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Engaging patients and caregivers in prioritizing symptoms impacting quality of life for Duchenne and Becker muscular dystrophy

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Abstract

Purpose Patient preference information (PPI) have an increasing role in regulatory decision-making, especially in benefit–risk assessment. PPI can also facilitate prioritization of symptoms to treat and inform meaningful selection of clinical trial endpoints. We engaged patients and caregivers to prioritize symptoms of Duchenne and Becker muscular dystrophy (DBMD) and explored preference heterogeneity.

Methods Best–worst scaling (object case) was used to assess priorities across 11 symptoms of DBMD that impact quality of life and for which there is unmet need. Respondents selected the most and least important symptoms to treat among a subset of five. Relative importance scores were estimated for each symptom, and preference heterogeneity was identified using mixed logit and latent class analysis.

Results Respondents included patients ($n=59$) and caregivers ($n=96$) affected by DBMD. Results indicated that respondents prioritized "weaker heart pumping" [score = 5.13; 95% CI (4.67, 5.59)] and pulmonary symptoms: "lung infections" [3.15; (2.80, 3.50)] and "weaker ability to cough" [2.65; (2.33, 2.97)] as the most important symptoms to treat and "poor attention span" as the least important symptom to treat [−5.23; (−5.93, −4.54)]. Statistically significant preference heterogeneity existed (p value < 0.001). At least two classes existed with different priorities. Priorities of the majority latent class (80%) reflected the aggregate results, whereas the minority latent class (20%) did not distinguish among pulmonary and other symptoms.

Conclusions Estimates of the relative importance for symptoms of Duchenne muscular dystrophy indicated that symptoms with direct links to morbidity and mortality were prioritized above other non-skeletal muscle symptoms. Findings suggested the existence of preference heterogeneity for symptoms, which may be related to symptom experience.

Keywords Best–worst scaling · Duchenne muscular dystrophy · Patient preferences · Outcomes research

Introduction

The muscular dystrophies are a group of muscle diseases characterized by progressive muscle loss and shortened lifespan [1]. Duchenne muscular dystrophy (DMD) is the most common and most severe form. DMD is a rare, genetic disease occurring in approximately 1 in 5000 live male births [2, 3]. The average age of diagnosis is 5 years old, although boys usually begin to exhibit symptoms as toddlers [4, 5]. Loss of ambulation usually occurs in the early teen years. In addition to orthopedic symptoms, muscle loss leads to respiratory and cardiovascular complications that on average, lead to death in the early 30s [4]. Becker muscular dystrophy has similar characteristics to DMD, but is often milder and with slower progression [1]. At the time of this study, there were no treatments

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for Duchenne and Becker muscular dystrophy (DBMD) approved by the Food and Drug Administration (FDA) [4], although there are now two FDA-approved therapies: one appropriate for all patients [6, 7] and a mutation-specific therapy appropriate for less than 15% of Duchenne patients [8–10].

Patient preference information (PPI) are data about healthcare decisions [11]. Patients or caregivers provide PPI, which can be used to evaluate their perspective on the relative desirability of treatment alternatives, outcomes, or other attributes that differ among alternative options [11, 12]. PPI are valuable when treatment choice impacts quality of life or other subjective outcomes [11]. Historically, qualitative approaches have been most often used to provide PPI, which provide a valuable contribution but have limited ability to reflect variation in perspectives. On the other hand, quantitative preference elicitation methods can identify preference heterogeneity and be useful in defining subpopulations and developing clinical endpoints for trials [13–26].

Quantitative PPI have primarily been targeted to health technology assessment or the regulatory review process for drugs or devices [12, 27–31]. Less public attention has been paid to using these data to inform early phases of product development. An early exception came from the Medical Device Innovation Consortium (MDIC), a group that developed a framework for incorporating PPI throughout the product development lifecycle and identified potential uses for these data [11]. Specific to discovery and ideation phases, PPI can be used to understand areas of opportunity for therapy and pathways to addressing them [11]. More recently, the FDA advised industry to capture and integrate the patient experience in all phases of drug development [32].

Given the long timeline for drug development, there is a need to account for patient preferences in early phases. Industry's selection of treatments to pursue should be made with an understanding of how patients prioritize the symptoms those treatments target. The neuromuscular community supports concurrent treatment development efforts that aim to reduce secondary symptoms and preserve quality of life for those with DBMD [33]. Previous research demonstrated caregiver preference for slowing the loss of muscle function, a major quality-of-life issue, over life-extending treatments for their children [34, 35]. However, there are no data about which secondary symptoms of DBMD (excepting the primary skeletal muscle impacts) are prioritized by patients or caregivers as treatment targets. Given the meaningful impact of these symptoms on quality of life, this is a missed opportunity to inform early phases of drug development because PPI can identify symptoms that are priority treatment targets among secondary symptoms of DBMD and also promote the use of meaningful exploratory and patient-centered primary endpoints for future clinical trials.

To fill this need this study used best–worst scaling to obtain quantitative PPI in a disorder community for which there is considerable unmet need. The specific aims were to obtain PPI to (1) quantify how patients and caregivers prioritize symptoms that impact quality of life; (2) determine if heterogeneity exists in those priorities; and (3) identify factors that drive variability in priorities.

