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Symptom clusters in patient-reported outcomes of medical cannabis patients

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Abstract

Medical cannabis has been reported to be efficacious for managing symptoms associated with a variety of conditions, including cancer, anxiety, depression, and post-traumatic stress disorder. Symptom clusters have been identified in patients across a variety of conditions, and can be used by healthcare professionals to better manage patient quality of life. We aimed to identify baseline symptom clusters in patients registered with a Canadian medical cannabis provider. Principal component analysis (PCA) was performed using the PRINQUAL procedure to identify symptom clusters among the 10 most prevalent symptoms patients reported through a voluntary online survey administered after registration with their cannabis provider. The majority of respondents were male (69.2%), Caucasian (91.8%) and employed (50.9%). The average age of respondents was 46.5 years. Common conditions reported included chronic pain, sleep disorders, anxiety disorders, depression and post-traumatic stress disorder. Three clusters were identified using PCA, and displayed in biplots. Cluster 1 contained anxiety, depression, exhaustion, and sleep interference. Cluster 2 consisted of limited mobility, numbness, and pain. Cluster 3 included constipation, digestion problems, and headache. All clusters displayed good internal consistencies. Three symptom clusters were identified at baseline using PCA, with cluster 1 previously observed in cancer patients. The demographic and symptom profiles of respondents in the present study are also consistent with the limited literature that currently exists. Identifying symptom clusters in medical cannabis patients may allow physicians to make dosing and strain recommendations that will more effectively manage patients' overall condition(s) and commonly associated symptoms.

Keywords: Medical cannabis, symptom clusters, survey

Introduction

Across various medical conditions, patients often present with multiple, interrelated symptoms, posing unique challenges to health care providers in terms of

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diagnosis and symptom management. Recent research on symptom clusters, defined as groups composed of a minimum of two concurrent symptoms, has helped mitigate this challenge (1). Symptom cluster research has been widely explored in the cancer patient population, as these patients often experience multiple symptoms which can be predictive of changes in patient function, treatment failures and post-therapeutic outcomes (2). Outside of cancer, symptom clusters have also been significantly reported in cardiovascular diseases such as angina, heart failure, acute coronary syndrome and stroke (3-5). Due to their clinical significance, it is important that symptom clusters in various patient populations are identified so that health care providers may facilitate effective therapies in symptom management.

Medical cannabis has garnered much interest of late for its therapeutic potential in the treatment of various symptoms and conditions (6). In their review article, Grotenhermen and Muller-Vahl commented on its use for only a few of these indications, including multiple sclerosis, nausea, chronic and neuropathic pain. Despite the increasing use of medical cannabis, there is little evidence regarding the demographic and symptom profile of current medical cannabis patients. A better understanding of symptom clusters in this population may help medical cannabis providers and clinicians strategically target concurrent symptoms with specific cannabis varieties. The purpose of the present study was to identify baseline symptom clusters in patients before beginning treatment with medical cannabis.

Methods

Patients registered with a single Canadian licensed cannabis provider were invited to complete a voluntary online survey upon registration (baseline). The online survey was developed in consultation with various healthcare professionals knowledgeable on the topic of medical cannabis. The survey was dynamic, with answers to earlier questions determining subsequent questions asked. Patients were given the option to skip questions or choose more than one applicable answer for several questions. Information pertaining to patient demographics, current condition(s) and symptom(s), corresponding severity, and quality of life, was collected at baseline.

To examine whether any interrelationships existed among symptoms, a principal component analysis (PCA) for qualitative data was performed on the 10 most prevalent symptoms reported at baseline. The PRINQUAL procedure in Statistical Analysis Software (SAS version 9.4 for Windows) was used. The PCA transforms ordinal variables monotonically by scoring the ordered categories, so that the covariance matrix is optimized (7). The PRINQUAL procedure iterations produce a set of transformed variables. Each symptom's new scoring satisfies a set of constraints based on the original scoring of the symptom and the specified transformation type. The new set of scores is selected from the sets of possible scorings that do not violate the constraints so that the method criterion is locally optimized. The varimax rotation is an orthogonal rotation which results in uncorrelated components. Compared to other types of rotations, it tends to maximize the variance of a column of the factor pattern matrix.

