



Published in final edited form as:

*Phys Med Rehabil Clin N Am.* 2012 November ; 23(4): 895–902. doi:10.1016/j.pmr.2012.08.008.

## Chronic Pain in Neuromuscular Disease:

### Pain Site and Intensity Differentially Impacts Function

Jordi Miró, PhD<sup>a</sup>, Kevin J. Gertz, PhD<sup>b</sup>, Gregory T. Carter, MD, MS<sup>c,d,e,\*</sup>, and Mark P. Jensen, PhD<sup>b</sup>

<sup>a</sup>Unit for the Study and Treatment of Pain - ALGOS, Centre de Recerca en Avaluació i Mesura del Comportament, Institut d'Investigació Sanitària Pere Virgili, Universitat Rovira i Virgili, Carretera de Valls s7N, 43007 Tarragona, Catalonia, Spain

<sup>b</sup>Department of Rehabilitation Medicine, University of Washington School of Medicine, Box 359612, Seattle, WA 98195, USA

<sup>c</sup>Department of Clinical Neurosciences, Providence Medical Group, Olympia, WA 98506, USA

<sup>d</sup>Department of Physical Medicine and Rehabilitation, University of California at Davis, Sacramento, CA 95817, USA

<sup>e</sup>MEDEX Division, University of Washington School of Medicine, Seattle, WA 98195, USA

### Keywords

Neuromuscular disease; Chronic pain; Pain intensity; Muscular dystrophy; Regional pain

## INTRODUCTION

A growing body of research indicates that chronic pain is a significant problem for many persons with chronic, slowly progressive neuromuscular disease (NMD).<sup>1–16</sup> However, it is still not clear how much pain intensity factors in to the negative bio-psychosocial and physical consequences of chronic pain in the setting of slowly progressive NMD. Pain intensity is one of the most common dimensions assessed by clinicians and researchers who treat and study pain. Reduction in global pain intensity is also the standard by which most pain treatments are judged. However, although average pain intensity is an important pain domain, other pain domains are also potentially important (eg, pain frequency, duration, location, and quality) as factors that could contribute to patient dysfunction, especially in individuals with chronic pain.<sup>17</sup> Unfortunately, research is lacking regarding the relative importance of these additional domains for understanding adjustment to pain.

The research that has been conducted on this topic in other pain populations suggests that pain site may contribute to adjustment to chronic pain over and above the effects of global pain intensity. For example, Marshall and colleagues<sup>18</sup> found that the intensity of back pain in patients with amputation explained a significant amount of variance in interference in daily activities beyond the pain associated with limb amputation. Similarly, there is some preliminary evidence that pain in the low back and arms is more strongly associated with patient functioning than pain in other body locations in a sample of patients with a variety of chronic pain problems (Tan G, Jensen MP, unpublished data, 2011). Nonetheless, research in this area is sparse, and it is not known whether these preliminary findings replicate in

other samples of patients with chronic pain, including those with NMD. If these findings do replicate across different chronic pain populations, then clinicians should assess both pain intensity and its location(s) to better understand the potential impact that the pain might have on a specific patient. Moreover, if low back pain or pain in the extremities is more closely linked to a patient's quality of life than pain at other sites, then treatments that address pain at these sites may be more important to patients with chronic pain than treatments that address pain at other sites (eg, the head or torso). Thus, research in this area could help inform the work of clinicians and scientists who are developing new pain treatments for individuals with specific pain conditions. However, the authors are not aware of any research that has studied the relative importance of pain site to patient functioning in individuals with slowly progressive NMD.

