Non-Randomized Study

Examination of Symptom Clusters in Acute and Chronic Pain Patients

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Background: Symptom clusters have not been previously explored in acute pain patients (APPs) and chronic pain patients (CPPs) with non-cancer pain.

Objectives: The objectives of this study were to determine in CPPs and APPs which somatic and non-somatic symptoms cluster with each other, the number of clusters, and if cluster number and cluster symptom makeup differ by pain level.

Study Design: Study sample was 326 APPs and 341 CPPs who had completed a pool of questions that had included current symptom questions other than pain. Symptom cluster analyses were performed on 15 somatic and non-somatic symptoms for APPs and CPPs and for 2 CPP subgroups with moderate and severe pain.

Setting: APPs and CPPs were from rehabilitation facilities located in 30 states in all geographical regions of the United States.

Results: APPs had 4 symptom clusters and CPPs had 5. For CPPs, the clusters represented memory, neurological, behavioral, somatic, and autonomic problems. CPPs with moderate and severe pain had 3 and 4 symptom clusters, respectively, and differed in cluster symptom constitution.

Limitations: Patients selected themselves for study inclusion and were paid for their participation. This could have affected random selection. Lastly, we used the current time definitions of acute pain versus chronic pain (90 days) to separate our patients into these groups. Currently, no consensus exists regarding the optimal time duration to divide acute from chronic.

Conclusions: APPs and CPPs are characterized by symptom comorbidities that form clusters. In CPPs, cluster number and cluster symptom makeup are affected by pain level. This has implications for clinical practice and future research.

Key words: Comorbidity, somatic symptoms, comorbid symptoms, chronic pain patients, acute pain patients, community patients without pain, clusters, symptom clusters

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Comorbidity is defined as "any distinct clinical entity that has existed or may occur during a patient's clinical course of the index disease under study" (1). Comorbid disease can often complicate, interfere with, or make the treatment of the index disease more difficult, making the prognosis worse (1). Psychiatric comorbidity diagnosable on Axis I of the Diagnostic and Statistical Manual - IV (DSM-IV) is commonly found within chronic pain patients (CPPs) (2). However, CPPs also display comorbidities that are best described as symptoms not diagnosable on Axis I. Some examples of these symptomatic comorbidities

are sleep problems (3,4), fatigue (5,6), headache (6,7), irritable bowel syndrome (8), and restless leg syndrome (4), among others.

A complex relationship between comorbid symptoms was first described in the pain cancer literature. A cluster of symptoms (pain, fatigue, and insomnia) had a significant negative effect on function (9), explaining more than 48% of the variance in functional status (10). Two literature reviews have concluded the following in relationship to cancer symptom clusters: (a) a symptom cluster is defined as 2 or more concurrent symptoms related to each other (11); (b) symptom clusters are independent of other clusters (11); (c) relationships among symptoms within a cluster are stronger than relationships among symptoms across different clusters (11); (d) symptoms in a cluster may or may not share the same etiology (11); (e) pain, fatigue, insomnia, and depression constitute a cancer symptom cluster (12); (f) one way of determining if one symptom is related to another and thereby could be in a "cluster" is to determine if an increment in one symptom is associated with an increment or decrement in another symptom (12); (g) relationships between various symptoms could be determined by shared variance analysis, cluster analysis, or mediation analysis, indicating that symptoms may form a "cluster" (12); and (h) more research in this area is needed (12).

This concept has not diffused into non-cancer pain research. Cluster analysis has been utilized to develop CPP subgroups on psychological tests or inventories (13,14) and outcome instruments (15,16). To our knowledge, only 3 studies (17-19) have used factor analysis or cluster analysis to specifically investigate symptoms in non-cancer CPPs, specifically fibromyalgia patients (FMS). In the first study, 4 FMS groups were identified: (a) high on physical, cognitive, and psychological symptoms; (b) moderate on physical, cognitive, and psychological symptoms; (c) moderate physical but low cognitive and psychological symptoms; and (d) low on physical, cognitive, and psychological symptoms (19). The second study reported 4 FMS clusters: (a) low on all symptoms; (b) low on pain sites, somatic symptoms, and depression; (c) high on pain scales, moderate on somatic symptoms, and low on depression; and (d) lower health related quality of life and less social support (17). In the third study, 5 clusters were found and were labeled somatic, distress, fibromyalgia care, dyscognition, and sleep problems (18).