Methods

Best–worst scaling (BWS) is a choice-based preference elicitation method used to elicit respondents' relative importance for various objects. Introduced in 1992 and with its formal theoretical and statistical properties proven in 2005, it has become increasingly popular in healthcare as an alternative to rating scales [36–40]. This study utilized a specific BWS method called the "object case," in which respondents choose the best and worst among a subset of objects. Respondents complete multiple BWS choice tasks, each presenting a different combination of objects, and the resulting choices are analyzed together to estimate the relative importance of the objects to one another. Complete theoretical explanations and examples of healthcare applications are available elsewhere [40, 41].

Survey development

The objectivity of PPI is dependent upon the extent to which the objects, defined in this study as symptoms that impact quality of life, are relevant to patients. The survey was developed using a community-engaged approach so key stakeholders informed its design and ensured that it was meaningful to the community. Twenty stakeholders participated in training on the method and then contributed to defining eligibility criteria, selecting and refining the set of symptoms, and ensuring that the selected symptoms had a strong potential for quality-of-life impact. These stakeholders included six adults with DMD, six parents of children with DMD, three clinicians, four members of research and advocacy organizations, and an industry representative. A scientific team developed an initial set of symptoms and drafted eligibility criteria. Stakeholders reacted to it through in-person meetings or conference calls. After the survey instrument was designed, cognitive interviews were conducted to refine it. A detailed description of the process designed and utilized for this specific study was published elsewhere [42].

Choice task design

In this study, the objects were symptoms affecting quality of life for people with DBMD that are potential treatment targets. The list of 11 symptoms were as follows: weaker ability

to cough, lung infections, weaker heart pumping, frequent waking at night, bone fractures, constipation, headaches, feeling tired, non-healthy weight, poor attention span, and depression. See Table 1 for definitions of each symptom.

A choice task presented a subset of five symptoms and asked the respondent to select the most and least important symptom to treat. An example choice task is provided ("Appendix," Fig. 3). The experiment comprised 11 choice tasks. Before beginning the choice tasks, respondents were provided with definitions of each symptom and a question about their own experience with that symptom. For instance, after a brief definition of "lung infections" caregiver respondents were asked, "Has your child with DBMD ever been treated for pneumonia?" These salient questions paced the respondent's reading of the material and provided data for exploring the relationship between experiences with the symptoms and preferences for treatments that target those symptoms. Respondents completed a warm-up choice task to familiarize themselves with the activity and answered questions about demographics and clinical characteristics of the individual affected with DBMD.

Experimental design

An experimental design provided a systematic way for how the 11 symptoms occurred together in subsets of 5 symptoms that made up the individual choice tasks and across the 11 choice tasks. The experimental design was identified from the SAS database of orthogonal arrays [43]. A balanced-incomplete experimental design was used so that across all choice tasks each symptom occurred the same number of times and co-occurred with other symptoms equally. The experimental design also had Youden design properties, which ensured that every symptom appeared in the same position the same number of times (once) [44, 45]. This prevented respondents from attributing importance to symptoms based on the composition of the choice task [41].

Sample recruitment

The intended respondents were adult and adolescent patients with DBMD and caregivers of children with DBMD. Respondents were recruited via flyers at an annual DBMD patient and family conference in June 2015. Also, Parent Project Muscular Dystrophy (PPMD), the advocacy organization that organized the conference, sent emails to its DuchenneConnect registry participants who met survey eligibility criteria. DuchenneConnect registry participants were encouraged to invite others to participate (e.g., snowball sampling). These sequential but overlapping recruitment approaches were practical for a rare disease population, but made it impossible to determine a response rate or gather information on non-responders. The survey was administered online using Qualtrics (Qualtrics, Provo, Utah) and fielded for 5 weeks.

Inclusion criteria for caregivers were that they had to be at least 18 years of age and the legal guardian of at least one child with DBMD who was at least 10 years old. Patient respondents had to be at least 14 years of age and living with DBMD. All respondents had to be living in the United States and able to take the survey in English. Respondents provided informed consent electronically. Patient respondents

Table 1 Symptoms of Duchenne and Becker muscular dystrophy (DBMD) included as objects in the best–worst scaling experiment

Objects	Definitions
1	*Weaker ability to cough* DBMD progression results in decline in respiratory function and the ability to cough forcefully, making it harder to clear the airway and breathe deeply. Sometimes assistive devices are used
2	*Lung infections* Lung infections require doctor visits and taking antibiotics. Serious infections like pneumonia have to be treated in the hospital and might make it harder for the lungs to work well over time
3	*Weaker heart pumping* Over time, people with DBMD experience weaker heart pumping and have to take heart medication
4	*Frequent waking at night* Teens and adults with DBMD may have more trouble sleeping soundly through the night, partly due to decline in lung function. This may require help from caregivers to sleep comfortably
5	*Bone fractures* Loss of ambulation and steroid use can contribute to weakened bones, which leads to an increased risk of fractures
6	*Constipation* Immobility or medication side effects results in people with DBMD having trouble with constipation (going more than 2 days without a bowel movement)
7	*Headaches* Poor respiratory functioning in teens and adults with DBMD may cause them to experience frequent bad headaches
8	*Feeling tired* People with DBMD may have trouble with feeling tired after they wake-up and throughout the day (also known as "daytime sleepiness")
9	*Non-healthy weight* People with DBMD can have trouble maintaining their weight (some may have trouble gaining enough weight, while others have the problem of gaining too much weight)
10	*Poor attention span* Some people with DBMD experience more problems with paying attention and staying focused on a task than other people
11	*Depression* Living with DBMD may increase the chance for symptoms of depression, such as feeling sad, irritable, or not being interested in activities

between 14 and 17 years of age had to electronically assent and attest to the presence of a parent to witness their participation. The protocol for the study was approved by the Institutional Review Board of Johns Hopkins Bloomberg School of Public Health, Baltimore, MD (IRB # 00006299).

