Published in final edited form as:

J Neurosci Nurs. 2010 August ; 42(4): 212–216.

Symptom Cluster and Quality of Life: Preliminary Evidence in Multiple Sclerosis

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Abstract

The present study examined the symptom cluster of fatigue, pain, and depression as a **correlate** of reduced quality of life (QOL) in individuals with multiple sclerosis (MS). The sample included 291 individuals with a definite diagnosis of MS who were enrolled in a 6-month longitudinal study of physical activity and QOL. The participants completed baseline measures of fatigue, depression, and pain and follow-up measures of QOL. Cluster analysis initially identified three sub-groups differing in experiences of fatigue, depression, and pain, and analysis of variance then indicated that the three sub-groups differed in QOL. The sub-group with lowest scores on all three symptoms had the highest QOL, whereas the sub-group with the highest scores on the symptoms had the worst QOL. Such findings provide preliminary support for fatigue, pain, and depression as a symptom cluster that **correlates with** reduced QOL in persons with MS.

Quality of life (QOL) describes an individual's overall judgment regarding satisfaction with life (Diener, Emmons, Larsen, & Griffin, 1985) and has been more extensively studied in persons with multiple sclerosis (MS) than in any other neurological disease (Mitchell, Benito-León, González, & Rivera-Navarro, 2005). This widespread interest is based on the growing recognition that QOL represents an important index of disease burden beyond that of impairment and disability and the abundant evidence that QOL is compromised in persons with MS (Mitchell et al., 2005).

Researchers have examined numerous **correlates** of reduced QOL in persons with MS (Mitchell et al., 2005). One consistent observation has been that the individual symptoms of fatigue, depression, and pain are primary correlates of reduced QOL in this population (Mitchell et al., 2005). Nevertheless, **few researchers have** considered fatigue, depression, and pain as a cluster of symptoms that **correlates with** reduced QOL among individuals with MS.

Symptom clusters or complexes have been defined as “three or more concurrent symptoms (e.g., pain, fatigue, sleep insufficiency) that are related to each other (Dodd, Miaskowski, & Paul, 2001, p. 465).” This definition underscores two primary features of a symptom cluster – the existence of three or more symptoms and the symptoms must be inter-related through a common etiology or statistically as a cluster or latent variable. Such concurrent symptoms likely have a synergistic influence on behavioral, functional, and QOL outcomes (Barsevick, 2007; Miaskowski, Aouizerat, Dodd, & Cooper, 2007) and co-occurring symptoms seemingly

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provide a more efficient target for management than a single, isolated symptom taken out of its clinical context (Barsevick, 2007).

There are several reasons to believe that fatigue, pain, and depression might represent a symptom cluster that **correlates with** reduced QOL in persons with MS. The first reason is that the three symptoms are often co-occurring and possibly synergistic in persons with MS (Crayton & Rossman, 2006; Krupp, 2004) and are etiologically linked through cytokine-induced manifestations of sickness behavior (Heesen et al., 2006) and co-occurring and diffuse axonal damage across different regions of the central nervous system (Lublin, 2005). The second reason is that previous researchers have identified fatigue, depression, and pain as a symptom cluster that was associated with reduced physical activity (Motl & McAuley, in press) and QOL (Forbes, While, Mathes, & Griffiths, 2006) in persons with MS. For example, one group of researchers identified fatigue, depression, and pain as a symptom cluster using bivariate correlation analysis, confirmatory factor analysis, and cluster analysis, and this cluster was negatively related with physical activity behavior by way of functional limitations in a sample of individuals with MS (Motl & McAuley, in press). The other group of researchers identified four clusters of individuals with MS who differed in experiences of fatigue, pain, and depression, and the clusters of individuals differed in domains of QOL (Forbes et al., 2006). The third and final reason is that recent research on outpatients with cancer receiving active treatment identified four sub-groups of individuals with different experiences of fatigue, sleep disturbance, depression, and pain, and the sub-groups demonstrated significant differences in multiple sub-domains of QOL (Miaskowski et al., 2006). Such observations provided preliminary support for fatigue, pain, and depression as a symptom cluster that correlates with reduced QOL in persons with MS.