The objectives of this study were to examine 15 somatic and non-somatic symptoms in acute pain patients (APPs) and CPPs. Based on the previous cancer and FMS literature, we generated the following hypotheses for our study:

1. APPs and CPPs will not differ from each other in cluster symptom composition and number of clusters.
2. APPs and CPPs will differ in cluster symptom composition from pain cancer patients.
3. In CPPs, cluster symptom composition and number of clusters will differ by pain level as some somatic symptoms could be associated with pain (20-27).

To our knowledge, this is the first such study in the literature.

Methods

Study Participants

This study utilized a data pool of 600 items/questions previously used to develop the Battery for Health Improvement 2 (BHI 2), which is made up of a subset of items from this data pool (28). It was conducted at the item level and did not utilize the BHI 2 scales in the analyses. This study analyzed 15 somatic and non-somatic symptoms from this data pool frequently associated with chronic pain: (a) fatigue, (b) numbness or tingling in an extremity, (c) dizziness, (d) difficulty opening/closing mouth, (e) sudden muscle weakness, (f) difficulty staying asleep, (g) depression, (h) muscle tightness, (i) nervousness, (j) irritability, (k) memory problems, (l) falling because legs give way, (m) nausea, (n) difficulty concentrating, and (o) migraine or tension headaches.

The total number of patients who had been administered the data pool items was 2,487. Of these, 223 patients were eliminated from the data pool for the following reasons: (a) one subject did not sign the informed consent form; (b) 41 subjects had missing or contradictory age or gender; and (c) 57 patients failed to complete assigned forms. BHI 2 test results were scored for all patients, and patients whose profiles on that measure did not meet criteria for validity were eliminated. Patients were also administered either the Minnesota Multiphasic Personality Inventory - Z (MMPI-2) or Millon Clinical Multiaxial Inventory - III (MCMI-III) test. Those with invalid profiles (n = 124) on any of these measures were also eliminated, leaving 2,264 subjects with complete, valid information.

Of the 2,264 patients, 777 came from rehabilitation facilities located in 30 states and all geographical

regions of the continental United States where they were being treated for pain and functional problems. They were recruited by flyers given to them by their health care providers and came from a variety of rehabilitation clinical settings: multidisciplinary chronic pain programs, multidisciplinary work hardening programs, various physician specialty offices (orthopedic, neurology, psychiatry, physiatry, and occupational medicine), and from other types of office settings (physical therapy, dental, psychology, and chiropractic). Of these 777 patients, 19.3% were from multidisciplinary chronic pain programs and 7.2% from multidisciplinary work hardening programs. We do not have information on the percent of patients recruited from various physician and non-physician offices. These patients also represented various payer systems (Medicare/Medicaid, private insurance, worker's compensation, and personal injury insurance). Their non-specific and specific diagnoses are reported as a percentage of the total rehabilitation patient group (n = 777; some patients had more than one diagnosis): headache 12.2% (n = 95), whiplash 6.8% (n = 53), non-whiplash cervical sprain 8.1% (n = 63), upper extremity injury 25.2% (n = 196), low back injury 44.4% (n =345), lower extremity injury 25.4% (n = 197), head injury pain 11.2% (n = 87), carpal tunnel syndrome 6% (n = 47), thoracic outlet syndrome 2.2% (n = 17), reflex sympathetic dystrophy 1.4% (n = 11), and FMS 1.4% (n = 11). These non-specific and specific diagnoses were received from the treating facilities either before referral to the facility or during treatment. We have no information as to what types of physicians assigned these diagnoses.

Of these 777 rehabilitation patients, 667 had pain (Numerical Rating Scale [NRS] score greater than zero) and 110 had no pain. Of patients with pain, 341 were CPPs (greater than or equal to 90 days duration from an item in the data pool on the duration of pain). The remaining 326 were APPs (less than 90 days duration). For the purposes of one of the analyses, CPPs were further divided into those whose highest pain in the last month was mild (NRS 1 – 4; n = 19), moderate (NRS 5 – 7; n = 99), or severe (NRS 8 – 10; n = 223). The subsequent analyses were only performed on the APPs and CPPs of the rehabilitation patient group.