The first principal component accounts for as much variability in the data as possible. The number of significant principal components was selected using a minimum Eigenvalue of 1.0. Each component explained more than 10% of the variance. The highest loading score predicted the assignment of individual symptoms to an independent factor. The internal consistency and reliability of the derived clusters were assessed with Cronbach's alpha. Robust relationships and correlations among symptoms were displayed with the biplot graphic. The longer the length and closer the arrows were together, the higher the correlations between symptoms.

Results

Baseline responses collected between January 2015 and December 2016 from a total of 863 patients were included in the analysis. The majority of respondents were male (69.2%) and Caucasian (91.8%) (see Table 1). The average age of respondents was 46.5 years, and more than half were employed (50.9%).

Table 1. Patient demographics (n = 863)

Demographic	n (%)
Gender (Total n = 859)	
Male	594 (69.2%)
Female	265 (30.8%)
Ethnicity (Total n = 784)	
Caucasian	720 (91.8%)
Spanish/Hispanic/Latino	5 (0.6%)
Native Canadian	40 (5.1%)
Black/African American	9 (1.1%)
Asian	10 (1.3%)
Age (Years) (Total n = 832)	
19 – 29	71 (8.5%)
30 – 39	210 (25.2%)
40 – 49	185 (22.2%)
50 – 59	247 (29.7%)
60 – 69	98 (11.8%)
≥ 70	21 (2.5%)
Average (min, max)	46.5 (20, 80)
Previous Experience with Cannabis (Total n = 802)	
Yes	681 (84.9%)
No	121 (15.1%)
Employment (Total n = 776)	
Full-time	276 (35.6%)
Part-time	43 (5.5%)
Self-employed	76 (9.8%)
Unemployed	122 (15.7%)
Homemaker	32 (4.1%)
Retired	199 (25.6%)
Student	28 (3.6%)

Table 2. Descriptive analysis of symptom scores at baseline (n = 863)

Symptoms	Total (n = 863) n (%)	
Anxiety		
None	177	(20.5%)
Mild	164	(19.0%)
Moderate	348	(40.3%)
Severe	174	(20.2%)
Constipation		
None	522	(60.5%)
Mild	172	(19.9%)
Moderate	119	(13.8%)
Severe	50	(5.8%)
Depression		
None	294	(34.1%)
Mild	170	(19.7%)
Moderate	271	(31.4%)
Severe	128	(14.8%)
Digestion Problems		
None	486	(56.3%)
Mild	129	(15.0%)
Moderate	181	(21.0%)
Severe	67	(7.8%)
Exhaustion		
None	378	(43.8%)
Mild	121	(14.0%)
Moderate	247	(28.6%)
Severe	117	(13.6%)
Headache		
None	421	(48.8%)
Mild	179	(20.7%)
Moderate	175	(20.3%)
Severe	88	(10.2%)
Sleep Interference		
None	148	(17.2%)
Mild	135	(15.6%)
Moderate	335	(38.8%)
Severe	245	(28.4%)
Limited Mobility		
None	487	(56.4%)
Mild	120	(13.9%)
Moderate	185	(21.4%)
Severe	71	(8.2%)
Numbness		
None	533	(61.8%)
Mild	133	(15.4%)
Moderate	143	(16.6%)
Severe	54	(6.3%)
Pain		
None	179	(20.7%)
Mild	60	(7.0%)
Moderate	277	(32.1%)
Severe	347	(40.2%)

The ten most prevalent symptoms reported at baseline were anxiety (79.5%), constipation (39.5%), depression (65.9%), digestion problems (43.7%), exhaustion (56.2%), headache (51.2%), sleep interference (82.8%), limited mobility (43.6%), numbness (38.2%) and pain (79.3%). Proportions of patient-reported symptom severity (none, mild, moderate, severe) is displayed in Table 2. Spearman correlations among the 10 symptoms are included in Table 3.