Model estimation

Priorities

Choices made regarding the most important and least important symptoms to treat across 11 choice tasks were used as outcome (dependent) variables to estimate the relative importance associated with 11 symptoms (independent variables). Responses were effects coded and analyzed using sequential best–worst scaling. Mixed logistic regression models with effects coding produced estimates for the aggregate sample. The survey did not allow respondents to skip any choice tasks, therefore there were no missing choice task data.

Preference heterogeneity

Mixed logistic models allowed for the examination of unobserved preference heterogeneity by estimating a distribution around the mean relative importance score. To further explore heterogeneity identified from the mixed logistic model, stratified analyses were conducted for disaggregated samples of caregivers and patients to determine if preferences differed by respondent type. Model variables were identical to the mixed logistic models, but conditional logit models were used because the subgroup sample sizes were not large enough to run mixed logistic regressions. Overall models and individual parameter estimates were compared using Wald tests.

We conducted a latent class analysis to explore potential additional sources of preference heterogeneity other than respondent type. In the latent class analysis, patients were grouped into latent classes by the preferences they expressed in the BWS rather than by their observed characteristics. As such, individuals in each class had similar relative importance scores, and average relative importance scores differed between classes [46]. The latent class analysis model assumed the existence of two latent classes. To determine the optimal number of latent classes to assume for the model, nine models with varying number of classes were evaluated for best model fit using minimum Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) values. AIC and BIC are criteria used to select the best fitting model among a finite set of models for a given set of data. However, model selection criteria were ultimately disregarded in favor of a 2-class model due to the small sample size [47]. The results of this latent class analysis were two class-specific sets of estimated coefficients and a class-probability estimate for each respondent. The class-probability estimate is the probability that the respondent belonged to a particular class based on his or her preferences [46].

Factors driving variability

Latent classes were compared on the basis of demographic and clinical characteristics of class members using t-tests. Variables that were statistically significantly different across classes were used as the independent variables in a logistic regression model that would uncover associations between patient characteristics and latent class. The independent variables were diagnosis, ambulatory status, respondent type, income, and all 11 clinical characteristics corresponding to experience with the symptoms from the experiment. The dependent variable for this model was whether respondents had been assigned to the minority (e.g., smaller) latent class. The result of this analysis was the regression coefficient that indicated the impact of a clinical characteristic on latent minority class membership. The data were analyzed using STATA 13 (StataCorp LP, College Station, TX).

Results

Study sample

The survey link was distributed via email invitation. Of 323 recipients who opened the email, 93 clicked on the link (response rate: 29%). Additional people accessed the survey through the aforementioned snowball strategy. The survey was accessed 235 unique times, of which 198 respondents met the inclusion criteria and provided informed consent (consent rate: 83%). The final sample included 155 respondents (completion rate: 78%). Of the 43 that dropped out, 86% did not answer the first choice task, 11% dropped out before the second task, and one respondent completed all but the final task.

Table 2 summarizes respondent characteristics. Of the 155 respondents, 62% were caregivers ($n=96$) and 38% were patients ($n=59$). The majority of caregivers were 45 years or older (56%), whereas patient respondents were 22% under age 18, 49% 18–30 years, and 27% over 30 years old. The majority of respondents were white (89%) and reported annual household income greater than $50,000 (61%). The majority of caregivers were married or in long-term relationships (73%), but only 15% of patient respondents were married. Of the caregivers, an overwhelming majority were mothers (76%) and highly educated (58% college graduates).

As shown in Table 3, the majority of affected individuals had Duchenne (85%), compared to 12% with Becker muscular dystrophy. Most affected individuals had history

Table 2 Characteristics of caregiver and patient survey respondents

	Respondents ($n=155$)	
	Frequency	Percent
Survey respondents		
Relationship to affected individual		
Mother	73	47
Father	17	11
Adoptive mother	5	3
Grandmother	1	1
Self (patient)	59	38
Age categories		
30–39 years	13	8
40–49 years	29	19
50–59 years	49	32
65+ years	63	41
Race		
White	138	89
Hispanic	13	8
Native	5	3
Black	7	5
Asian	3	2
Other	2	1
Income		
< $50k	35	23
$50k–$75k	31	20
$75k–$100k	34	22
> $100k	30	19
Region		
Northeast	27	17
Midwest	26	17
South	60	39
West	42	27
Marital status		
Single	42	27
Married/long-term relationship	79	51
Divorced/separated/widowed	19	12
Highest level of education[a]		
High school	39	25 (41)
College graduate	35	23 (36)
Professional degree	21	14 (22)
Not asked	59	38

Not all rows will add to 100% due to missing data not shown. Race categories are not mutually exclusive

[a]Indicates question not asked for patient respondents percentages; in parenthesis reflect percentage based on caregiver population ($n=96$)

Table 3 Characteristics of patients with Duchenne and Becker muscular dystrophy represented in the survey