Instrumentation

The 600 data pool items are not an inventory, contain no scales, and have no associated reliability and validity data. However, each of the 15 items had the following one-week test-retest reliability scores: fatigue, r = .909; numbness or tingling in an extremity, r = .862; dizziness, r = .738; difficulty opening/closing mouth, r = .763; sudden muscle weakness, r = .683; difficulty staying asleep, r = .810; depression, r = .879; muscle tightness, r = .857; nervousness, r = .871; irritability, r = .865; memory problems, r = .831; falling because legs give way, r = .712; nausea, r = .809; difficulty concentrating, r = .865; and headaches, r = .884.

Data Collection Procedures

Participation was by self-selection, and patients were reimbursed for their participation. Any patient was allowed to participate after passing the exclusion criteria of being less than 18 years or over 65 and not being able to read the data pool items. Data pool items were administered in a confidential manner (questionnaires were assigned a random ID number). No records were kept regarding which ID number a patient or non-patient was assigned. Data were processed by persons having no contact with, or knowledge of, the respondents and were de-identified of any identifying information per Health Insurance Portability and Accountability Act (HIPAA) requirements. All groups signed an informed consent form advising the patient of the risks and benefits of participation. The consent form advised that the information would be used for research purposes pertaining to developing better methods for the assessment of medical patients, that no results or feedback would be given, and that the information gathered would not influence the course of their clinical care. The consent form had been developed by an internal committee at Pearson Assessments whose function was to monitor the process of information gathering into the data pool at various sites. Before implementation, the consent form had been sent out for approval to an external Institutional Review Board (IRB). The internal committee reported on information gathering and consent form implementation to the external IRB. The data pool set was presented for BHI 2 development in a de-identified format and years later in a de-identified format for further analysis for this study.

Data Analysis

Response groups (affirmation versus non-affirmation) to the data pool items were established as follows. Each item was scored on a 4-point Likert scale in one of 2 formats. On most items, the available responses were: not a problem, small problem, moderate problem, and big problem (assigned scores 0 through 3, respectively).

For the analyses, these items were transformed into a dichotomy, where patients were classified as reporting that somatic complaint if they characterized it as a small, moderate, or big problem and thereby had the symptom. On some items, the available responses were: strongly disagree, disagree, agree, and strongly agree (assigned scores 0 through 3, respectively). On these items, patients were classified as being in the affirmative if they agreed or strongly agreed and thereby had the symptom.

Data were managed and analyzed using SPSS 19 (IBM, Inc., Chicago, IL) and SAS 9.1.3 (SAS Institute, Inc., Cary, NC) software. Frequency and descriptive statistics were calculated to check all relevant characteristics of the data for each patient group. We then performed a cluster analysis on the 15 symptoms for APPs and CPPs with the primary objective of splitting the symptoms into homogenous groups. We wanted to minimize within-group variation and maximize between-group variation as suggested by the literature (29-33); thus, the cluster analysis was done in 2 steps.

In the first step, factor analysis was performed to identify the optimal number of clusters. We derived components that retained as much of the information in the original variables as possible (maximize variance extracted). The method for factor extraction was principal component analysis (34,35). The analysis was performed with the Factor procedure in SAS. Various solutions were developed and each solution had a certain number of components. Then, we analyzed the data structure and perceptual map of each solution. We studied the meaning of the components and their relationship with the underlying variables. In order to determine the proper number of components, we used the following indicators and criteria: (a) a few components could represent the original variables without losing much information, (b) the components were distinguished and independent, (c) the variables that loaded on a given component shared the same conceptual meaning, and (d) low cross-loading (i.e., a simple structure) (36).

