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GAUCHER DISEASE AND ENZYME REPLACEMENT THERAPY: HAVE PATIENTS' EXPECTATIONS BEEN MET?

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Gaucher Disease type 1 is the most common lysosomal storage disorder. Enzyme replacement therapy (ET) was approved as treatment in 1991 (7). ET improves symptoms and quality of life (17, 23). This study hypothesized that non-severely affected patients are more likely than those severely affected to have their expectations of ET met. Disease severity is often a function of bone involvement and ET has not effectively reversed this symptom (1, 9). Patients 18 or older diagnosed with GD type 1 who had received ET for at least one year were surveyed. Patients' prior expectations were identified and categorized: hematologic response, organomegaly response, bone response, social quality of life and physical quality of life. The proportion having expectations met was high; greater than 65% agreed that 21 of 26 expectations were met. A non-significant trend indicated severely affected patients may be more likely to have expectations met than non-severely affected patients.

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INTRODUCTION

Gaucher disease is the most common inherited lysosomal storage disorder. Inherited in an autosomal recessive manner, Gaucher disease (GD) type 1 affects 1/40,000- 60,000 in the general population and 1/400-2000 in the Ashkenazi Jewish population (1, 2, 16). This disease is the result of a deficiency of glucocerebrosidase, an inborn error of metabolism. Patients store glycosphingolipids in the lysosomes of macrophages throughout the body, but with major involvement of the spleen, liver, and bone marrow. This results in a variety of clinical symptoms including hematologic abnormalities, organomegaly, fatigue, and skeletal complications such as Erlenmeyer flask deformity of the distal femur, bone pain, bone crises, osteopenia, infarction, and fracture (15, 35, 43). GD type 1 is the most common form of the disease and, unlike GD types 2 and 3, the GD type 1 phenotype does not have primary neuropathic signs and symptoms.

Glucocerebrosidase infusion, commonly termed enzyme therapy (ET), results in the breakdown of stored glycosphingoolipids and has been an approved treatment for GD type 1 since 1991 (7). Studies indicate that both symptom severity and quality of life have shown improvement with ET (17, 23, 37). Patients monitored after receiving ET have presented with increased hemoglobin levels, increased platelet counts, increased energy levels, reduced hepatosplenomegaly, and decreased bone pain (6, 26, 33, 35, 37, 43). Bone pain resolves in ~50% of symptomatic patients after two years of ET (37). Improvement in radiological signs has not occurred as quickly as in other signs, particularly in splenectomized patients (4, 12, 27, 33). A recent study by Rudzki *et al.* (2003) provides evidence that ET may actually accelerate the process of osteopenia in

men and premenopausal women, though this suggestion is based on a very small sample size (32). In 1995, Rosenthal *et al.* reported that 3 1/2 years of ET were required to normalize the fat in marrow of 12 patients and to increase the trabecular or cortical bone mass in 10 of 12 patients (31). Patients have also experienced bone crises and avascular necrosis following the initiation of ET (37). A 1998 case report described the long-term effects of ET, listing signs and symptoms in which the patient showed improvement, including bone pain, abdominal pain, fatigue, bleeding, and hepatosplenomegaly (26). Signs and symptoms associated more severe disease, including mineral skeletal disease, did not show improvement in this case.

Historically, the symptoms of patients with GD type 1 have shown great variability in age of onset, presence and severity (17). This is partially explained by the 200 mutations that occur in the gene encoding glucocerebrosidase. A possible correlation between genotype and disease severity was suggested in the late 1980's (42), but it has subsequently been shown that the identification of a single N370S allele through genotyping is only useful to identify a non-neuronopathic disease course (15). Neither the measurement of enzyme levels nor the molecular identification of genotype can accurately predict the clinical course of Gaucher disease. Patients are therefore categorized based on clinically assessed severity of symptoms.