	Respondents ($n=155$)	
	Frequency	Percent
Age		
10–13 years	42	27
14–17 years	44	28
1–25 years	37	24
25+ years	31	20
Diagnosis		
Duchenne	132	85
Becker	19	12
Intermediate	3	2
Ambulatory status		
Ambulatory	56	36
Non-ambulatory	98	63
Steroid use		
Currently or previously	120	77
Never	33	21
Insurance		
Private	67	43
Public	28	18
Both	58	37
Signs and symptoms		
Use of cough assist	78	50
Treatment for pneumonia	41	26
Use of cardiac medication	13	73
Bone fractures	72	46
Trouble sleeping		
Never/rarely	104	67
Sometimes	27	17
Often/always	21	14
Bowel movement frequency		
Less than daily	69	45
Daily	70	45
More than daily	12	8
Headaches		
Less than 2 per week	134	86
More than 2 per week	14	9
Fatigue		
Never/rarely	62	40
Sometimes	65	42
Often/always	26	17
Weight		
Overweight	60	39
Healthy	82	53
Underweight	11	7
Trouble concentrating		
Never/rarely	85	55
Sometimes	42	27
Often/always	26	17

of steroid use (77%), which at the time of the survey was not an FDA-approved therapy. The majority were non-ambulatory (63%), which was defined as requiring wheelchair outdoors. Most had either private health insurance coverage (43%) or a combination of private and public

Table 3 (continued)

	Respondents ($n = 155$)	
	Frequency	Percent
Depression		
Never/rarely	88	57
Sometimes	54	35
Often/always	10	6

Not all rows will add to 100% due to missing data not shown

plans (37%). Reflective of the differences in eligibility criteria between caregivers and patients and the larger proportion of caregiver respondents than patient respondents, the age distribution for affected individuals skewed young with 86% being 10–17 years old. The mean age of affected individuals among patient respondents was 27.5 years old (SD = 14.1). Details about experience with DBMD symptoms are available in Table 3.

Statistical results

Priorities

The main results were the relative importance scores of the 11 symptoms for the aggregate sample (Fig. 1). The horizontal bars around each point estimate represent the 95% confidence interval (CI) of that estimate. The boxes around each point estimate are a measure of preference heterogeneity and represent the 95% CI of the distribution around the mean; 95% of respondents' relative importance scores fall within this box. The most important symptom was "weaker heart pumping" [score = 5.13; 95% CI (4.67, 5.59)], followed by "lung infections" [3.15; (2.80, 3.50)] ,and "weaker ability to cough" [2.65; (2.33, 2.97)]. The confidence intervals for "weaker heart pumping" and "lung infections" were non-overlapping, indicating that respondents differentiated the importance of cardiac and pulmonary targets. The confidence intervals of "lung infections" and "weaker ability to cough" overlapped, indicating that respondents did not differentiate priorities between these two pulmonary targets. The confidence intervals of all three of the most important symptoms did not overlap with any of the lower-ranked symptoms, indicating respondents strongly prioritized cardiac and pulmonary targets. The least important symptom was "poor attention span" [−5.23; (−5.93, −4.54)] and its confidential interval did not overlap with any other symptoms, indicating it was significantly different from other targets.

The next most prioritized symptom was "bone fractures" [0.83; [0.51, 1.14)] followed by "non-healthy weight" [−0.38; (−0.72, −0.04)]. The differences in relative importance for many of the middle-importance symptoms were not statistically significant. The overlapping confidence intervals for "non-healthy weight," "depression," and "constipation" indicates that relative importance of these symptoms were not distinguishable from one another. Although "non-healthy weight" and "depression" were barely overlapping with "constipation": "non-healthy weight" [−0.38; (−0.72, −0.04)] and "depression" [−0.44; (−0.75, −0.13)] vs. "constipation" [−1.06; (−1.42, −0.71)]. The relative importance of "constipation," "headaches," "frequent waking at night," and "feeling tired" were not significantly different.

Preference heterogeneity

The distributions (i.e., standard deviations) around the mean preference estimates from the mixed logistic model were the main result for identifying heterogeneity (Fig. 1) and they were significant for each included symptom (except for poor attention span which was treated as a fixed variable) (Table 4). This indicates significant preference heterogeneity among respondents. The presence of preference heterogeneity was corroborated by the distribution of estimated individual posterior relative importance scores ("Appendix," Fig. 4). A test between the caregiver and patient models indicated that neither the overall models nor the relative importance scores were significantly different from one another (p values > 0.05) (data not shown).

Latent class analyses were conducted to identify potential sources of preference heterogeneity. For the 2-class model, 80 and 20% of respondents make up the majority and minority class, respectively. As shown in Fig. 2, the majority class reflected patterns similar to aggregate results and demonstrated greater prioritization for the three cardiac and pulmonary symptoms that were prioritized in the aggregate analysis. Like the aggregate results, the majority latent class placed greatest priority on "weaker heart pumping" and did not differentiate between pulmonary symptoms. For the minority latent class, "weaker heart pumping" [1.41; (1.09, 1.74)] was also significantly different from the both pulmonary measures: "weaker ability to cough" [0.24; (−0.22, 0.70)] and "lung infections" [0.14; (−0.25, 0.54)]. However, the minority latent class considered the two pulmonary benefits to be indistinguishable from "bone fractures," "depression," "non-healthy weight," "constipation," and "feeling tired." Like the aggregate results, many of the middle symptoms were not statistically significantly different from one another. One exception was that the minority class prioritized "feeling tired" [0.48; (0.05, 0.91)] above "frequent waking at night" [−0.96; (−1.27, −0.64)] and "headaches" [−0.78; (−1.10, −0.47)].

