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Disability and Health Journal 5 (2012) 277−283

Disability and Health Journal

www.disabilityandhealthjnl.com

Research Paper

Effects of pain and fatigue on physical functioning and depression in persons with muscular dystrophy

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Abstract

Background: Pain and fatigue are common symptoms experienced by persons with muscular dystrophy (MD). However, it is unclear from previous studies whether pain and fatigue have independent effects on physical functioning and depression, and whether age moderates the relationship of pain and fatigue with physical functioning and depression.

Objective: This cross-sectional study aimed to describe the relationship of pain and fatigue to physical functioning and depression in persons 20−89 years old with MD.

Method: A convenience sample of 332 individuals with MD completed a questionnaire that included measures of physical functioning (PROMIS item bank items), depression (PHQ-9), pain intensity (0−10 NRS), and fatigue (0−10 NRS).

Results: Pain and fatigue were each independently associated with physical functioning and depression. Depressive symptoms were most severe among middle-aged participants (45−64 years old) relative to older and younger participants. Physical functioning had a negative relationship with chronological age.

Conclusions: Symptoms of pain and fatigue are significantly and independently related to physical functioning and depression in persons with MD. Research is needed to determine if treatments that target both pain and fatigue in patients with MD have more beneficial effects than treatments that target only one of these symptoms.

Keywords: Pain; Fatigue; Muscular dystrophy; Depression

Individuals with muscular dystrophy (MD) frequently endorse symptoms of pain and fatigue.[1−7] For example, Jensen and colleagues[7] found that 71% of participants with MD reported having experienced pain in the three months prior to being surveyed. Of those who reported pain, the average pain intensity was in the ‘‘moderate’’ range (i.e., 5−6 on a 0−10 scale of pain intensity) and approximately one quarter of the participants reported pain in the ‘‘severe’’ range (i.e., 7−10/10). Pain was most frequently present in the lower back, legs, shoulders, neck, hips and knees, and may be musculoskeletal pain related to stress from the muscle weakness and strength imbalance, or may be related to spasticity or neuropathy. Rates of fatigue are similar to those of pain, with studies of persons with facioscapulohumeral muscular dystrophy (FSHD) and myotonic muscular dystrophy (MMD) reporting severe or excessive fatigue in 61−74% of participants.[3,4]

Pain and fatigue have also been shown to be associated with measures of both physical and psychological dysfunction in individuals with MD. For example, bodily pain correlated moderately with measures of satisfaction with life and activities of daily living in a sample of individuals with a variety of MD diagnoses.[8] Severity of fatigue has been shown to be correlated with more problems with physical functioning, mental health, and bodily pain,[3] as well as with overall impairment.[9] A study of participants with myotonic dystrophy who had symptoms of fatigue had

Source of support: The contents of this paper were developed under a grant from the Department of Education, NIDRR grant number H133B080024. However, those contents do not necessarily represent the policy of the Department of Education, and you should not assume endorsement by the Federal Government.

Conflict of interest: No party having a direct interest in the results of the research supporting this article has or will confer a benefit on the authors or on any organization with which they are associated.

Financial relationships: Mark P. Jensen has received research support and/or consulting fees from Analgesic Research, Bristol-Myers Squibb, Covidien, Depomed, Eli Lilly, Endo Phamaceuticals, Medtronic, Merck, Pfizer, RTI Health Solutions, Schwartz Biosciences, Smith & Nephew, and ZARS Pharma within the past 36 months. The other co-authors report no financial relationships.

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1936-6574/$ - see front matter
http://dx.doi.org/10.1016/j.dhjo.2012.07.002

lower scores on measures of physical functioning than participants without fatigue.[4] Participants also reported more limitations due to physical problems, bodily pain, and lower levels of general health, vitality, and social functioning. Those with fatigue and excessive daytime sleepiness also exhibited lower scores on measures of mental health and had greater role limitations secondary to emotional difficulties.[4] Because it is widely believed that pain and fatigue contribute to one another in a cyclical fashion,[3,7,9] it is unclear in the literature whether they uniquely impact physical function.

