosuppression
Psychological factors	Personality and temperament, coping skills, over vigilance of bodily symptoms	Poor coping style, mal-adaptive behavior, illness-related anxiety, and negative thinking	Coping style, social support, compensatory behavior, negative thoughts, and avoidance behavior
Social factors	Social class, geography, family structure, education, job, and childhood experience	Life-related events, social support, interpersonal relations, and natural disasters	Social support, work schedule rigidity, social stigma, financial obligations, unemployment, and secondary gain

Questionnaire for 3P model: adopted from Write CD *et al.* 2019 [ref; 23]