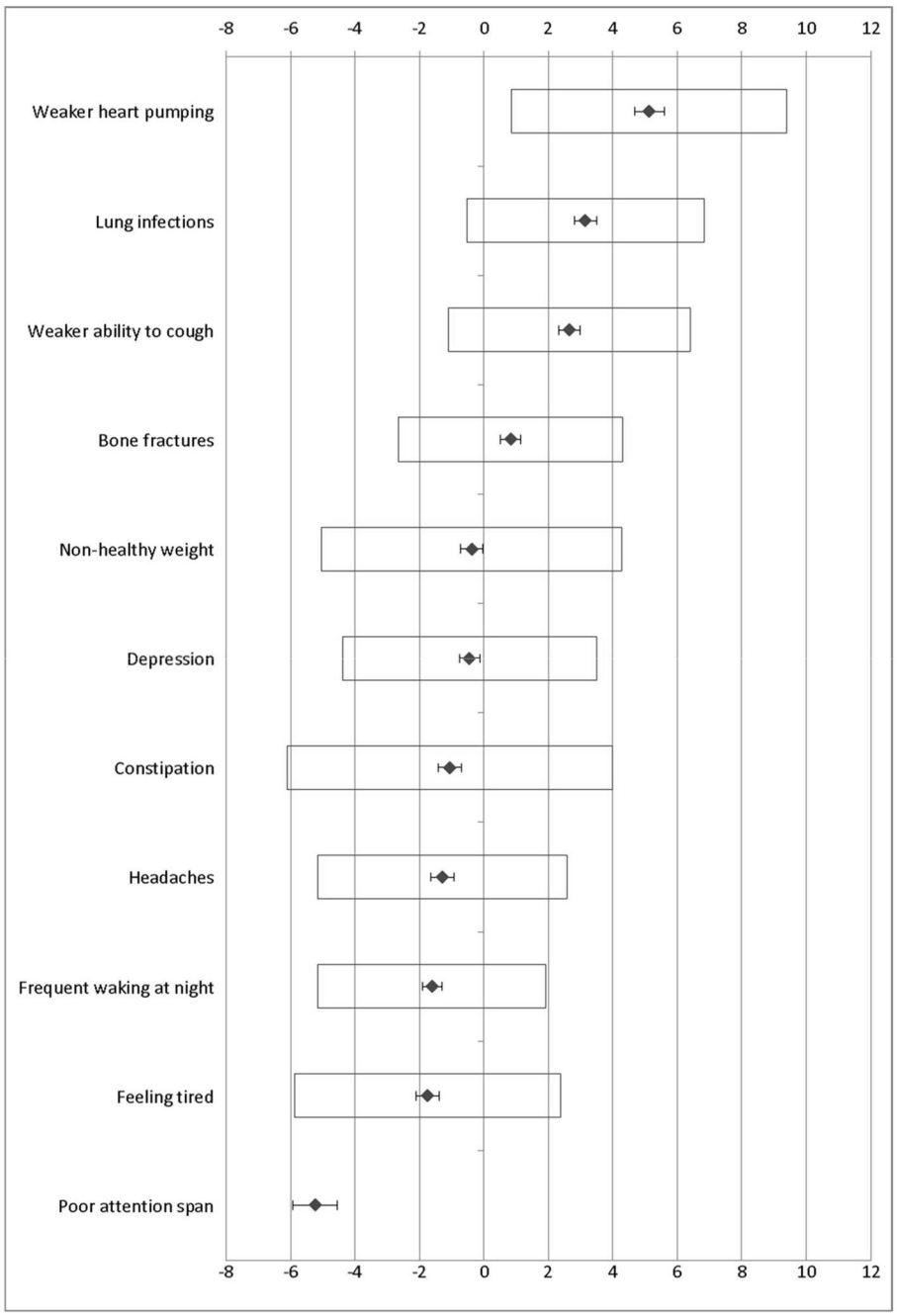


Fig. 1 Relative importance for symptoms as treatment targets for aggregate sample (caregivers and patients). Diamond = mean coefficient; whiskers = 95% confidence interval of the mean; box = 95% of the distribution of individual importance; attributes without a box were treated as deterministic