The fact that symptoms of MD progress over time suggests that chronological age could also be associated with increases in dysfunction in MD. As people age and have fewer physiological reserves, the effects of pain and fatigue on functioning may become more pronounced. On the other hand, it is possible that as people with MD age, factors other than pain and fatigue may begin to play increasing roles in patient functioning, thereby reducing the associations between both pain and fatigue and functioning in older individuals. Not surprisingly, the current literature is both limited and mixed concerning these questions. Kalkman and colleagues[3] found that increased age was associated with more fatigue severity, bodily pain, and decreased physical functioning among individuals with MD. They also found that higher age was correlated with more functional impairment, more pain, less motivation and less activity. On the other hand, other investigators have found no significant associations between fatigue severity and age in MD.[4] Jensen and colleagues[7] found that age was related to the onset of pain, such that those with MD who reported pain were younger than those who did not report pain. In contrast, pain severity was not related to age in their sample. Thus, although age could potentially be an important factor, the literature is unclear on the moderating role that age might play on the associations between the severity of symptoms such as pain and fatigue, and criterion measures of psychological and physical functioning in individuals with MD.

The present study was designed to gain a better understanding of the relationship of pain and fatigue to patient functioning, as well as to investigate the role that age may play in these relationships in individuals with MD. Specific aims included (1) determining if pain and fatigue are independently associated with physical functioning and depression and (2) evaluating the potential moderating effects of age on these relationships. Based on previous studies that investigated the effects of pain or fatigue on functioning in persons with MD[3,7,9] and a previous study examining these same questions in a sample of patients with post-polio syndrome,[10] we hypothesized that (1) pain and fatigue would demonstrate significant independent associations with both physical functioning and depression in our sample of individuals with MD, (2) depression would be lower in participants who are middle-aged than participants who are younger or older, and (3) age would not moderate the associations between the symptoms of pain and fatigue and measures of physical functioning and depression.

Methods

Measures

Physical functioning

Items from the 124-item PROMIS Physical Functioning item bank[11–13] were used to measure physical activity. The PROMIS item bank has been developed such that any subset of items can be used to estimate the latent trait, in this case physical activity.[14] Thus, study investigators selected twelve items from the pool for their applicability for use in persons with disabilities. The PROMIS Physical Functioning item bank evaluates an individual's average ability to perform a range of physical activities, and is measured on a 5-point scale from ‘‘without any difficulty’’ to ‘‘unable to do.’’ Items ask individuals to rate the difficulty they have completing a wide range of activities, including difficulty: (1) putting on and taking off a coat or jacket; (2) walking more than a mile; (3) carrying a bag of groceries for a short distance; (4) preparing simple meals for themselves or for others; (5) doing housework like vacuuming or sweeping floors; (6) moving around on a slippery surface outdoors; (7) doing vigorous activities, such as playing sports; (8) standing up from sitting on a low, soft couch; (9) washing and drying their body; (10) making a bed, including spreading and tucking in bed sheets; (11) getting up off the floor from lying on their back without help; and (12) going for a walk of at least 15 min. Scores are transformed into *t*-scores with higher scores indicating better physical functioning. The validity and reliability of this PROMIS item bank has been supported by preliminary assessment.[14]

Depression

Depressive symptoms were assessed using The Patient Health Questionnaire-9 (PHQ-9). This 9-item measure uses a 4-point scale to ask respondents how frequently they were bothered by nine symptoms of depression in the past two weeks. The response scale ranges from ‘‘Not at all’’ to ‘‘Nearly every day,’’ with scores ranging from 0 to 3, respectively. The total score on the PHQ-9 can range from 0 to 27, with higher scores representing higher levels of depressive symptoms. The PHQ-9 is commonly used to assess depression severity and has a great deal of evidence supporting its reliability and validity as a measure of depression for use in populations with physical disabilities, such as spinal cord injury, traumatic brain injury, and multiple sclerosis.[15,16]

Pain intensity and fatigue

Numerical Rating Scales (NRSs) were used to measure pain intensity and fatigue. Participants were asked to rate the severity of these symptoms over the past week on

0 to 10 scales, with 0 = "None" and 10 = "Very severe." NRSs are frequently used to assess symptom severity, and a significant amount of research supports their validity for measuring pain and fatigue severity.[17–19]