Pain extent is a separate and distinct domain from intensity and refers to the overall number of body areas with pain. Research suggests that this pain domain may also be important to patient functioning. For example, Tait and colleagues<sup>19</sup> found a significant association between pain extent and the tendency of patients to report greater complaints of weakness, fatigue, and depression. Similarly, Toomey and colleagues<sup>20</sup> reported that patients with more pain sites were more likely to report pain as having a greater negative impact in their functioning. Türp and colleagues<sup>21</sup> found that pain extent, along with pain intensity, was a significant predictor of pain-related disability in a sample of female patients with chronic facial pain. Patients with pain at multiple sites have shown a reduced level of health-related functioning, are more likely to have difficulties with mobility regardless of physical impairments than those with no pain or localized pain, and have worse prognosis for future work ability.<sup>22–24</sup> In a series of studies, Kamaleri and colleagues<sup>25</sup> reported significant associations between pain extent and functioning in patients with musculoskeletal pain. They found a strong and linear association between increasing number of pain sites and decreasing functional ability; a strong relationship with decreasing psychological health, sleep quality, and overall health; and future work disability after a 14-year period.<sup>25,26</sup>

As with research on the importance of specific pain sites to patient functioning, it is unclear if these findings regarding pain extent replicate in other populations of individuals with chronic pain, including persons with slowly progressive NMD. Most published studies on these issues have been conducted with low back patients receiving treatment at secondary and tertiary care facilities. Thus, these findings may not generalize to other populations of patients with pain.<sup>27</sup>

Further delineating the relative importance of pain site and extent in relation to patient functioning is particularly important in patients with NMD, because research indicates they typically experience pain in more than one location.<sup>5</sup> Given what previous studies have found in other pain populations, the authors hypothesize that pain extent would be negatively associated with psychological functioning and positively associated with pain interference, whereas pain intensity in specific pain sites would show stronger associations with measures of patient functioning than pain at other sites. More specifically, one would expect that pain in the low back and arms might evidence stronger associations with pain interference and psychological functioning than pain at other sites.

## DISEASE-SPECIFIC PAIN TRAITS

There are intriguing differences among degrees of pain in the slowly progressive forms of NMD. It is not unexpected that neuropathic diseases like Charcot Marie Tooth would rank high in pain intensity, given the pathogenesis of the disease, particularly the demyelinating forms. However, it is clear that 2 of the most common forms muscular dystrophy, myotonic type 1 (DM1), and facioscapulohumeral (FSHD), are also high on the list of painful NMDs.<sup>5</sup>

Worldwide, DM1 and FSHD are the first and third most common forms of dystrophic myopathies, respectively, with the dystrophinopathies coming in second.<sup>28</sup> Both DM1 and FSHD are autosomal dominant, slowly progressive neuromuscular disorders (NMDs).<sup>29,30</sup> DM1 is caused by a polynucleotide (CTG) triplet expansion located on the 3' untranslated region of chromosome 19q13.3.<sup>31</sup> This location results in a toxic gain of function of abnormally stored RNA in the nuclei of affected cells, leading to deregulation of RNA binding protein levels and mRNA splicing processes of multiple genes.<sup>32,33</sup> This action is presumed responsible for the multisystem features typical of DM1, with involvement of skeletal, cardiac, and smooth muscles, and the central nervous, endocrine, ocular, respiratory, and gastrointestinal systems to varying degrees.<sup>34</sup>

In FSHD, most patients possess a large deletion in the polymorphic D4Z4 macrosatellite repeat array at 4q35, presenting with up to 10 repeats, as opposed to 11–150 repeats in unaffected individuals.<sup>35–37</sup> This situation is complicated by a nearly identical repeat array present at 10q26.<sup>34</sup> The remarkably similar sequence identity between these 2 arrays can cause difficulties in molecular diagnosis. Each 3.3-kb D4Z4 unit contains a DUX4 (double homeobox 4) gene that is activated on contraction of the 4q35 repeat array via induction of chromatin remodeling.<sup>36</sup> Myofiber synthesis of both DUX4 transcripts and protein causes significant cell toxicity. As a transcription factor, DUX4 may target several genes, resulting in cellular deregulation with inhibition of myogenesis, muscle degradation, and oxidative stress.<sup>35</sup>