Factors driving variability

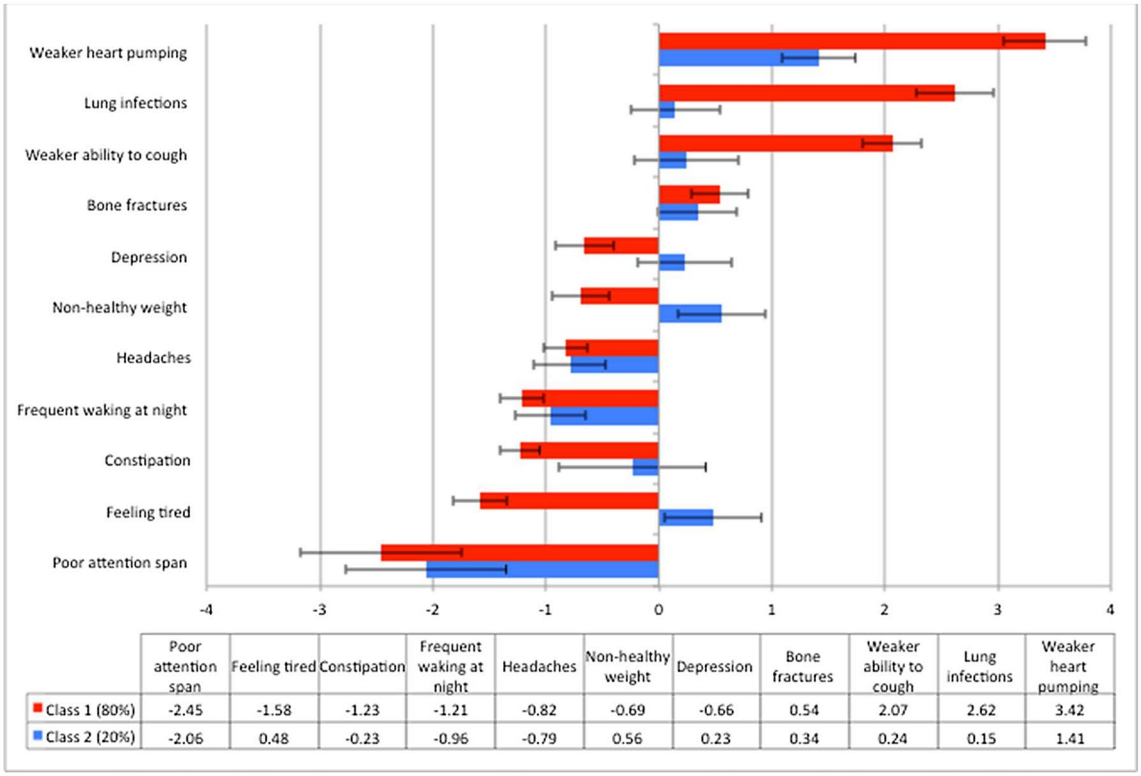
Respondent type (caregivers and patients) was significantly different between classes, but did not perfectly predict latent class membership. Comparing demographic and clinic characteristics of each latent class, we found significant differences in diagnosis and ambulatory status between classes. In the majority latent class, a larger proportion of the affected individuals had Duchenne and a smaller proportion had Becker compared to the minority latent class (89% Duchenne and 10% Becker in majority class vs. 71% Duchenne and 19% Becker in minority class; p value = 0.04). A much larger proportion of minority latent class respondents identified as ambulatory compared to majority latent class respondents (58 vs. 31%; p value = 0.01).

The main results of the logistic regression examining sources of heterogeneity are presented in "Appendix," Table 5. Minority latent class membership was associated with being ambulatory compared to non-ambulatory (OR 6.16; p value = 0.03), history of bone fractures compared to no history of bone fractures (OR 4.83; p value = 0.04), and occasional trouble sleeping compared to never or rarely

Table 4 Mixed logit results for relative importance of symptoms and preference heterogeneity

Attribute	Mean			Standard deviation		
	Coefficient	Std. error	*p* value	Coefficient	Std. error	*p* value
Weaker heart pumping	5.13	0.2	< 0.001	2.18	0.2	< 0.001
Lung infections	3.15	0.2	< 0.001	1.88	0.1	< 0.001
Weaker ability to cough	2.65	0.2	< 0.001	1.92	0.1	< 0.001
Bone fractures	0.83	0.2	< 0.001	1.78	0.1	< 0.001
Non-healthy weight	− 0.38	0.2	0.029	2.38	0.2	< 0.001
Depression	− 0.44	0.2	0.005	2.02	0.2	< 0.001
Constipation	− 1.06	0.2	< 0.001	2.57	0.2	< 0.001
Headaches	− 1.28	0.2	< 0.001	− 1.97	0.1	< 0.001
Frequent waking at night	− 1.61	0.2	< 0.001	1.80	0.2	< 0.001
Feeling tired	− 1.75	0.2	< 0.001	2.11	0.1	< 0.001
Poor attention span	− 5.23	0.4	< 0.001	n/a	n/a	n/a

Coeff coefficient, *Std. error* standard error, *n/a* not applicable because attribute was treated as deterministic



	Poor attention span	Feeling tired	Constipation	Frequent waking at night	Headaches	Non-healthy weight	Depression	Bone fractures	Weaker ability to cough	Lung infections	Weaker heart pumping
Class 1 (80%)	-2.45	-1.58	-1.23	-1.21	-0.82	-0.69	-0.66	0.54	2.07	2.62	3.42
Class 2 (20%)	-2.06	0.48	-0.23	-0.96	-0.79	0.56	0.23	0.34	0.24	0.15	1.41

Fig. 2 Relative importance of symptoms as treatment targets for two preference-based (latent) classes. Class 1 and class 2 represent two different segments of the sample that are identified as such based on their preferences. Class 1 is the majority latent class and class 2 is the minority latent class. (Color figure online)

having trouble sleeping (OR 13.79; *p* value = 0.03). Minority latent class membership was inversely associated with using cough-assistive devices compared to not having used a device (OR 0.027; *p* value = 0.01), and frequent trouble concentrating compared to never or rarely having trouble concentrating (OR 0.031; *p* value = 0.03).

Discussion

In this study, we estimated the relative importance for secondary, non-skeletal-muscle symptoms of DBMD to better understand how to prioritize treatments for DBMD. Because there was little distinction among the top three symptoms or between symptoms of middle-level importance, results were

best ordered according to four groups of symptoms. Among an aggregate sample, cardiac (weaker heart pumping) and pulmonary benefits (lung infections and weaker ability to cough) were the most highly prioritized symptoms. This represents a group of symptoms that strongly impact lifespan in DBMD, and thus are relevant across ages and stages of DBMD, and have considerable quality-of-life impact in patients with more disease progression. We labeled this group "lifespan targets."

Bone fractures, non-healthy weight, and depression were the second most prioritized group of symptoms to target. Though these symptoms are also exacerbated with disease progression, they may impact quality of life and activities of daily living of patients at less advanced stages than cardiac and pulmonary outcomes. We labeled this group "primary quality-of-life targets." The third group of symptoms included constipation, headaches, frequent waking at night, and feeling tired, and these less-prioritized targets were labeled "secondary quality-of-life targets." All of above were desired treatment targets more so than "poor attention span."