Procedures

Eligible participants were persons 18 years of age or older who were able to read and write English and had a self-reported diagnosis of MD. Participants were recruited from (1) a pool of adults with MD who had previously participated in studies with the University of Rochester and indicated a willingness to be contacted for participation in future studies, as well as (2) individuals responding to advertisements through the Muscular Dystrophy Foundation, other publications, and clinics. A total of 405 individuals responded to these invitation letters and advertisements. Surveys were sent to 382 individuals who met inclusion criteria. A total of 340 surveys were completed and returned (311 from past University of Rochester participants; 29 from other sources), resulting in an 89% response rate. Participants received $25 for their participation. This study was approved by the Institutional Review Board at the University of Washington and informed consent was obtained from all participants. One paper comparing the severity of fatigue with U.S. norms across age cohorts in a sample that included almost all of the participants in the current paper has been published.[20]

Data analysis

Prior to hypothesis testing, participants' MD diagnoses were reviewed. We limited our analyses to the 332 participants (of 340) who had either MMD (all subtypes) or FSHD. We then conducted exploratory analyses to ensure that there was no missing data and that the variables met the assumptions of hierarchical multiple regression. Analyses indicated that there were no missing data for the variables used in our analyses, and further suggested there was no evidence for significant skew, kurtosis, outliers, or heteroscedasticity for any of the variables. We then computed descriptive statistics of the study variables for each type of MD and computed *t*-tests to assess for group differences in scores. Next, we computed Pearson correlation coefficients between the study variables to determine their zero-order associations. The primary analyses were two hierarchical regression analyses to determine whether pain and fatigue were independently associated (i.e., when controlling for the other) with depression and physical functioning (represented by the PHQ-9 and PROMIS Physical Functioning scale, respectively) after controlling for chronological age. To reduce any potential problems associated with multicolinearity, all variables were centered before being inputted into the model in order. The centered chronological age variable and type of MD were entered in step one, (centered) age^2 was entered in step two to test for a possible quadratic association between age and the criterion variables, average pain intensity and fatigue (the 0–10 NRS ratings) were entered in step three, Age-X-Pain Intensity and Age-X-Fatigue Intensity interaction terms were entered in the fourth step (to test for linear age moderation effects), and Age^2-X-Pain Intensity and Age^2-X-Fatigue Intensity interaction terms were entered in the fifth step to test for quadratic age effects. The beta weights and significance levels of each variable were examined to evaluate their effects.

Results

Participants

The sample of 332 participants included 58.1% (N = 193) with MMD and 41.9% (N = 139) with FSHD. Among participants with MMD, 60.1% (N = 116) were women and 39.9% (N = 77) were men. Average age was 53.2 years (SD = 12.3; range = 20–80 years). The overwhelming majority reported their race/ethnicity as Caucasian (N = 189, 97.9%) and had completed at least some college (N = 149, 52.3%). Among participants with FSHD, 55.4% (N = 77) were women and 44.6% (N = 62) were men. Average age was 53.6 years (SD = 13.8; range = 22–89 years). Again, the overwhelming majority reported their race/ethnicity as Caucasian (N = 134, 96.4%) and had completed at least some college (N = 108, 64.0%).

For supplemental analyses, participants were also divided into five age-based cohorts: less than 45 years old (N = 76, 22.4%), 45–54 years old (N = 102, 30.0%), 55–64 years old (N = 95, 27.9%), 65–74 years old (N = 53, 15.6%), and 75 years old and older (N = 14, 4.1%).

Means, standard deviations, and associations among the study variables

Table 1 reports the descriptive analyses for the study variables within each MD type. *t*-tests showed that persons with MMD reported higher levels of physical functioning, higher levels of depressive symptoms, and lower pain relative to persons with FSHD. The MD diagnostic groups did not differ in terms of fatigue or age. In Table 2, zero-order correlations between the variables are reported, revealing that physical functioning, depression, fatigue, and pain are all statistically significantly associated with each other, while age is only associated with physical functioning.

Regression analyses

Results of the regression analysis for physical functioning is reported in Table 3. The overall model was significant ($F(9, 323) = 24.01$, $p < 0.0001$) and accounted for 38.8% of the variance. In step 1, age ($\beta = -0.37$, $p < 0.0001$) and type of MD ($\beta = -0.25$, $p < 0.0001$)

Table 1
Descriptive statistics for physical functioning, depression, fatigue, pain, and age