The symptoms of GD type 1 have previously been identified and evaluated. Though there is no consensus as to which disease symptoms correlate with more progressive disease, most would agree that a patient's age of diagnosis gives clues as to how progressive their disease may be and, in turn, the relative severity of their current disease. While disease severity may be measured at a single point in time, it is important

to take a patient's age of diagnosis into account when anticipating their disease progression. A younger age of diagnosis is generally thought to correlate to more progressive disease. ET may slow the progression of GD type 1 without noticeably affecting severity, particularly if a patient begins treatment early, before irreversible bone involvement occurs. Those patients with a younger age of diagnosis who have lived without ET into adulthood would therefore be expected to have more severe disease. In 1989, Zimran *et al.* created a severity score index (SSI) specific to GD (42). This index scored symptoms numerically, including age of diagnosis and extent of organ involvement, in order to place patients into a mild, moderate, or severe disease severity category (42). Boot *et al.* (1997) subsequently showed that the SSI does not correlate with specific glucocerebrosidase genotypes (5). In fact, the SSI's of siblings with the same mutations were determined to be different. This reinforces the variety of clinical presentation found in patients with GD type 1. Although the SSI has been used by several groups to assess clinical severity, the assignment of numerical values to certain disease parameters has not been justified.

Data from the Gaucher Disease Registry, the most comprehensive database of its kind, was first published in 2000. The signs and symptoms of 1698 GD patients, 94% of whom had GD type 1, were reported and the degree of hematologic and visceral abnormalities were organized into three categories: mild, moderate, and severe (15). Bone manifestations generally result in the greatest morbidity and long-term disability, but it is not possible to predict the severity of GD type 1 using this single disease symptom exclusively, since patients may present with radiological skeletal disease but show no other symptoms (6). Overall, it is important to evaluate several parameters,

including the extent of bone manifestation, the age of diagnosis, and the degree of hepatosplenomegaly, when assessing disease severity.

Given the range of symptoms and clinical severities associated with GD type 1, as well as the varying natural history, it is challenging for patients to know what expectations to have of ET. At this point, there are no published studies identifying the expectations of GD type 1 patients prior to beginning ET, nor is there an evaluation of whether or not patients' expectations have been met. In order to appreciate the potential significance of identifying and evaluating the expectations of GD type 1 patients, it is necessary to look at the literature regarding patient expectations.

The importance of identifying patient expectations has been recognized by clinicians, policymakers, and researchers (20). Clinicians who are aware of patients' expectations are better able to address those which are justified and attend to those which are unrealistic, thereby leading to more productive clinical interactions (21). Several patient expectations appear to be prevalent: patients expect to consult with a health professional who is knowledgeable, communicates well, and provides effective treatment (34). Unsuccessful communication between physician and patient has been shown to directly result in unmet expectations (3). It can thus be predicted that the relationship between physician and patient is a critical factor in whether or not a patient's expectations are met. Knowledge of those factors which may predispose patients to hold certain expectations, coupled with the implementation of strategies to address patient expectations, has the potential to improve communication between physician and patient and, as a result, medical care.

The task of improving medical care for GD type 1 patients thus appears simple: improve physician-patient communication, and this may, in turn, improve the patient's perception of the effectiveness of treatment (ET). The value of treatment received by a patient is dependent not only upon measurable therapeutic outcomes, but also upon a patient's health-related burden (psychological well-being, social interactions, activity level) (28) and upon whether or not the patient believes his or her expectations have been met. As listed previously, therapeutic outcome measures of ET for patients with GD type 1 have been studied and identified. In order to examine the contribution of expectations to the value a patient places upon ET, it is necessary to determine which factors influence the patients' perception of "effective" treatment. Besides therapeutic outcomes, what outcomes can be evaluated? There are two measurable outcomes that have been shown to be directly related to the meeting of patient expectations: patient satisfaction and quality of life. The relationships between (1) a patient's expectations being met and their resulting high quality of life or satisfaction, and (2) a patient's expectations not being met and a resulting low quality of life or satisfaction, have been reported (11, 18, 19, 30, 39).