These distinct groups of symptom targets also serve as a way to prioritize endpoints when researchers designing clinical trials face important tradeoffs between minimizing respondent burden and maximizing precision in estimating a treatment effect. For instance, symptoms within the primary quality-of-life group may be more relevant as secondary clinical trial endpoints than those found in the secondary quality-of-life group. However, it warrants emphasizing that these are relative importance scores, and therefore no symptoms should be viewed as unimportant in terms of selecting treatment targets or endpoints. Furthermore, the significant standard deviations estimated from the mixed logit model indicate that different people might have valued various treatments targets differently.

When two latent classes were distinguished, the majority class prioritized lifespan symptoms, then primary quality-of-life symptoms, and then secondary quality-of-life symptoms as potential treatment targets. The minority latent class prioritized differently; though they prioritized cardiac symptoms above all else, they considered pulmonary benefits to be undifferentiated from bone fractures, depression, non-healthy weight, and feeling tired. Feeling tired was included by the minority class as a primary quality-of-life symptom.

Regression results estimating the impact of clinical characteristics on class membership indicated a higher prioritization for symptoms for which there was more experience with that symptom. Bone fracture was attributed greater relative importance in the minority latent class, a group in which those with history of bone fracture had five times greater odds of minority latent class membership. In addition, ambulatory respondents had six times greater odds of minority latent class membership. The greater importance of fracture may be explained by the larger implications of a fracture for a person who ambulates vs. one who regularly uses a wheelchair. Along similar lines, the minority latent class attributed less relative importance to pulmonary benefit and also tended to have less experience with pulmonary symptoms. Results showed that the minority latent class was more likely to have Becker and less advanced disease, and that those who had used cough-assistive devices had lower odds of minority latent class membership. That lack of experience with pulmonary symptoms may make it a less desirable treatment target. This result is consistent with the qualitative community-engagement work conducted during survey development. While stakeholders overall perceived pulmonary function as highly important, some caregivers and patients were challenged in relating to a nuanced description of downstream pulmonary benefits which are not experienced until later stages of disease progression [42].

An intentional limitation of this work is that progressive loss of muscle function, the keystone characteristic of DBMD, was not included in the list of symptoms. Stopping and slowing the progressive loss of muscle has been shown to be very important to caregivers, even in the presence of a serious risk [34], and if included would have dominated other symptoms. Along similar lines, the study was inherently limited by the initial choice of symptoms included in the study. This was minimized by engaging with the community to ensure the symptoms represented those important to most patient and caregivers.

Another limitation of this study is with regards to the latent class analysis. An alternate theory to the existence of two preference classes is that there was a group of people who did not respond to the choice task in a consistent manner as the other group. If this were true, then the aggregate results were at risk of type II error, meaning a "false negative." This is the less egregious error compared to type I error. An alternate theory is that there were two classes, one with stronger preferences.

A third limitation of our study is that we used different models for our analyses. Mixed logit was utilized for aggregate analysis to determine the extent to which preference heterogeneity existed and latent class analysis explored the sources of preference heterogeneity. However, sample size limitations did not allow us to use mixed logit with latent class analysis. The different model types did not allow for direct comparisons of coefficients across models, but both suggested similar patterns as well as preference heterogeneity. Furthermore, because these models were estimated separately, and because this study discussed averages and not individuals, conclusive statements cannot be made with regards to influential factors on individual-level preferences for treatment targets. However, we can conclude that preference heterogeneity does exist and should be accounted for in future research and needs assessment.

A final limitation of our study is that the study results may not be generalizable. A pragmatic decision was made in favor of a targeted strategy because obtaining a representative sample was not feasible in this rare disease population. Although not nationally representative, a strength of the sample (drawn from registry participants and conference attendees) was that respondents are highly activated community members with greater capacity to complete the survey.

Conclusions

We estimated the relative importance for symptoms impacting quality of life for Duchenne and Becker muscular dystrophy. Understanding patient and caregiver priorities for symptoms to target has implications for drug development. We found that, on average, respondents identified cardiac and pulmonary symptoms as the most important treatment targets. We found significant heterogeneity in prioritization among individuals and identified that there were at least two latent classes of respondents with different priorities. The minority latent class considered pulmonary symptoms to be equally important as other symptoms that may not impact lifespan, whereas the majority latent class considered symptoms that may not impact lifespan to be less important than symptoms that impact lifespan. Further research is needed to better understand preference heterogeneity for treatment targets and characteristics associated with that heterogeneity.

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Compliance with ethical standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

Appendix

See Table 5 and Figs. 3, 4.