	MMD			FSHD			t-test	
	Mean	SD	Range	Mean	SD	Range	t	p-value
PROMIS Physical Functioning (t-score)	39.5	9.9	14.0–59.9	34.4	14.0	34.4–9.4	4.66	<0.001
PHQ-9 Depression	7.5	5.7	0–25	5.5	5.1	0–27	3.25	<0.01
Average pain over past week	3.2	2.8	0–10	5.2	2.7	0–10	−1.95	0.50
Average fatigue over past week	5.8	2.9	0–10	3.8	2.7	0–10	1.76	ns
Age	53.2	12.3	20–80	53.6	13.8	22–89	−0.23	ns

were significantly associated with the criterion variable and accounted for 20.0% of the variance in the PROMIS Physical Functioning score. The direction of the associations indicated that participants who were relatively younger reported higher levels of physical functioning than those who were relatively older, and persons with MMD reported higher levels of physical functioning than those who had FSHD. In step 2, age^2 was not significantly associated with the criterion variable and did not significantly contribute to the variance in physical functioning. In step 3, pain and fatigue accounted for an additional 19.5% of the variance in the PROMIS Physical Functioning score ($F(R^2\Delta) = 51.64$, $p < 0.0001$). Pain ($\beta = -0.19$, $p < 0.0001$) and fatigue ($\beta = -0.31$, $p < 0.0001$), after controlling for age and type of MD, each made significant independent contributions to PROMIS Physical Functioning, with the direction of the association indicating that those reporting higher levels of pain and fatigue also report lower levels of physical functioning. The interaction terms entered in steps 4 and 5 did not contribute significantly to the model.

The overall regression model for depression was significant ($F(9, 323) = 17.54$, $p < 0.0001$) and accounted for 33.3% of the variance (see Table 4). In the first step, type of MD ($\beta = -0.18$, $p < 0.01$) was significantly associated with the criterion variable and accounted for 3.4% of the variance in PHQ-9 Depression score ($F(R^2\Delta) = 5.68$, $p < 0.01$). Age was not significantly associated with the criterion variable. In step 2, age^2 was significantly associated with the criterion variable ($\beta = -0.11$, $p < 0.05$) and accounted for 1.1% of the variance in PHQ-9 Depression score. This curvilinear association was further explored by examining the depression scores for each of five age cohort groups: (1) younger than 45 years old (PHQ-9 score = 5.67); (2) 45–54 years old (PHQ-9 score = 7.91); (3) 55–64 years old (PHQ-9 score = 7.02); (4) 65–74 years old (PHQ-9 score = 5.09); and (5) 75 years old and older (PHQ-9 score = 5.71). These findings indicate that participants between 45 and 64 years old reported the highest levels of depression, with the younger and older participants reporting statistically significantly lower levels of depression than the middle-aged participants ($F = 3.27$, $p < 0.05$). In step 3, pain and fatigue accounted for an additional 28.1% of the variance in the PHQ-9 Depression score ($F(R^2\Delta) = 66.34$, $p < 0.0001$). Pain ($\beta = 0.16$, $p < 0.01$) and fatigue ($\beta = 0.43$, $p < 0.0001$) each were independently associated with the criterion, with the direction of the association suggesting that more pain and more fatigue are associated with greater depressive symptomatology. The interaction terms entered in steps 4 and 5 did not contribute significantly to the model.

Table 2
Zero-order correlation matrix of physical functioning, depression, fatigue, pain, and age

	1.	2.	3.	4.
1. PROMIS Physical functioning				
2. PHQ-9 Depression	−0.30***			
3. Average pain intensity over past week	−0.36***	0.37***		
4. Average fatigue over past week	−0.37***	0.52***	0.50***	
5. Age	−0.36***	−0.03	−0.02	0.01

***$p < 0.001$.

Discussion

The results of the present study demonstrate significant independent associations of pain and fatigue with lower physical functioning and greater depression in individuals with MD, even after controlling for type of MD. Previous studies reported associations of pain and fatigue with physical functioning and depressive symptoms, but did not consider pain and fatigue together to determine whether their associations with functioning were independent of each other.[1–7] Further analysis of the results suggests that pain and fatigue account for more of the variance in depression than to physical functioning. Age was associated with physical functioning and depression differently. A significant linear association was found between age and physical function, in contrast to a significant curvilinear relationship between age and depression. Type of MD was associated with both physical functioning and depression, with FSHD being associated with relatively lower physical functioning and MMD associated with relatively more depression. However, type of MD does not moderate the associations of age, pain, and fatigue, with physical functioning or depression. Taken together, these results highlight that both