When a patient's expectations are met, resulting in high levels of satisfaction, both physician and patient experience the benefits (3). Patients who have unmet expectations are reported to be less satisfied with the care they receive, while physicians report that interactions with patients who have unmet expectations are more demanding and less satisfying (3). In a study of symptomatic walk-in patients at a military clinic, Jackson *et al.* (2001) reported that unmet expectations had the strongest independent correlation with low patient satisfaction (18). According to a three-month follow up survey, the proportion of patients "not fully satisfied" with their care and having at least

one unmet expectation was 69%, while the proportion of patients "fully satisfied" with their care and having at least one unmet expectation was 8% (18). If patient satisfaction is to be valued as an important outcome measure of medical care and a contributing factor to the patient's perception of effective treatment, then the meeting of expectations and the extent to which this contributes to patient satisfaction need to be taken into account. This will be a step towards helping patients construct reasonable expectations that have a greater likelihood of being met, therefore leading to increased patient satisfaction.

Quality of life measures allow for an assessment of patient-reported effects of disease, including such parameters as psychological well-being, mental health, emotional health, activity levels, and social interactions (10). An association between met expectations of healing and the maintenance of a high quality of life has been established (19). Importantly, patients who expect healing but perceive that treatment has failed have been found to experience a decreased quality of life (19). Patients who find their expectations of treatment unmet are less likely to report satisfaction with care, follow medical advice, attend medical appointments, or show symptom improvement (3, 30). In a sample of 688 internal medicine patients, Kravitz *et al.* (1996) found that 18% of patients had at least one unmet expectation, while a survey of 909 general practice, cardiology, and internal medicine patients by Bell *et al.* identified 11.6% of patients with one or more unmet expectations (3, 20). A study specific to the quality of life of patients with GD type 1 has shown that 80% of patients reported improvements in their general health status since beginning ET (10). These figures beg the question: did those GD type 1 patients who did not report improvement in general health status have unmet

expectations and, if so, what were they? Assessing the correlation between meeting of expectations and improved quality of life for patients with GD type 1 may lead towards improved treatment outcomes.

Defining expectations for specific patient groups has been challenging due to the nature of expectations themselves; expectations are beliefs that can be modified over time as influencing factors, such as knowledge gained, direct personal experience of symptoms, and degree of optimism regarding outcome, change (20, 34). Expectations may be unrealistic, based on misperceptions, or function as a patient's coping strategy. The range of expectations within a patient group can be large and may depend upon the immediacy of the expectation. Using the SF-36 Health Survey, the general health profile of GD type 1 patients, including physical function, general health, social function, emotional function and mental health, has been shown to improve upon treatment with ET (10, 23). However, an assessment of disease-specific expectations was not performed. Due to the association between patient expectations of treatment and subsequent levels of satisfaction and quality of life, it is important that specific GD type 1 patient expectations be identified. This identification has the potential to impact two factors which could influence patient expectations: knowledge and communication.

The current retrospective study represents the first attempt to identify the expectations of GD type 1 patients prior to beginning ET. Participants identified those expectations that they held prior to beginning ET, including expectations of therapeutic outcomes (hematologic response, organomegaly response, bone response) and quality of life outcomes (mental, social and physical). Participants then either agreed or disagreed that the expectations they held had been met following at least one year of ET. In order

to compare the proportion of expectations that were met between severity groups, individual severity of GD type 1 prior to beginning ET was assessed. The expectations held by severely affected participants prior to ET were compared to those held by non-severely affected participants prior to ET. Next, the proportion of severely affected participants having their expectations met following ET was compared to the proportion of non-severely affected participants having their expectations met following ET. It was expected that severely affected participants would be significantly less likely to have their expectations of ET met than non-severely affected participants. This was based on indications that severely affected patients are more likely than non-severely affected patients to have established bone disease, a complication which has shown less response to ET than others.

METHODS

The protocol for this study was approved by the Institutional Review Board at Cincinnati Children's Hospital Medical Center. Patients from Gaucher Disease treatment centers in Cincinnati, New York, Florida, and Pittsburgh were invited to participate, as were individuals attending patient meetings in Washington state and Atlanta, GA. An advertisement for the study was also posted on the National Gaucher Foundation's website and listserv. A consent form within the questionnaire informed participants that returning the questionnaire indicated consent to participate in the study.