The present study involved secondary data analysis and examined fatigue, pain, and depression as a symptom cluster that correlates with reduced QOL in persons with MS. This was conducted using data from a previously published study of the association between physical activity and QOL (Motl, McAuley, Snook, & Gliottoni, 2009) that was the basis for our initial examination of a symptom cluster in this population (Motl & McAuley, in press). Our initial examination identified three sub-groups of individuals with low, moderate, and high symptom experiences on fatigue, pain, and depression (Motl & McAuley, in press) and we examined the possibility that the three sub-groups would demonstrate significant differences in QOL based on previous research in MS and oncology.

Methods

Participants

The recruitment and demographic/clinical characteristics of the sample have been reported elsewhere (Motl et al., 2009). Briefly, the sample was recruited from three Midwestern chapters of the National MS Society using (a) mailed research announcements, (b) advertisements placed in *MS Connection* quarterly publications, and (c) email messages. Individuals who were interested in participation underwent a brief screening for inclusion criteria by a member of the research team. The inclusion criteria were (a) having a definite diagnosis of MS, (b) being relapse free in the last 30 days, and (c) being ambulatory with minimal assistance (i.e., able to walk with or without a cane). The final sample consisted of 291 individuals with MS as one person did not provide data on the three symptoms. The sample consisted of 244 women and 47 men. There were 245 individuals who were diagnosed with relapsing-remitting MS, 12 who were diagnosed with primary progressive MS, and 34 who were diagnosed with secondary progressive MS. The mean age was 48.0 years ($SD = 10.3$, range = 20 – 69 years) and the mean duration of MS (time since definite diagnosis) was 10.3 years ($SD = 7.9$, range = 1 – 35 years).

Instruments

Fatigue—Fatigue was measured with the Fatigue Severity Scale (FSS; Krupp, LaRocca, Muir-Nash, & Steinberg, 1989). The FSS has 9 items that are combined to form an overall measure of a person's severity of fatigue symptoms. Higher scores reflect more severe perception of fatigue. This scale has good evidence of internal consistency, test-retest reliability, and score validity (Krupp et al., 1989). Coefficient alpha for the FSS was .93 in the present study.

Depression—Depression was measured by the Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983). The HADS contains 14 items; 7 items measure anxiety symptoms and 7 items measure depression symptoms. Higher scores reflect more frequent symptoms of depression. This scale has good evidence of score reliability and validity (Zigmond & Snaith, 1983). Coefficient alpha for the depression component of the HADS-D was .82 in the present study. We only included the measure of depression because of our a priori focus on its role in the symptom cluster.

Pain—Pain was measured with the short-form McGill Pain Questionnaire (SF-MPQ; Melzack, 1987). This scale contains a 15-item adjective checklist that captures sensory and affective dimensions of pain. The scores from the items are summed to form a pain rating index such that higher scores reflect stronger perceptions of pain. The SF-MPQ is internally consistent, reliable across time, and has evidence of score validity (Melzack, 1987). Coefficient alpha for the SF-MPQ was .88 in the present study.

Quality of life—QOL was measured using the Leeds Multiple Sclerosis Quality of Life Scale (LMSQOL; Ford et al., 2001) and the Satisfaction With Life Scale (SWLS; Diener et al., 1985). The LMSQOL is an 8-item, unidimensional disease-specific measure of overall QOL. The LMSQOL has good internal consistency, test-retest reliability, and evidence of score validity (Ford et al., 2001). Coefficient alpha for the LMSQOL was .85 in the present study. The SWLS is a 5-item, unidimensional generic measure of overall QOL. The SWLS too has good internal consistency, test-retest reliability, and evidence of score validity (Diener et al., 1985). Coefficient alpha for the SWLS was .90 in the present study. The items on both scales were scored and summed such that higher scores reflect better QOL.

Procedure

The procedures were approved by a University Institutional Review Board and participants provided written informed consent. The baseline and follow-up materials for the study were delivered and returned through the U.S. postal service, and participants received \$40 upon returning the study materials. The participants completed the FSS, HADS-D, and SF-MPQ at baseline and then six-months later completed the LMSQOL and SWLS. The six-month follow-up allowed for the proper temporal sequencing between the symptom cluster and subsequent perceptions of QOL.