Table 3
Regression model for PROMIS Physical Functioning score

Step and variable	B	t	p-value	$R^2\Delta$	$F(R^2\Delta)$	p-value
Step 1				0.200	40.57	<0.0001
Age (centered)	−0.37	−7.43	<0.0001			
Type of muscular dystrophy	−0.25	−4.95	<0.0001			
Step 2				0.000	0.00	0.98
Age^2 (centered)	0.00	−0.20	0.98			
Step 3				0.195	51.64	<0.0001
Pain (centered)	−0.19	−3.58	<0.0001			
Fatigue (centered)	−0.31	−6.02	<0.0001			
Step 4				0.005	1.32	0.27
Age (centered) X Pain (centered)	0.06	1.19	0.24			
Age (centered) X Fatigue (centered)	0.01	0.35	0.73			
Step 5				0.005	1.45	0.24
Age^2 (centered) X Pain (centered)	0.07	1.12	0.26			
Age^2 (centered) X Fatigue (centered)	0.04	0.62	0.54			

Note: Overall model: $F(9, 323) = 24.01$, $p < 0.0001$.

pain and fatigue are associated with patient functioning, and suggest that these may be important targets for treatment in persons with MD.

Previous studies have reported similar associations between pain *or* fatigue with functioning in persons with MD,[3,7] but we are unaware of any study that has simultaneously examined the independent effects of pain and fatigue on physical functioning and depression. Given the significant associations found in the present study, the results suggest the possibility that treatments that decrease pain and fatigue might *each* subsequently result in better physical functioning and fewer depressive symptoms. The current findings support the need for research testing this hypothesis.

A number of interventions might be considered to treat pain in persons with MD. A recent descriptive study of pain in persons with MMD and FSHD revealed an extensive list of treatments used.[7] Patients reported most commonly using ibuprofen, aspirin, acetaminophen, or muscle strengthening and range of motion exercises. The treatments rated as most effective by persons with MMD and FSHD were ibuprofen and aspirin, opioids, massage, chiropractic manipulation, nerve blocks, heat, and marijuana. From a biopsychosocial perspective, it would also be important to consider the potential benefits of using treatments targeting psychological and social factors in addition to the pharmacologic and physical management of pain. The most common psychosocial treatments for chronic pain in persons presenting with pain as a primary problem with demonstrated efficacy include cognitive behavioral strategies.[21] Yet relatively few participants in the Jensen et al[7] study reported that they had been offered or tried cognitive behavioral interventions such as counseling, biofeedback/relaxation training, or hypnosis. Our findings that pain impacts both physical functioning and depression in persons with MD suggests that the continued development of effective strategies for pain management in this population may be important to patient well-being.

In contrast to pain, there are a limited number of trials testing interventions for improving symptoms of fatigue in persons with MD. One recent review offered exercise and modafinil as the treatments with the best evidence for

Table 4
Regression model for PHQ-9 depression score

Step and variable	B	t	p-value	$R^2\Delta$	$F(R^2\Delta)$	p-value
Step 1				0.034	5.68	<0.01
Age (centered)	−0.04	−0.73	0.47			
Type of muscular dystrophy	−0.18	−3.28	<0.01			
Step 2				0.011	3.53	0.05
Age^2 (centered)	−0.11	−2.01	0.05			
Step 3				0.281	66.34	<0.0001
Pain (centered)	0.16	2.91	<0.01			
Fatigue (centered)	0.43	7.83	<0.0001			
Step 4				0.009	2.08	0.13
Age (centered) X Pain (centered)	−0.03	−0.57	0.57			
Age (centered) X Fatigue (centered)	−0.08	−1.40	0.16			
Step 5				0.002	0.38	0.69
Age^2 (centered) X Pain (centered)	−0.02	−0.35	0.73			
Age^2 (centered) X Fatigue (centered)	−0.04	−0.54	0.59			

Note: Overall model: $F(9, 323) = 17.54$, $p < 0.0001$.

efficacy for MD-related fatigue.[5] The use of exercise for treatment relates directly to findings that decreased activity is associated with greater fatigue in persons with MD.[9] Although exercise is offered as a potentially effective treatment, a review of studies specifically targeting muscle training or strengthening revealed mixed results.[22] Of note, strength training and albuterol did not result in significant improvements in fatigue[23] and group exercise did not have an effect on sleepiness.[24] Clearly, further research is needed to develop more effective interventions for fatigue in persons with MD.