Prior studies indicate that as many as nearly 90% and 70% of patients with FSHD and DM1 report pain, respectively.<sup>5,38,39</sup> In addition to indentifying pain as a major problem for patients with either of these NMDs, these studies also indicate that pain is more common in patients with FSHD versus DM1.<sup>1,5,9</sup> The average severity of pain in patients with FSHD (approximately 4.4 of 10 on an ordinal pain scale) is less than that reported by patients with DM1 (6.28 of 10).<sup>5</sup> The reasons these disease in particular have more pain are not clear but they involve membrane-related pathology, and both disorders have underlying genetic expansion-type mutations and are multisystem disorders.<sup>40</sup>

As already mentioned, almost all previously published studies on the effects of pain extent have been conducted on patients with musculoskeletal problems. Results from these reports seem to support that simply counting the number of pain sites might be important when assessing a patient's pain problem.<sup>41</sup> This approach does not seem adequate, however, for people with an NMD. At least, for this specific population, our data suggest that overlooking the pain intensity of the specific sites may result in a failure to capture the true meaning and implications of the pain experience of these patients. Reasons for this failure include the fact that NMDs involve pathophysiology in the peripheral nerves or muscles as part of the underlying disease process, which is distinctly different from a musculoskeletal disorder. Thus, a variety of abnormal processes may generate and maintain the symptom of pain in NMDs, and conceptually, it is likely that no one mechanism may be disease specific, although this topic remains to be studied. It is more likely that any given NMD would have several mechanisms associated with it. Thus, accounting for the pain in any single patient may require hypothesizing one or more mechanisms at work simultaneously. Once neuropathic pain is present, all levels of the nervous system, peripheral, central, and autonomic, may play a role in the generation and maintenance of pain.<sup>42–44</sup> Therefore, independent of actual clinical diagnosis, several different pathophysiologic processes may be present simultaneously. Further, some patients with neuropathic pain may also develop secondary myofascial pain. Myofascial pain may mimic neuropathic pain and result in referred pain distant from the actual soft tissue source and is a logical explanation for the chain of events occurring in a hereditary neuropathy like Charcot Marie Tooth disease.

However, these myofascial pain generators are likely further accentuated in diseased, dystrophic muscle such as seen in DM1 or FSHD.

It is probable that, to some extent, skeletal muscle pathophysiology plays a significant role in pain generation in this setting. Because of active, ongoing muscle degeneration, there is significant risk for overwork weakness and exercise-induced muscle injury, even with simply doing activities of daily living.<sup>45</sup> Dystrophic muscle is susceptible to exercise-induced muscle injury, particularly eccentric (lengthening) muscle contractions.<sup>45</sup> Patients with NMD are susceptible to overwork weakness and muscle injury, resulting in excessive delayed-onset muscle soreness. This soreness usually occurs 24–48 hours after exercise. Other symptoms might include muscle cramping, heaviness in the extremities, prolonged dyspnea, and fatigue. Fatigue in this setting is likely multifactorial because of deconditioning and impaired muscular activation, but likely contributes to pain.<sup>46</sup>

## WHAT ARE THE NEXT STEPS?

The importance of considering pain site when assessing pain and its impact in persons with chronic pain is reinforced by data indicating that pain extent is significantly associated with pain interference and psychological functioning.<sup>5,10</sup> Pain extent likely plays a significant role in many chronic pain populations. The nature of pain in individuals with DM1 and FSHD suggests that this would be important in patients with these diagnoses as well. However, it is not clear whether pain in the low back and arms is more strongly associated with pain interference and psychological functioning than pain at other locations; research is needed to address this specific question. Nonetheless, the study findings reviewed support the idea that pain site matters, although further study is clearly warranted. It seems, however, that the pain sites that matter most to persons suffering from chronic pain in the setting of an NMD like DM1 or FSHD may differ significantly from those of persons with other chronic pain conditions.<sup>47,48</sup> The findings have important implications for understanding and treating, pain in persons with NMD.