Data Analysis

The data were analyzed using descriptive statistics, cluster analysis, and one-way analysis of variance (ANOVA) in SPSS, version 16.0. We initially performed a cluster analysis as a method of clustering persons with MS into sub-groups based on experiences with the three symptoms. We then conducted one-way ANOVAs for examining differences in QOL based on LMSQOL and SWLS scores between the sub-groups identified in the initial cluster analysis. The overall magnitude of differences was based on eta-squared (η^2) for the *F*-statistic. The specific differences between groups in QOL were decomposed using post-hoc comparisons (independent samples *t*-tests) with a Bonferroni adjustment of alpha (adjusted alpha = .016).

The data appeared to satisfy the assumptions of normal distribution (i.e., estimates of skewness and kurtosis < 1.96), homogeneity of variance (i.e., non-significance of Levene's Test), and independence of observations (i.e., minimal intraclass correlation coefficient).

Results

Descriptive Statistics

The mean scores, standard deviations, and range of scores for the FSS, MPQ, HADS-D, LMSQOL, and SWLS are provided in Table 1.

Cluster Analysis

The cluster analysis identified three sub-groups or clusters of individuals based on experiences with the symptoms of fatigue, pain, and depression. The 1st cluster had relatively low scores on all three symptoms ($n = 58$; 20%), whereas the 2nd and 3rd clusters had moderate ($n = 140$; 48%) and high ($n = 93$; 32%) scores on the measures of fatigue, depression, and pain, respectively. This is displayed in Figure 1 using mean scores that are standardized based on the range of scores rather than raw scores for the three measures. The clusters did not differ significantly in age [$F(2,289)=2.54, p = .08$] nor the distribution of sex [$\chi^2(2, N = 291) = 1.86, p = .40$] and MS type [$\chi^2(4, N = 291) = 3.56, p = .47$], but there was a difference in duration of MS [$F(2,289) = 3.04, p = .05$]. Those with lowest scores on the three symptoms had a shorter duration of MS compared with those who had the highest scores on all three symptoms.

Quality of Life

The ANOVAs indicated that there were large differences between the three sub-groups identified from the cluster analysis on LMSQOL [$F(2,272)=139.94, p < .0001, \eta^2 = .51$] and SWLS [$F(2,272)=59.67, p < .0001, \eta^2 = .31$] scores. Post-hoc analyses indicated that there were significant differences in LMSQOL and SWLS scores between all three sub-groups (all t -values were ≥ 4.05 for the post-hoc comparisons and the associated p -values were $\leq .001$). The subgroup or cluster with lowest scores on all three symptoms had the highest QOL, whereas the subgroup with the highest scores on the symptoms had the worst QOL. This is displayed in Figure 2.

Discussion

The present study examined fatigue, pain, and depression as a cluster of symptoms that **correlates with** reduced QOL in a sample of individuals with MS. Overall, the cluster analysis identified three sub-groups differing in experiences of fatigue, depression, and pain, and the three sub-groups differed on two measures of QOL. The sub-group with lowest scores on all three symptoms had the highest QOL, whereas the sub-group with the highest scores on the symptoms had the worst QOL. Such findings are consistent with previous research in persons with MS (Forbes et al., 2006) provide additional support for the importance of a symptom cluster as a correlate of compromised QOL in persons with MS.

Previous research has provided the preliminary evidence for the existence of a symptom cluster in persons with MS (Forbes et al., 2006; Motl & McAuley, in press). For example, our previous study (a) identified a symptom cluster that included fatigue, pain, and depression using bivariate correlation analysis, confirmatory factor analysis, and cluster analysis and (b) demonstrated that the symptom cluster was associated with a behavioral outcome, namely physical activity. The present study expanded upon that previous work by identifying QOL as an outcome of the same symptom cluster and this finding is consistent with previous research (Forbes et al., 2006) that identified four clusters of individuals with MS who differed in experiences of fatigue, pain, and depression, and the clusters of individuals differed in domains

of QOL. Overall, there is preliminary evidence that fatigue, depression, and pain represent a cluster of symptoms that is linked with both behavioral and QOL outcomes in the same sample of persons with MS. Such observations should be further replicated in other samples of persons with MS.