Beyond pain and fatigue, the findings also indicated a linear relationship between increasing age and decreasing physical functioning. It is unclear whether this is a reflection of ''normal'' aging, disease progression over time, or both. Further research is needed to better understand this relationship in persons with MD. At the same time, age did not appear to moderate the associations between either symptom (pain or fatigue) and the criterion measures of depressive symptoms and physical functioning, suggesting that pain and fatigue have a similar impact on patient functioning across all age cohorts, and that therefore treatments found to be effective for treating these symptoms in one age group might be expected to be of similar benefit in patients from other age groups.

A growing body of literature demonstrates depression tends to be lower in older populations relative to younger populations in persons with[25] and without disabilities.[10,26,27] Consistent with these findings, we found that older participants reported some of the lowest levels of depression, although in our case it was a curvilinear relationship, with middle-aged participants reporting the highest levels of depressive symptoms and younger and older participants reporting the lowest levels. These findings are consistent with results we previously reported for persons with post-polio syndrome.[10] One possible explanation for this relationship is that stress (and associated depressive symptoms) may be at its worst during middle age due to declining functioning in the context of high performance expectations.[28] Then, following retirement, some research suggests that depression may decrease due to an increased sense of control over environmental demands and fewer daily hassles.[29] Our findings of highest depression scores among persons 45–64 years old supports the previous findings regarding depression in middle age and suggests that additional treatments are needed to specifically target this demographic. Such treatments might consist of training in effective stress and depression management in the young adult age group as a way of *preventing* depression in middle-aged individuals, as well as the development of interventions that target the major issues confronting middle-aged individuals, such as work-related stress, impending retirement, parenting teenagers, and caring for elderly parents.

A number of limitations should be considered when interpreting the results of this study. First, this was a survey study comprised of individuals willing to complete and return the survey. No results are available to determine whether the potential participants with MD who did not complete the survey differ in any significant way from those that did. Therefore, we cannot be certain that the results generalize to the broader population of persons with MD. On the other hand, the survey methodology allowed for the collection of data from a relatively large number of persons with MD from diverse locations, potentially improving generalizability from that perspective. Second, the survey design yielded data only suitable for cross-sectional analyses, thus limiting our ability to make causal conclusions. The associations found in our study suggest the possibility that improvement in pain and fatigue (separately or together) may improve patient functioning. Experimental studies examining whether treatments that reduce pain and fatigue are needed to confirm this hypothesis. Third, the measurement of fatigue both in general and in persons with MD has been noted to be complicated, particularly in terms of differentiating fatigue from excessive daytime sleepiness.[4] The best way to differentiate fatigue from other sleep-related problems may be through clinical interview.[4] Future research should examine how different types of fatigue might be associated with each other, and how they might be differently associated with measures of patient functioning. Fourth, one of the limitations of considering depressive symptoms in any analysis is the overlap between some of the depressive symptoms and common sequelae of medical problems, such as difficulty with sleep and poor appetite. This can make it difficult to interpret findings related to depression in persons with medical problems. Future research should assess and then control for these overlapping symptoms, when possible. Fifth, the participants in this study represented only two types of MD. Although MD type was associated with the criterion variables, the (independent) importance of pain and fatigue remained even when controlling for MD type, supporting the generalizability of the findings across these two diagnostic groups. Whether the findings would also generalize to individuals with other MD diagnoses cannot be determined from the current findings, and will need to be confirmed in future research. Finally, although our analyses accounted for a moderate amount of the variance in physical functioning and depression, it is apparent that there are a number of other factors that are contributing to both depressive symptoms and physical functioning in persons with MD. It is recommended that subsequent studies consider additional variables that may contribute for more of the variance in these important criterion variables.

Conclusions

The present study improves upon previous research on pain and fatigue in persons with MD by identifying significant independent effects of each to physical functioning and depression. Thus, treatment programs targeting improved functioning should consider including targeted interventions for both symptoms. We are unaware of comprehensive treatment programs that include interventions for both pain and fatigue for these patients and thus recommend that such multitarget interventions be a focus of future treatment outcome studies. Our results also suggest that it is important to consider age in clinical formulations of patients' physical function and depression. For example, treatments for depression should consider the issues relevant to an individual's age and stage in life, particularly in terms of how declining physical functioning might interact with the level of functioning expected of the patient at home and work. Taken together, the present study highlights pain, fatigue, and age as factors worthy of consideration when trying to improve functioning in persons with MD.

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