In the second step, the 15 variables were divided into proper clusters (37). This was done with the Varclus procedure in SAS. Varclus tries to maximize the variance that is explained by the cluster components, summed over all the clusters. The principle and method of this procedure are similar to those of the Factor procedure in the first step. However, the goal in this step is to group variables rather than to explore the structure. The algorithm is both divisive and iterative, and begins with all variables in a single cluster. It then repeats the following steps:

1. One cluster is split into 2 clusters by finding the first 2 principal components, performing an orthoblique rotation and assigning each variable to the rotated component with which it has the higher squared correlation (38).
2. Variables are iteratively reassigned to clusters to try to maximize the variance accounted for by the cluster components. The reassignment algorithms are required to maintain a hierarchical structure for the clusters.
3. The procedure stops splitting when the predetermined number of clusters is reached (39).

The 2-step cluster analysis was performed similarly for the APPs and CPPs and then for CPPs with moderate and severe pain (we did not have enough CPPs in the mild pain group to do this analysis).

Results

Tables 1 and 2 display the cluster analysis solutions for the 15 symptoms for APPs in Table 1 and CPPs in Table 2. For the APPs, a 4-cluster solution was extracted and cluster 1 centered on problems with fatigue, tight muscles, nervousness, irritability, and headaches. For CPPs, a 5-cluster solution was extracted and cluster 4 contained symptoms related to fatigue, sleep, tight muscles, and headaches.

Tables 3 and 4 display the cluster analysis solutions for the 15 symptoms for CPPs with moderate pain in Table 3 and CPPs with severe pain in Table 4. For the moderate-pain CPPs, a 3-cluster solution was extracted with the majority of symptoms in cluster 1 that consisted of problems related to fatigue, depression, nervousness, irritability, memory loss, nausea, concentration, and headaches. For the severe-pain CPPs, a 4-cluster solution was extracted and cluster 1 centered on problems with fatigue, sleep, tight muscles, nausea, and headaches.

Discussion

As noted in the introduction, previous cancer and FMS literature led to a number of hypotheses for the current study. The first hypothesis was that APPs and CPPs should not differ in number of clusters and cluster composition. This was not the case. The solution generated 4 clusters for APPs and 5 clusters for CPPs. For cluster symptom composition, some clusters were very

Table 1. *Cluster analysis solution for acute pain patients.*

Cluster	Variable	R^2 with Own Cluster	R^2 with Next Closest	(1- R^2 Own) / (1- R^2 Closest)
Cluster 1	Fatigue	0.426	0.172	0.693
	Muscle tightness	0.413	0.162	0.701
	Nervousness	0.534	0.195	0.579
	Irritability	0.546	0.132	0.522
	Migraine or tension headaches	0.636	0.214	0.463
Cluster 2	Dizziness	0.579	0.220	0.540
	Being unable to open or close mouth	0.435	0.057	0.599
	Nausea	0.654	0.144	0.405
Cluster 3	Numbness or tingling	0.467	0.146	0.624
	Sudden paralysis or muscle weakness	0.613	0.190	0.478
	No difficulty staying asleep (Note: Sleeping item is in the reverse direction.)	0.408	0.140	0.688
	Falling because legs give away	0.505	0.119	0.562
Cluster 4	Depression	0.511	0.114	0.552
	Memory problems	0.593	0.187	0.501
	Difficulty concentrating	0.735	0.333	0.398

Table 2. *Cluster analysis solution for chronic pain patients.*

Cluster	Variable	R^2 with Own Cluster	R^2 with Next Closest	(1- R^2 Own) / (1- R^2 Closest)
Cluster 1	Memory problems	0.760	0.177	0.291
	Difficulty concentrating	0.760	0.156	0.284
Cluster 2	Numbness or tingling	0.457	0.025	0.556
	Sudden paralysis or muscle weakness	0.727	0.110	0.307
	Falling because legs give away	0.577	0.060	0.449
Cluster 3	Depression	0.407	0.096	0.656
	Nervousness	0.691	0.107	0.346
	Irritability	0.538	0.054	0.488
Cluster 4	Fatigue	0.419	0.102	0.647
	No difficulty staying asleep (Note: Sleeping item is in the reverse direction.)	0.245	0.024	0.773
	Muscle tightness	0.497	0.078	0.546
	Migraine or tension headaches	0.532	0.145	0.547
Cluster 5	Dizziness	0.533	0.138	0.542
	Being unable to open or close mouth	0.419	0.022	0.594
	Nausea	0.565	0.165	0.521