There is emerging evidence for a symptom cluster as an important correlate of reduced QOL in persons with MS (Forbes et al., 2006) and other chronic disease conditions (Miaskowski et al., 2006; Pud et al., 2008). Our analyses indicated that there were significant differences in LMSQOL and SWLS scores between all three sub-groups identified in the cluster analysis. The sub-group with lowest scores on all three symptoms (i.e., fewest experiences with fatigue, pain, and depression) had the highest QOL, whereas the sub-group with the highest scores on the three symptoms had the worst QOL. Such findings are consistent with those observed in the field of oncology whereby symptom clusters were associated with outcomes such as reduced functional status and QOL (Miaskowski et al., 2006; Pud et al., 2008). For example, one recent study of outpatients with cancer receiving active treatment identified four sub-groups of individuals with different experiences of fatigue, sleep disturbance, depression, and pain, and the sub-groups demonstrated significant differences in multiple sub-domains of QOL (Miaskowski et al., 2006). We highlight the importance of continued and expanded examinations of symptom clusters as a correlate of QOL and other consequences in persons with chronic conditions such as MS and cancer. Such examinations might prompt future efforts directed toward developing symptom management interventions that target either multiple, concurrent symptoms or a single symptom and its associated effects on other symptoms in a cluster as a method of improving QOL and other consequences in persons with chronic conditions. Implications for neuroscience nursing practice might involve the identification and treatment of multiple co-occurring symptoms in persons with MS as a method of improving QOL. This might involve the delivery of information that discusses multidisciplinary approaches for managing MS symptoms.

There are limitations of the current study. One limitation is the focus on only three symptoms of fatigue, depression, and pain. This was a consequence of the secondary analysis of existing data, and future researchers might consider additional symptoms within this cluster or other clusters. For example, some of the additional symptoms might include cognitive impairment, sleep insufficiency, and sensory disturbances, whereas other clusters of symptoms might involve gait, balance, and posture or nausea and vomiting in persons with MS. Those additional clusters may be prevalent in MS because of the centrality of movement and treatment-related side-effects, respectively. Another limitation is that the sample primarily consisted of middle-aged, women with relapsing-remitting MS thereby limiting the generalizability of the study findings. This lack of generalizability is associated with the correlational research design and convenience sampling and should be addressed in future work using a more representative and diverse sample of persons with MS. The correlational research design does not allow for an interpretation of the symptom cluster as a causal predictor of reduced QOL in persons with MS.

The present study provides an expanding empirical basis for focusing on symptom clusters and the associated QOL outcomes in persons with MS. We provided evidence that fatigue, depression, and pain represent a symptom cluster that is correlated with reduced QOL in persons with MS. We hope that our focus on symptom clusters will expand subsequent efforts in persons with MS as has been done in oncology. Such efforts will highlight the role of symptom clusters in the lives of those with MS.

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Figure 1.

Standardized mean scores and standard errors for the measures of fatigue, depression, and pain based on the low, moderate, and high symptom clusters identified in the cluster analysis with the sample of 291 individuals with multiple sclerosis. *Note:* FSS = Fatigue Severity Scale; HADS-D = Hospital Anxiety and Depression Scale-Depression Subscale; MPQ = Short-form of McGill Pain Questionnaire.

Figure 2. Observed mean scores and standard errors for the measures of quality of life based on the subgroups of low, moderate, and high symptom experiences identified in the cluster analysis with the sample of 291 individuals with multiple sclerosis. *Note:* LMSQOL = Leed's Multiple Sclerosis Quality of Life scale; SWLS = Satisfaction with Life Scale.

Table 1

Descriptive Statistics for the Measures in the Sample of 291 Individuals with Multiple Sclerosis

Measure	Mean Score	Standard Deviation	Range of Scores
FSS ^a	5.0	1.4	1 – 7
HADS-D ^a	6.0	4.1	0 – 18
MPQ ^a	10.7	7.8	0 – 33
LMSQOL ^b	30.9	4.9	19 – 42
SWLS ^b	22.0	8.2	5 – 35

Note FSS = Fatigue Severity Scale; HADS-D = Hospital Anxiety and Depression Scale-Depression Subscale; MPQ = Short-form of McGill Pain Questionnaire; LMSQOL = Leed's Multiple Sclerosis Quality of Life scale; SWLS = Satisfaction with Life Scale. The mean scores for the FSS, HADS-D, and MPQ have been previously reported in Motl and McAuley (in press).

^aHigher scores indicate a more frequent or severe symptom.

^bHigher scores indicate better quality of life.