This study is an observational study using a retrospective cohort of patients with GD type 1. In order to participate, participants were required to meet three eligibility criteria: (1) have a self-reported clinical diagnosis of GD type 1, (2) have been receiving enzyme replacement therapy for at least one year, and (3) are age 18 or older.

Participants received and completed a written questionnaire. This was novel since a standardized instrument to assess the expectations of patients with GD type 1 had not yet been developed. Research of the literature and consultation with experts in the field of Gaucher disease aided in the development of the questionnaire. The questionnaire included three sections: (1) assessment of disease severity based on particpant-reported signs and symptoms prior to ET, (2) identification and evaluation of expectations held and met, and (3) demographic information. This was the first time this questionnaire was used and therefore no data regarding reliability and validity are available.

The severity of participants' disease was established as the independent variable. Since there is no universally agreed-upon measurement of the severity of GD type 1, criteria for determining disease severity was developed. A participant was designated as

having severe disease if they had a diagnosis of GD type 1 prior to 18 years of age, plus one of the following: (1) spleen size greater than fifteen times normal, (2) liver size greater than four times normal, (3) joint replacement due to complications of GD type 1, (4) major bone fracture due to complications of GD type 1, or (5) vertebrae collapse due to GD type 1.

The dependent variable was the meeting of participants' expectations of ET. This evaluation included two components: (1) identification of participants' expectations prior to beginning ET and (2) evaluation of whether or not held expectations had been met following ET. Twenty-six expectation statements were presented for participants to agree with, disagree with, or state that they did not have the specific symptom/concern. The expectation statements were grouped into five categories: expectations of (1) hematologic response, (2) organomegaly response, (3) bone response, (4) social quality of life, and (5) physical quality of life. An expectation statement about overall health was also presented. At the time of this study, no expectation scale regarding ET for patients with GD type 1 had been developed. A list of expectation statements corresponding to the signs and symptoms of GD type 1 was developed in cooperation with physicians and after a review of the literature. The Short Form 36 (SF-36) Health Survey was used as a guide when developing the quality of life expectation statements. The responses to this component of the questionnaire grouped participants in to two categories: those having an expectation and those not having an expectation. For the group of participants holding a specific expectation, the meeting of that expectation following ET was evaluated using a five-point Likert scale. This scale included five possible responses ranging from "strongly disagree" to "strongly agree".

The data obtained through the written questionnaire was analyzed using SPSS statistical software (SPSS for Windows version 11.0). The analysis consisted of several components. First, descriptive statistics, including mean, SD, median, minimum, and maximum were used to analyze participants' demographic variables. Second, participants were categorized as having "severe" disease or "non-severe" disease.

Third, each expectation statement was analyzed to determine the proportion of participants who held the expectation prior to beginning enzyme replacement therapy. This resulted in two groupings: (1) participants who held an expectation prior to starting ET, and (2) participants who did not hold an expectation prior to starting ET. This analysis was performed for each individual expectation statement and for each category of expectation statements. Additionally, a statistical comparison between severely affected participants and non-severely affected participants holding each expectation was performed. Results of χ^2 tests with $P < 0.05$ were declared to be statistically significant.

Finally, of those participants who did hold an expectation prior to starting ET, the extent to which the expectation was met was analyzed. Participants responding "agree or "strongly agree" to a five-point Likert scale were grouped as having a met expectation. Participants responding "strongly disagree", "disagree", or "neutral" to a five-point Likert scale were grouped as having an unmet expectation. A statistical comparison was made between severely affected participants and non-severely affected participants having met expectations. Due to small sample size, Fischer's exact tests were performed. Results with $P < 0.05$ were declared to be significant. Descriptive statistics were used to describe trends between severely affected and non-severely affected patients who had their expectations met.

RESULTS

Response Rates

A total of 219 questionnaires were distributed. 67 participants returned completed questionnaires, 62 of which met eligibility criteria (28.3%). Questionnaires not meeting eligibility criteria included three parents who filled out a questionnaire for their underage children, and two respondents who did not indicate the age at which they were diagnosed with GD type 1 and could therefore not be classified as having severe or non-severe disease. The response rates by site are indicated in Table 1.