Clearly, a comprehensive assessment of these persons will require going beyond the mere assessment of overall or general pain intensity and will require to gather information about the intensity of each pain problem. Thus, in this population, both a quantitative and qualitative assessment of the pain experience should be promoted. Especially relevant would be to attend to the pain in legs, feet, hips, and knees beyond overall pain intensity, because they are all significantly related to pain interference. Pain experienced in the head should also be addressed given its potential impact on psychological functioning above and beyond what is expected from overall pain intensity.

The authors also hypothesize that pain interference and psychological functioning are associated with pain intensity at different sites, although this hypothesis needs empiric confirmation with data. Intuitively, the sites most likely to exert the strongest (and unique) associations are the ones related to ambulation (ie, legs, feet, hips, and knees), which makes biomechanical sense, given that these muscles are particularly taxed physically and consequently susceptible to contraction-induced injury, as discussed earlier. Thus, it is important from a treatment perspective to address these individuals functionally, that is, devising specific strategies or activities to improve strength, flexibility, and endurance of those muscles and related areas. These areas are those that inflict higher interference and functioning tolls to the patients and should be addressed in any rehabilitation paradigm for these patients.

Turner and colleagues,<sup>49</sup> found that patients who reported more pain sites before participating in a cognitive-behavioral treatment had higher activity interference at 1 year; therefore, treatments for NMD patients should rely on pain intensity in specific sites rather

than overall pain intensity ratings. Moreover, each pain site might require different approaches, with specific combinations of rehabilitation alternatives.

Our pilot study found that the “other” pain location significantly contributed to the variance of pain interference. It was just a small group of participants (N = 19) that reported experiencing pain in a location or locations other than those in the survey (Miró J, et al, 2012). However, there seem to be other location(s) that are important to explain pain interference in people with an NMD and chronic pain beyond those analyzed in this study. Future work might build on the findings of this study by attempting to determine other pain locations that might be of importance for these patients to address them when developing treatment programs.

Some important limitations to the available published literature should be considered when interpreting the results. Most patient samples primarily include patients registered with the national Institutes of Health–funded MD National Registry, and the extent to which the findings from these patients are broadly applicable to individuals with other forms of NMD is not known. Moreover, all information is usually based on self-report measures. Therefore, it is possible that some of the significant associations found between measures may, therefore, be related to shared method variance. Future researchers should examine the associations between pain at different sites and more objective measures of patient functioning, such as ratings made by spouses or significant others, or objective measures of activity (eg, actigraphy).

Despite limited data, the available studies provide support for the potential utility of assessing specific pain qualities and overall pain intensity measures in persons with slowly progressive NMD, hence, the need for more studies of the influence of pain site and extent in patients with slowly progressive NMDs. Further studies are needed to explore and confirm these complex interrelationships. Nevertheless, there seem to be enough data, both from chronic pain populations and from patients whose pain is secondary to a disability, to support the inclusion of pain quality characteristics as outcome variables in pain research.<sup>18,22,25,26</sup>

## Acknowledgments

This research was supported by the National Institutes of Health, National Institute of Child Health and Human Development, National Center for Rehabilitation Research (grant no. P01HD33988), the National Registry of Myotonic Dystrophy and Facioscapulohumeral Muscular Dystrophy Patients and Family Members, and the National Institute on Disability Rehabilitation Research (grant no. H133B031118). JM’s work is supported by grants from the Government of Catalonia, AGAUR (Refs: 2009 SGR 434, and DGR 2011BE1 00611), and Vicerectorat de Recerca of Universitat Rovira i Virgili.