similar, while others were not. For example, cluster 2 for APPs was exactly the same as cluster 5 for CPPs. Other clusters were also very similar except for perhaps one missing symptom. The makeup of the symptoms in the 5 clusters for CPPs indicated that they could be labeled as memory problems (#4), neurological problems (#2), behavior problems (#3), somatic symptoms (#4), and autonomic nervous system symptoms (#5). The fact that the symptoms in the clusters are clinically interpretable supports the contention that the clusters represent meaningful constructs.

Does the literature support our findings? Memory problems are a prominent FMS complaint (40). These patients have been shown to have neuropsychological deficits that are similar to those with mild cognitive impairment (41), possibly related to a disturbance in

Table 3. *Cluster analysis dolution for chronic pain patients with moderate pain.*

Cluster	Variable	R^2 with Own Cluster	R^2 with Next Closest	(1- R^2 Own) / (1- R^2 Closest)
Cluster 1	Fatigue	0.224	0.014	0.788
	Depression	0.246	0.034	0.780
	Nervousness	0.303	0.032	0.720
	Irritability	0.250	0.039	0.780
	Memory problems	0.423	0.073	0.622
	Nausea	0.343	0.023	0.673
	Difficulty concentrating	0.555	0.026	0.457
	Migraine or tension headaches	0.254	0.033	0.772
Cluster 2	Numbness or tingling	0.221	0.008	0.785
	Dizziness	0.497	0.171	0.606
	Sudden paralysis or muscle weakness	0.731	0.039	0.280
	Falling because legs give away	0.488	0.010	0.518
Cluster 3	Being unable to open or close mouth	0.223	0.009	0.785
	No difficulty staying asleep (Note: Sleeping item is in the reverse direction.)	0.501	0.006	0.502
	Muscle tightness	0.588	0.109	0.462

Table 4. *Cluster analysis solution for chronic pain patients with severe pain.*

Cluster	Variable	R^2 with Own Cluster	R^2 with Next Closest	(1- R^2 Own) / (1- R^2 Closest)
Cluster 1	Fatigue	0.423	0.125	0.660
	No difficulty staying asleep (Note: Sleeping item is in the reverse direction.)	0.166	0.023	0.853
	Muscle tightness	0.438	0.075	0.607
	Nausea	0.462	0.151	0.634
	Migraine or tension headaches	0.539	0.167	0.554
Cluster 2	Numbness or tingling	0.435	0.011	0.571
	Sudden paralysis or muscle weakness	0.697	0.113	0.342
	Falling because legs give away	0.508	0.034	0.509
Cluster 3	Depression	0.435	0.084	0.617
	Nervousness	0.705	0.121	0.336
	Irritability	0.588	0.066	0.441
Cluster 4	Dizziness	0.495	0.115	0.571
	Being unable to open or close mouth	0.252	0.045	0.783
	Memory problems	0.690	0.115	0.350
	Difficulty concentrating	0.502	0.166	0.597

the hippocampal system (42) and/or amygdala (43). These cognitive deficits may also be associated with pain (44) and related to the level of pain (45). Some evidence from acute pain induction studies suggests that working memory is affected by pain (46). Non-FMS CPPs also have prominent memory complaints (47,48). Neurological symptoms (poor balance, weakness, tingling, numbness, etc.) are often a complaint in FMS (49,50) and in other CPPs (48). Some evidence (51) also suggests that pain inhibits muscle activation, thereby promoting weakness and increasing fatigue. FMS and other CPPs also often have symptoms indicative of autonomic dysfunction, i.e., dizziness (52). These symptoms were found in our CPPs in cluster 5. Overall, the literature supports our finding for these 3 clusters (memory, neurological problems, and auto-

nomic). This adds to the likelihood that our generated clusters are meaningful.