Table 1: Response rate by site.

Site	Questionnaires Distributed	Questionnaires Returned (met eligibility criteria)	Response Rate (%)
Atlanta patient meeting	15	4	26.7
Cincinnati Children's Hospital Medical Center	52	17	32.7
Florida (Neal Weinreb, M.D.)	50	11	22.0
National Gaucher Foundation Listserve	22	12	54.5
New York (Gregory Pastores, M.D.)	60	7	11.7
Pittsburgh	10	9	90.0
Washington state patient meeting	10	2	20.0
Totals	219	62	28.3

Participant Characteristics

Characteristics of the study population are shown in table 2. 51.6% of participants were Ashkenazi Jewish, 43.6% made more than $75,000 per year, and 62.9% had at least a college degree. 96.8% of participants were currently receiving ET, most (60.7%) by clinic infusion and most (78.7%) every two weeks.

Table 2: Participant Characteristics

Characteristic	N	Mean	SD	Range
Age	60	51.5	16.57	18-83
Age at first symptoms	57	18.4	17.22	0-70
Age at diagnosis	62	25.9	19.52	0-70
Age when started ERT	58	42.7	17.59	7-77
Total years on ERT	60	7.4	3.30	1-12
gender	61			
female	35	57.4		
male	26	42.6		
ethnicity	62			
Ashkenazi Jewish	32	51.6		
Caucasian	29	46.8		
other	1	1.6		
marital status	62			
single	10	16.1		
married	44	71.0		
other	8	12.9		
children	62			
yes	45	72.6		
no	17	27.4		
annual income	55			
< $25,000	7	12.7		
$25-49,999	10	18.2		
$50-74,999	14	25.5		
> $75,000	24	43.6		
schooling completed	62			
≤high school	9	14.5		
some college	14	22.6		
college degree	21	33.9		
Masters or PhD	18	29.0		
currently able to work?	61			
yes	50	82.0		
no	11	18.0		
currently employed?	62			
yes	39	62.9		
no	23	37.1		
currently receive ERT?	62			
yes	60	96.8		
no	2	3.2		
ERT protocol	61			
home infusion	24	39.3		
clinic infusion	37	60.7		
dosage schedule	61			
once every two weeks	48	78.7		
other	13	21.3		

Before beginning ET, 29 of 62 (46.8%) participants reported having a bone crisis that required hospitalization or the use of narcotics for pain relief. 54 of 60 (90%) reported having an enlarged spleen and 27 of 62 (43.5%) reported having their spleen removed before beginning ET. 54 of 62 (87.1%) participants reported having an enlarged liver, 16 of 62 (25.8%) reported having a joint replaced, 17 of 62 (27.4%) reported having a fracture of a major bone, and 4 of 61 (6.6%) reported having a vertebrae collapse prior to receiving ET.

Expectations

A. Expectations held prior to ET: overall response

Table 3 shows the overall proportion of participants that (1) held each expectation prior to receiving ET and (2) either agreed or strongly agreed that the expectation had been met following ET. For individual expectation statements, the percentage of participants agreeing that they held an expectation prior to receiving ET ranged from 16.9% (expected to have little difficulty eating regular meals) to 89.8% (expected general health to improve). Following the expectation of improved general health, the most commonly held expectations held prior to beginning ET included: (1) improved anemia, (2) decreased frequency of feelings of fatigue, (3) decreased liver size, (4) decreased spleen size, (5) decreased amount of bone pain, and (6) to have no side effects from ET.

The three individual expectation statements receiving the least agreement from participants included (1) to have less difficulty eating regular meals (16.9%), (2) to have fewer mood swings (19.0%), and (3) to experience a decrease in the number of times feeling shortness-of-breath (20.0%).

Analysis of grouped expectation statements resulted in the following average proportions of participants: (1) 55.5% held a hematologic response expectation, (2) 48.0% held a bone response expectation, (3) 46.8% held a physical quality of life expectation (4) 42.2% held an organomegaly response expectation, and (5) 31.0% held a social quality of life expectation.