## References

1. Jensen MP, Moore MR, Bockow TB, et al. Psychosocial factors and adjustment to chronic pain in persons with physical disabilities: a systematic review. *Arch Phys Med Rehabil.* 2011; 92(1):146–60. [PubMed: 21187217]
2. Jensen MP, Abresch RT, Carter GT, et al. Chronic pain in persons with neuromuscular disorders. *Arch Phys Med Rehabil.* 2005; 86(6):1155–63. [PubMed: 15954054]
3. Suokas KI, Haanpää M, Kautiainen H, et al. Pain in patients with myotonic dystrophy type 2: a postal survey in Finland. *Muscle Nerve.* 2012; 45(1):70–4. [PubMed: 22190310]
4. Abresch RT, Carter GT, Jensen MP, et al. Assessment of pain and health-related quality of life in slowly progressive neuromuscular disease. *Am J Hosp Palliat Care.* 2002; 19(1):39–48. [PubMed: 12173612]

5. Jensen MP, Hoffman AJ, Stoelb BL, et al. Chronic pain in persons with myotonic and facioscapulohumeral muscular dystrophy. *Arch Phys Med Rehabil.* 2008; 89(2):320–8. [PubMed: 18226657]
6. Hirsch AT, Kupper AE, Carter GT, et al. Psychosocial factors and adjustment to pain in individuals with postpolio syndrome. *Am J Phys Med Rehabil.* 2010; 89(3):213–24. [PubMed: 20068433]
7. Molton I, Jensen MP, Ehde DM, et al. Coping with chronic pain among younger, middle-aged, and older adults living with neurologic injury and disease: a role for experiential wisdom. *J Aging Health.* 2008; 20:972–96. [PubMed: 18791184]
8. Stoelb BL, Carter GT, Abresch RT, et al. Pain in persons with postpolio syndrome: frequency, intensity, and impact. *Arch Phys Med Rehabil.* 2008; 89(10):1933–40. [PubMed: 18929021]
9. Carter GT, Jensen MP, Stoelb BL, et al. Chronic pain in persons with myotonic muscular dystrophy, type 1. *Arch Phys Med Rehabil.* 2008; 89(12):2382. [PubMed: 19061752]
10. Nieto R, Raichle KA, Jensen MP, et al. Changes in pain-related beliefs, coping, and catastrophizing predict changes in pain intensity, pain interference, and psychological functioning in individuals with myotonic muscular dystrophy and facioscapulohumeral dystrophy. *Clin J Pain.* 2012; 28(1):47–54. [PubMed: 21642844]
11. Engel JM, Kartin D, Carter GT, et al. Pain in youths with neuromuscular disease. *Am J Hosp Palliat Care.* 2009; 26(5):405–12. [PubMed: 19820205]
12. Engel JM, Kartin D, Jaffe KM. Exploring chronic pain in youths with Duchenne Muscular Dystrophy: a model for pediatric neuromuscular disease. *Phys Med Rehabil Clin N Am.* 2005; 16(4):1113–24. [PubMed: 16214064]