Table 3. Spearman correlation among 10 symptoms with p-values (Total n = 863)

Symptoms	Anxiety	Constipation	Depression	Digestion problems	Exhaustion	Headache	Sleep interference	Limited mobility	Numbness	Pain
Anxiety	**1.00******									
Constipation	**0.13*****	**1.00******								
Depression	**0.59******	**0.21******	**1.00******							
Digestion problems	**0.16******	**0.48******	**0.16******	**1.00******						
Exhaustion	**0.27******	**0.37******	**0.41******	**0.33******	**1.00******					
Headache	**0.22******	**0.30******	**0.23******	**0.28******	**0.41******	**1.00******				
Sleep interference	**0.30******	**0.23******	**0.33******	**0.19******	**0.32******	**0.26******	**1.00******			
Limited mobility	< 0.01	**0.28******	**0.17******	**0.20******	**0.33******	**0.17******	**0.19******	**1.00******		
Numbness	0.03	**0.26******	**0.18******	**0.23******	**0.32******	**0.23******	**0.19******	**0.42******	**1.00******	
Pain	**-0.07***	**0.19******	0.01	**0.14******	**0.21******	**0.20******	**0.20******	**0.46******	**0.34******	**1.00******

Bolded values indicate significance. *p < 0.05; ***p < 0.001; ****p < 0.0001.

Table 4. Eigenvalues and proportions of variance for 10 components

Component	**Eigenvalue**	**Proportion (%)**	**Cumulative (%)**
1	**3.4**	**33.9**	**33.9**
2	**1.6**	**15.9**	**49.9**
3	**1.0**	**10.3**	**60.1**
4	0.8	7.9	68.0
5	0.7	6.6	74.6
6	0.6	6.2	80.9
7	0.6	5.8	86.6
8	0.5	5.0	91.6
9	0.5	4.9	96.5
10	0.3	3.5	100.0

Clusters identified in the principle component analysis (PCA) are bolded.

Table 5. Factor loadings and final communality

Symptom	**Component 1**	**Component 2**	**Component 3**	**Final Communality**
Anxiety	**0.83**	-0.17	0.15	0.74
Depression	**0.81**	0.03	0.18	0.68
Exhaustion	**0.48**	0.34	0.44	0.54
Sleep interference	**0.65**	0.32	-0.04	0.52
Limited mobility	0.08	**0.75**	0.20	0.61
Numbness	0.10	**0.66**	0.28	0.52
Pain	0.01	**0.80**	0.05	0.64
Constipation	0.06	0.21	**0.79**	0.67
Digestion problems	0.07	0.09	**0.82**	0.69
Headache	0.34	0.20	**0.49**	0.40
% of variance	34%	16%	10%	
Cronbach's alpha	0.71	0.67	0.64	

Bolded values indicate inclusion of symptoms in respective components.

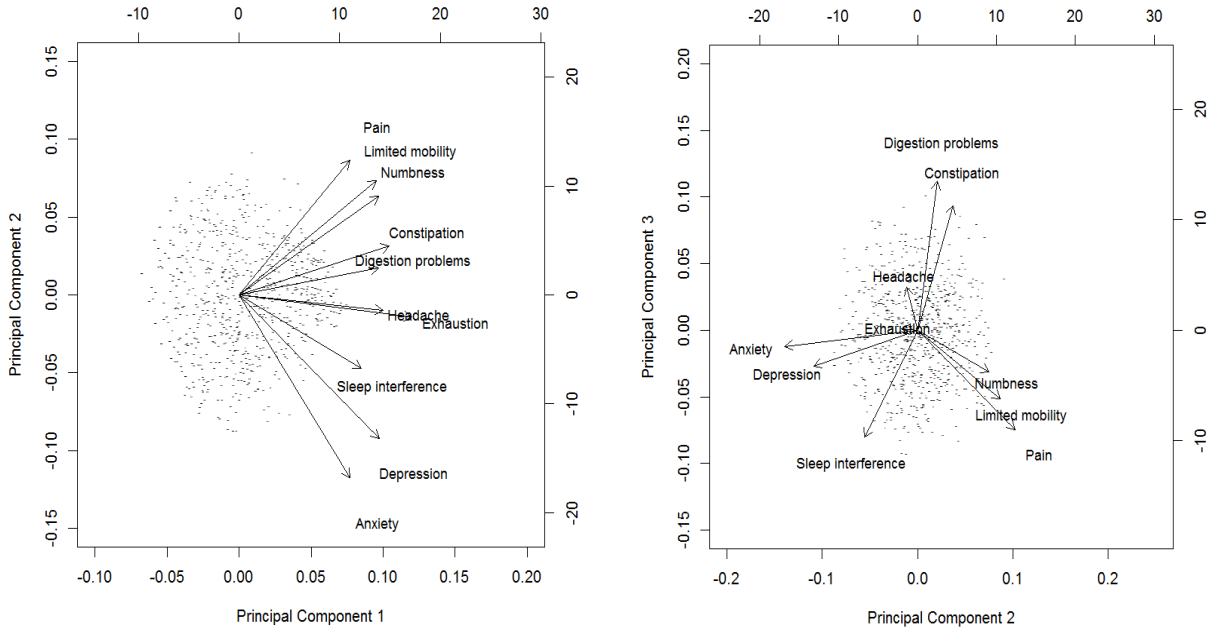

Figure 1. Biplots between principal components 1 and 2, 2 and 3.