Fisher's exact test showed that those participants who reported that they expected their general health to improve were statistically significantly more likely than those who did not expect their general health to improve to also expect (1) to bruise less easily ($P = 0.036$), (2) to feel fatigue less frequently ($P = 0.003$), (3) the amount of bone pain to decrease ($P = 0.001$), (4) the frequency of bone pain crises to decrease ($P = 0.026$), (5) the intensity of bone pain crises to decrease ($P = 0.028$), (6) to be able to accomplish more ($P = 0.008$) and (7) to have no side effects from ET ($P = 0.001$).

B. Expectations met following ET: overall response

Greater than 65% of participants either agreed or strongly agreed that most of their expectations had been met. However, the agreement rate was less than 65% for five expectation statements, four of which were in the category "Bone Response". These expectations included (1) decreased amount of bone pain, (2) decreased intensity of bone pain crises, (3) improvement in osteoporosis, and (4) to have no joints replaced. The fifth expectation statement involved expecting that one's weight would remain relatively constant after receiving ET. The smallest overall proportion of participants agreed or strongly agreed that this expectation had been met (43.3%).

Analysis of grouped expectation statements resulted in the following average proportions of participants agreeing that their expectation had been met: (1) 86.9% had a

hematologic response expectation met, (2) 84.3% had an organomegaly response expectation met, (3) 76.8% had a social quality of life expectation met, (4) 76.3% had a physical quality of life expectation met, and (5) 66.8% had a bone response expectation met.

Those participants who reported that their expectation regarding improved general health had been met were significantly more likely than those participants who reported that their expectation of improved general health was not met to also have their expectation regarding decreased frequency of feelings of fatigue met ($P = 0.047$).

Table 3: Expectations held prior to ET and met following ET

Expectation	Held Before ET	%	Met After ET	%
A. Hematologic Response				
number of bleeding episodes to decrease	21/60	35.0	18/20	90.0
length of bleeding episodes to decrease	21/55	38.1	18/20	90.0
to bruise less easily	35/60	58.3	30/34	88.2
anemia to improve	43/59	72.9	38/41	92.7
frequency of feelings of fatigue to decrease	44/60	73.3	31/42	73.8
B. Organomegaly Response				
size of spleen to decrease	28/35	80.0	20/26	76.9
size of liver to decrease	47/60	78.3	41/44	93.2
to have little difficulty eating regular meals	10/59	16.9	9/10	90.0
to have less abdominal pain after eating	13/60	21.7	10/13	76.9
C. Bone Response				
amount of bone pain to decrease	41/60	68.3	25/40	62.5
frequency of bone pain crises to decrease	27/59	45.8	20/27	74.1
intensity of bone pain crises to decrease	26/59	44.1	16/26	61.5
osteoporosis to improve	27/60	45.0	13/25	52.0
to have no bone fractures	26/60	43.3	22/25	88.0
to have no joints replaced	25/60	41.7	15/24	62.5
D. Social Quality of Life				
to feel down in the dumps less often	18/59	30.5	13/17	76.5
to feel anxious less often	17/59	28.8	13/17	76.5
to have fewer mood swings	11/58	19.0	8/11	72.7
to be able to take part in more social activities	27/59	45.8	22/27	81.5
E. Physical Quality of Life				
weight to remain relatively constant	31/60	51.7	13/30	43.3
to be able to resume vigorous activities (e.g., running, lifting heavy objects, participating in strenuous sports)	21/59	35.6	15/20	75.0
to be able to resume moderate activities (e.g., moving a table, a vacuum cleaner, playing golf)	29/59	49.2	24/29	82.8
number of times feeling short-of-breath to decrease	12/60	20.0	10/12	83.3
to be able to accomplish more	31/59	52.5	26/31	83.9
to have no side-effects from ET	41/57	71.9	35/39	89.7
F. general health to improve	53/59	89.8	44/52	84.6

C. Expectations held prior to ET: demographic findings

Fisher's exact test identified several significant findings involving demographic data. First, significant differences between the proportions of participants holding expectations prior to receiving ET were determined (see table 4). Female participants were significantly more likely than male participants to expect to bruise less easily after receiving ET (P = 0.003), to have no bone fractures after receiving ET (P = 0.009), to feel down in the dumps less often (P = 0.009), to be able to take part in more social activities (P = 0.004), to resume vigorous activities (P = 0.006), to resume moderate activities (P = 0.033), and to expect to be able to accomplish more (P = 0.033).