Table 5 Regression results for logistic regression for probability of minority latent class (20%) membership

	Odds ratio	95% CI
Diagnosis (ref: Duchenne)		
Becker	0.876	(0.13, 5.81)
Intermediate	2.337	(0.08, 65.59)
Ambulatory status (ref: non-ambulatory)		
Ambulatory	6.166	(1.17, 32.50)
Respondent type (ref: caregivers)		
Patients	2.978	(0.66, 13.35)
Income (ref: < $50k)		
$50,001–$75,000	0.275	(0.02, 3.57)
$75,001–$100,000	3.094	(0.37, 26.07)
> $100,000	0.256	(0.02, 2.83)
History of… (ref: no history)		(0.02, 4.58)
Use of cough assist	0.027	(0.00, 0.33)
Treatment for pneumonia	1.348	(0.22, 8.23)
Use of cardiac medication	0.852	(0.16, 4.58)
Bone fractures	4.825	(1.04, 22.36)
Trouble sleeping (ref: never)		
Sometimes	13.786	(1.38, 137.42)
Often/always	0.197	(0.00, 12.15)
Bowel movement frequency (ref: daily)		
Less than daily	1.810	(0.46, 7.06)
More than daily	3.928	(0.31, 49.45)
Headaches (ref: <2 per week)		
More than 2 per week	2.928	(0.41, 20.99)
Fatigue (ref: never/rarely)		
Sometimes	0.995	(0.20, 4.86)
Frequent	4.218	(0.38, 46.43)
Weight (ref: healthy weight)		
Overweight	2.431	(0.59, 10.04)
Underweight	1.996	(0.07, 59.41)
Trouble concentrating (ref: never/rarely)		
Sometimes	0.218	(0.04, 1.34)
Often/always	0.031	(0.00, 0.77)
Depression (ref: never/rarely)		
Sometimes	5.489	(1.03, 29.34)
Often/always	38.044	(0.87, 1662.26)

Ref reference (omitted) category, *CI* confidence interval

Most important to treat		Least important to treat
O	Frequent waking at night	O
O	Headaches	O
O	Feeling tired	O
O	Weaker ability to cough	O
O	Constipation	O

Fig. 3 Sample choice task used to elicit relative importance for symptoms as treatment targets

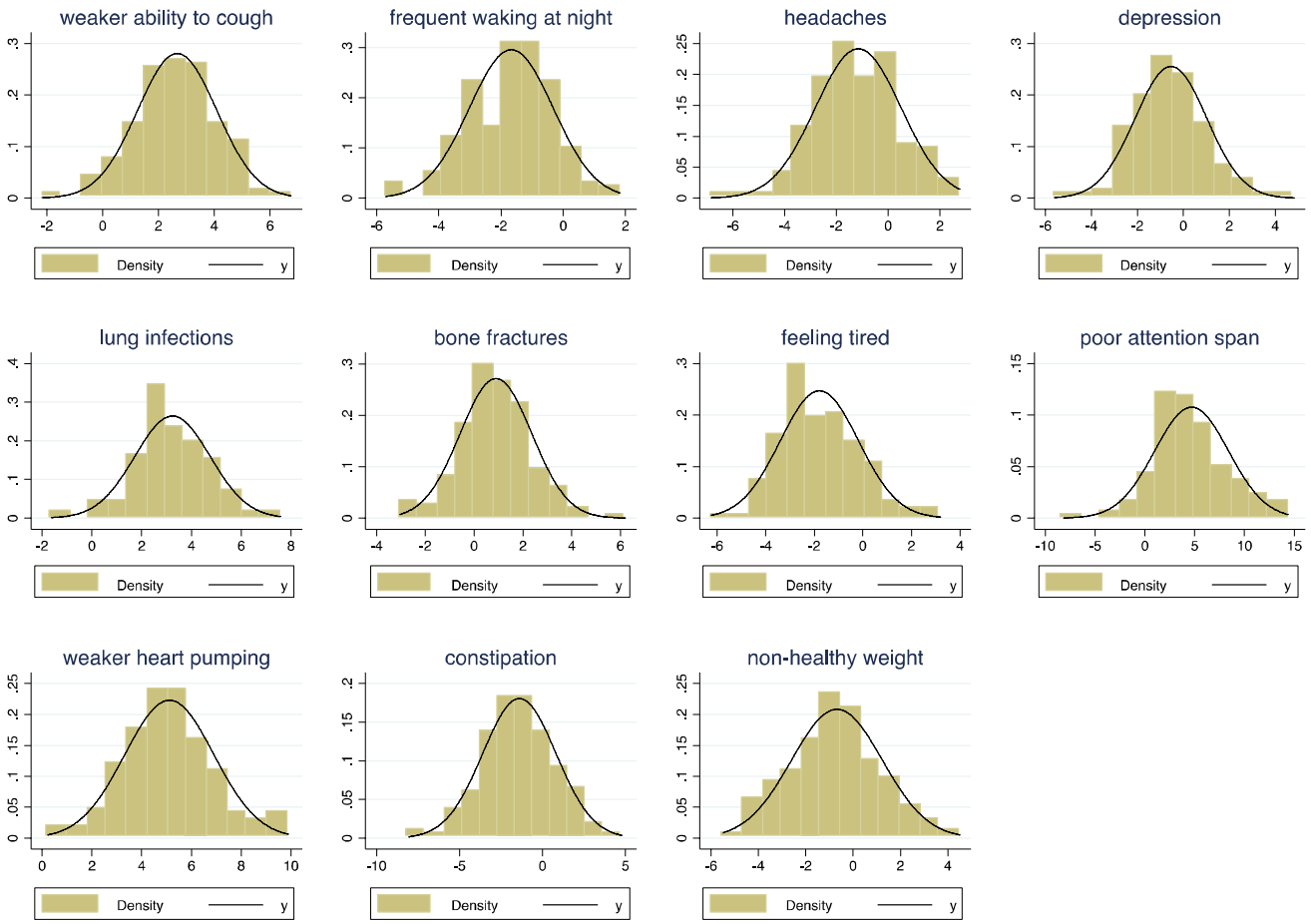

Fig. 4 Distributions of estimated individual posterior relative importance scores for symptoms

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