The second hypothesis was that APPs and CPPs would differ in cluster symptom composition from cancer pain patients. This was indeed the case. To date, the cancer literature has identified only one cluster: pain/fatigue/insomnia/depression. A question posed by the literature is how many symptoms make up a symptom cluster (12). Our results indicate more than one symptom cluster, when one examines a large number of symptoms (i.e., 4 for APPs and 5 for CPPs). In addition, 2 – 5 symptoms are in a symptom cluster. It is also noted that contrary to the cancer literature, in CPPs, depression clustered with other behavioral symptoms, but fatigue and sleep did cluster together as in the cancer literature. Comparing our results to the cancer literature, our CPPs are characterized by a greater number of clusters, differing in makeup from clusters identified in the cancer literature. This difference indicates that either the cancer research has not examined a wide enough range of symptoms or our CPPs differ in associated symptoms versus cancer CPPs.

The third hypothesis was that in CPPs the cluster solution would differ according to pain level. This was indeed the case. CPPs with moderate pain had 3 clusters, while those with severe pain had 4 clusters. In CPPs with moderate pain, the number of symptoms in the cluster varied from 3 to 8, while in CPPs with severe pain it varied from 3 to 5. This is a new finding, which has significant relevance to the pain literature. Consequently, future examinations of somatic symptom profiles in CPPs will need to control for pain levels. Does the literature support this finding? We were only able to find one study that addressed this issue through cluster analysis. In that study, patients with low back pain were clustered according to different pathways for their low back pain over time (53). Longitudinal latent class analysis was performed using pain intensity scores. Cluster 3 in that study had severe, chronic, permanently high pain, and different clusters showed significant differences in disability and psychological status.

Other questions posed in the cancer pain literature have been the following: (a) Is symptom etiology for one or more symptoms related (18)? (b) If so, can symptom clusters be treated similarly (54)? (c) Does treatment of one symptom affect others within the same clusters (54)? and (d) Does one symptom in a cluster lead to or cause other symptoms in a cluster (18)? These questions would answer why this research is important, but our study cannot answer these questions. However, many somatic symptoms are associated with pain and could be pain determined (appear to improve and worsen according to pain level) (3,20,24-26,55). Additionally, the relationship is linear between the number of non-musculoskeletal symptoms and number of pain sites (56). Some somatic symptoms, e.g., sleep (23), fatigue (26), and stiffness [tight muscles] (24) improve with successful pain treatment even when that treatment is in no way directed at the somatic symptoms. This type of evidence indirectly suggests that effective pain treatment may act to reduce the level of somatic symptoms. Also, as symptoms in these clusters co-vary for reasons that are not fully understood, this evidence would also suggest that treating insomnia as an example may act to reduce pain and fatigue (57).

Another question is: Why should somatic symptoms cluster with pain? Presently, we do not fully understand the physiological/neurological relationship between emotional symptoms and pain and other somatic symptoms and pain. The relationship between emotional symptoms such as depression and pain may be related to the close association of the neurological circuits for emotions and pain in the nervous system (20). These circuits for sensory and affective pain processing are thought to be parallel, but independent of each other (58). Another possible hypothesis is that this relationship could be mediated by the cytokine system. A very recent study (59) has demonstrated an association between pro- and anti-inflammatory cytokine genes and the symptom cluster of pain, fatigue, sleep disturbance, and depression.

We noted several potential limitations of this study. Patients self-selected themselves for inclusion and were paid for their participation. This could have affected random selection. We used the current time definitions of acute pain versus chronic pain to separate our patients into these groups. However, no current consensus exists regarding the optimal time duration to separate acute from chronic. Our result that CPPs and APPs differ in the number of symptoms in the cluster and cluster composition would indirectly support the empirical idea that subdividing these patients by 90 days for the time the pain was present yields different groups.

The results of this study likely have clinical utility. The cluster symptom results indicate that if a pain clinician identifies one somatic symptom in association with pain, then he/she should look for additional somatic

symptoms belonging to that cluster and should be able to find at least 2 others. Treatment should be directed at pain plus all the other identified somatic symptoms if possible. This is because treating a somatic symptom may also improve pain (57).

Conclusions

APPs and CPPs are characterized by symptom comorbidities that form symptom clusters. In CPPs, cluster number and cluster symptom makeup are affected by level of pain.

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