13. Miró J, Raichle KA, Carter GT, et al. Impact of biopsychosocial factors on chronic pain in persons with myotonic and facioscapulohumeral muscular dystrophy. *Am J Hosp Palliat Care.* 2009; 26(4):308–19. [PubMed: 19414560]
14. Carter GT, Jensen MP, Galer BS, et al. Neuropathic pain in Charcot Marie Tooth disease. *Arch Phys Med Rehabil.* 1998; 79:1560–4. [PubMed: 9862301]
15. Abresch RT, Jensen MP, Carter GT. Health quality of life in peripheral neuropathy. *Phys Med Rehabil Clin N Am.* 2001; 12(2):461–72. [PubMed: 11345018]
16. Hoffman AJ, Jensen MP, Abresch RT, et al. Chronic pain in persons with neuromuscular disorders. *Phys Med Rehabil Clin N Am.* 2005; 16(4):1099–112. [PubMed: 16214063]
17. Von Korff M, Dunn KM. Chronic pain reconsidered. *Pain.* 2008; 138:267–76. [PubMed: 18226858]
18. Marshall HM, Jensen MP, Ehde DM, et al. Pain site and impairment in individuals with amputation pain. *Arch Phys Med Rehabil.* 2002; 83:1116–9. [PubMed: 12161833]
19. Tait RC, Chibnall JT, Margolis RB. Pain extent: relations with psychological state, pain severity, pain history, and disability. *Pain.* 1990; 41:295–301. [PubMed: 2388768]
20. Toomey TC, Mann JD, Abashian S, et al. Relationship of pain drawing scores to ratings of pain description and function. *Clin J Pain.* 1991; 7:269–74. [PubMed: 1809440]
21. Türp C, Kowalski CJ, Stohler CS. Greater disability with increased pain involvement, pain intensity and depressive preoccupation. *Eur J Pain.* 1997; 1:271–7. [PubMed: 15102392]
22. Saastamoinen P, Leino-Arjas P, Laaksonen M, et al. Pain and health related functioning among employees. *J Epidemiol Community Health.* 2006; 60:793–8. [PubMed: 16905725]
23. Leveille SG, Bean J, Ngo L, et al. The pathway from musculoskeletal pain to mobility difficulty in older disabled women. *Pain.* 2007; 128:69–77. [PubMed: 17055167]
24. Natvig B, Eriksen W, Bruusgaard D. Low back pain as a predictor of long-term work disability. *Scand J Public Health.* 2002; 30:288–92. [PubMed: 12680505]
25. Kamaleri Y, Natvig B, Ihlebaek CM, et al. Localized or widespread musculoskeletal pain: does it matter? *Pain.* 2008; 138:41–6. [PubMed: 18077092]
26. Kamaleri Y, Natvig B, Ihlebaek CM, et al. Does the number of musculoskeletal pain sites predict work disability? A 14-year predictive study. *Eur J Pain.* 2009; 13:426–30. [PubMed: 18599328]
27. Carnes D, Parsons S, Ashby D, et al. Chronic musculoskeletal pain rarely presents in a single body site: results from a UK population study. *Rheumatology.* 2007; 46:1168–70. [PubMed: 17488750]