Three components or "clusters" were identified by the PCA at baseline. As shown in Table 4, the first component accounts for 3.4 units of total variance (equals to 10), the second component accounts for 1.6 units and the third accounts for 1.0 units of total variance. Therefore, the PCA extracted three components with eigenvalues greater than 1.0 and each component explained more than 10% of the variance. Cluster 1 was composed of anxiety, depression, exhaustion, and sleep interference. Cluster 2 included limited mobility, numbness, and pain. Cluster 3 consisted of constipation, digestion problems and headache. The first three components respectively accounted for 34%, 16%, and 10% of the total variance. Cumulatively, these components accounted for 60% of the total variance.

The three clusters showed good internal consistency with Cronbach's alpha values of 0.71, 0.67 and 0.64, respectively (see Table 5). The final communality estimates ranged from 0.40 (headache) to 0.74 (anxiety), indicating the variables were well accounted for by the three components.

The biplot between components 1 and 2, as well as the biplot between components 2 and 3, clearly indicate the three identified clusters (see Figure 1).

Discussion

There is little research investigating the demographic and symptom profiles of medical cannabis patients. A study conducted in California reported that the majority of patients using medical cannabis were male, Caucasian, between the ages 25-44 years, and employed (8). A similar demographic profile was also seen in the present study, with the majority of patients being male and Caucasian.

In the present study, the PCA produced three symptom clusters at baseline. The first cluster (anxiety, depression, exhaustion and sleep interference) has been commonly studied in cancer patients (9). In a sample of patients undergoing chemotherapy, Redeker et al. (10) reported a significant negative impact of insomnia, fatigue, anxiety and depression on quality of life ($p < 0.001$) (10). Sleep interference in particular has been indicated as an exacerbating factor in symptom clusters, contributing to a further decrease in quality of life. Fatigue and sleep interference are issues not limited to cancer patients, as they have been frequently reported in patients with multiple sclerosis and a number of other chronic conditions (11-12).

There is partial overlap between prevalent conditions observed in the present study and those reported by Ware et al. (13) in their nationwide survey

of medical cannabis users in the United Kingdom. The authors reported cannabis use in patients with chronic pain, multiple sclerosis, depression, arthritis, and neuropathy. Similarly, the most prevalent conditions reported in the present study sample included chronic pain and depression, along with sleep disorders, anxiety disorder, and post-traumatic stress disorder.

There is existing evidence of the efficacy of medical cannabis in these particular conditions. In another analysis of self-reported medical cannabis use and effectiveness, Bonn-Miller et al. reported its particular helpfulness in treating psychological symptoms and anxiety (14). A systematic review and meta-analysis of 18 trials conducted by Martin-Sanchez et al. suggested cannabis may be efficacious in managing chronic pain (15). A more recent review conducted by Jensen et al. reported strong evidence in support of cannabinoids for the treatment of cancer-related pain, particularly at mid-range doses (16). The authors remarked on the reduction in pain and improvement in sleep quality following cannabis treatment in this patient population. Recent discussion has also suggested the use of cannabis may be a safer and effective therapeutic alternative to conventional opioids for the treatment of chronic pain (17).

A more thorough understanding of symptom clustering in patients using medical cannabis may help healthcare providers more effectively manage symptomatology. With more research on the efficacy of different strains for the management of specific symptoms, clusters can be targeted and effectively managed with minimization of poly-pharmacy and potentially associated side-effects.

Conclusion

Medical cannabis patients often present with a variety of symptoms, such as pain, sleep interference, and anxiety. Symptoms reported by medical cannabis patients in a voluntary online survey were grouped into three distinct clusters. The understanding of symptom clusters in medical cannabis patients may allow more targeted treatment of concurrent symptoms with specific strains. Further research on the symptom profile of this patient population, and strain efficacy for different indications is required for more sensitive and effective management of symptoms.

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