28. Emery AH. Population frequencies of inherited neuromuscular diseases. A world survey. *Neuromuscul Disord.* 1991; 1:19–25. [PubMed: 1822774]
29. Kilmer DD, Abresch RT, Aitkens SG, et al. Profiles of neuromuscular disease: facioscapulohumeral dystrophy. *Am J Phys Med Rehabil.* 1995; 74(5):S131–9. [PubMed: 7576420]
30. Johnson ER, Carter GT, Kilmer DD, et al. Profiles of neuromuscular disease: myotonic muscular dystrophy. *Am J Phys Med Rehabil.* 1995; 74(5):S104–16. [PubMed: 7576418]
31. Ashizawa T, Dubel JR, Dunne PW, et al. Anticipation in myotonic dystrophy: II. complex relationships between clinical findings and structure of the GCT repeat. *Neurology.* 1992; 42:1877–81. [PubMed: 1407566]
32. Redman JB, Fenwick RG, Fu Y, et al. Relationship between parental trinucleotide GCT repeat length and severity of myotonic dystrophy in offspring. *JAMA.* 1993; 269:1960–72. [PubMed: 8464127]
33. Hunter A, Tsilfidis C, Mettler G, et al. The correlation of age of onset with CTG trinucleotide repeat amplification in myotonic dystrophy. *J Med Genet.* 1992; 29:774–81. [PubMed: 1453425]
34. Harley H, Rundle SA, MacMillan JC, et al. Size of the unstable CTG repeat sequence in relation to phenotype and parental transmission in myotonic dystrophy. *Am J Hum Genet.* 1993; 52:1164–71. [PubMed: 8503448]
35. Wijmenga C, Frants RR, Brouwer OF, et al. The facioscapulohumeral muscular dystrophy gene maps to chromosome 4. *Lancet.* 1990; 2:651–8. [PubMed: 1975852]
36. Upadhyaya M, Lunt PW, Sarfarazi M, et al. DNA marker applicable to presymptomatic and prenatal diagnosis of facioscapulohumeral disease. *Lancet.* 1990; 336:1320–7. [PubMed: 1978143]
37. Snider L, Geng LN, Lemmers RJ, et al. Facioscapulohumeral dystrophy: incomplete suppression of a retrotransposed gene. *PLoS Genet.* 2010; 6(10):e1001181. [PubMed: 21060811]
38. Bushby KM, Pollitt C, Johnson MA, et al. Muscle pain as a prominent feature of facioscapulohumeral muscular dystrophy (FSHD): four illustrative case reports. *Neuromuscul Disord.* 1998; 8:574–9. [PubMed: 10093064]
39. Kalkman JS, Schillings ML, van der Werf SP, et al. Experienced fatigue in facioscapulohumeral dystrophy, myotonic dystrophy, and HMSN-I. *J Neurol Neurosurg Psychiatry.* 2005; 76(10):1406–9. [PubMed: 16170086]
40. Verhagen WI, Huygen PL, Padberg GW. The auditory, vestibular and oculomotor system in facioscapulohumeral dystrophy. *Acta Otolaryngol.* 1995; 1:140–52.
41. Schmidt CO, Baumeister SE. Simple patterns behind complex spatial pain reporting? Assessing a classification of multisite pain reporting in the general population. *Pain.* 2007; 133:174–82. [PubMed: 17570587]
42. Pazzaglia C, Vollono C, Ferraro D, et al. Mechanisms of neuropathic pain in patients with Charcot-Marie-Tooth 1 A: a laser-evoked potential study. *Pain.* 2010; 149(2):379–85. [PubMed: 20334975]
43. Ribiere C, Bernardin M, Sacconi S, et al. Pain assessment in Charcot-Marie-Tooth (CMT) disease. *Ann Phys Rehabil Med.* 2012; 55(3):160–73. [PubMed: 22475878]
44. Padua L, Cavallaro T, Pareyson D, et al. Italian CMT QoL Study Group. Charcot-Marie-Tooth and pain: correlations with neurophysiological, clinical, and disability findings. *Neurol Sci.* 2008; 29(3):193–4. [PubMed: 18612771]
45. Abresch RT, Han JJ, Carter GT. Rehabilitation management of neuromuscular disease: the role of exercise training. *J Clin Neuromuscul Dis.* 2009; 11(1):7–21. [PubMed: 19730017]
46. Lou JS, Weiss MD, Carter GT. Assessment and management of fatigue in neuromuscular disease. *Am J Hosp Palliat Care.* 2010; 27(2):145–57. [PubMed: 20190203]
47. Tiffreau V, Viet G, Thévenon A. Pain and neuromuscular disease: the results of a survey. *Am J Phys Med Rehabil.* 2006; 85(9):756–66. [PubMed: 16924188]
48. Guy-Coichard C, Nguyen DT, Delorme T, et al. Pain in hereditary neuromuscular disorders and myasthenia gravis: a national survey of frequency, characteristics, and impact. *J Pain Symptom Manage.* 2008; 35(1):40–50. [PubMed: 17981001]
49. Turner JA, Holtzman S, Mancl L. Mediators, moderators, and predictors of therapeutic change in cognitive-behavioral therapy for chronic pain. *Pain.* 2007; 127:276–86. [PubMed: 17071000]

**KEY POINTS**

- Most patients with slowly progressive neuromuscular disease have chronic pain, to some degree. The studies done to date have typically assessed average pain intensity rather than occurrence and severity of pain in specific body locations. This assessment limits the usefulness of the data with respect to formulating treatment plans that address both physical and psychological aspects of pain.
- The available data suggest that pain extent and intensity at specific sites are associated with pain interference and negatively affect both physical and psychological functioning in patients with slowly progressive neuromuscular disease.
- Future studies assessing pain in persons with slowly progressive neuromuscular disease should address pain site in addition to global pain intensity. Investigating pain at multiple sites in future studies will enable clinicians to design more effective therapeutic interventions to treat pain in this patient population.