Participants who made less than $50,000 per year were significantly more likely than those who made more than $50,000 per year to expect their anemia to improve (P = 0.043), their weight to remain relatively constant (P = 0.008), to take part in more social activities (P = 0.032), to be able to resume moderate activities (P = 0.016), and to expect to be able to accomplish more (P = 0.013).

Participants who received home infusions were significantly more likely than participants infused at a clinic to expect their spleen size to decrease (P = 0.022). Participants infused at a clinic were significantly more likely than those infused at home to expect the amount of bone pain they experienced to decrease (P = 0.041) and to expect the frequency of their bone pain crises to decrease (P = 0.003).

No significant differences in the proportions of those holding expectations were found between participants of different ethnicity, marital status, child status, education, ability to work, time receiving ET, or infusion schedule.

Table 4: Expectations held: general demographic significant findings.

	...are significantly more likely than...	**...to expect...**	**p-value**
Females	males	to bruise les easily	0.003
Females	males	to have no bone fractures	0.009
Females	males	to feel down-in-the-dumps less often	0.009
Females	males	to take part in more social activities	0.004
Females	males	to resume vigorous activities	0.006
Females	males	to resume moderate activities	0.033
Females	males	to be able to accomplish more	0.033
Make < $50K	make > $50K	anemia to improve	0.043
Make < $50K	make > $50K	weight to remain relatively constant	0.008
Make < $50K	make > $50K	to take part in more social activities	0.032
Make < $50K	make > $50K	to resume moderate activities	0.016
Make < $50K	make > $50K	to be able to accomplish more	0.013
Home infused	clinic infused	spleen size to decrease	0.022
Clinic infused	home infused	amount of bone pain to decrease	0.041
Clinic infused	home infused	frequency of bone pain crises to decrease	0.003

D. Expectations met following ET: demographic findings

Significant differences between the proportions of participants having their expectations met were also identified (see table 5). Male participants were significantly more likely than female participants to have their expectation regarding maintaining a constant weight met (P = 0.023). Female participants were significantly more likely than male participants to have their expectation regarding being able to accomplish more met (P = 0.017). Participants who had children were significantly more likely than those without children to have their expectation of resuming vigorous activities met (P = 0.031). Those participants who were able to work were more likely than those not able to work to have their expectation of decreased liver size met (P = 0.003)

No significant differences in the proportions of participants having their expectations met were found between groups of different ethnicity, marital status, income, schooling, time receiving ET, type of infusion, or dose schedule.

Table 5: Expectations met: general demographic significant findings.

	...are significantly more likely than...	**...to have the following expectation met:**	**p-value**
Males	females	maintain a relatively constant weight	0.023
Females	males	be able to accomplish more	0.017
With children	without children	resume vigorous activities	0.031
Able to work	not able to work	decreased liver size	0.003

E. Expectations held: participants with spleens versus without spleens

A statistical comparison was made between those respondents who had their spleen removed prior to beginning ET (N=27) and those who had an intact spleen (N=35). The χ^2 test determined that there was a statistically significant difference between the proportion of participants without a spleen and the proportion of participants with a spleen that held three expectation statements prior to beginning ET. Those participants who had their spleens removed were significantly more likely than those with their spleens intact to expect the amount of bone pain to decrease (P = 0.005), the frequency of bone pain crises to decrease (P = 0.001), and the intensity of bone pain to decrease (P = 0.008). Although not statistically significant, Fisher's exact test determined that participants with their spleens removed were more likely than those with their spleens intact to expect to participate in more social activities after receiving ET (P = 0.065). Fisher's exact test also determined that those participants with their spleens removed prior to beginning ET were significantly more likely than those with their

spleens intact to expect their general health to improve after receiving ET (P = 0.03). Table 6 summarizes the proportions of participants with spleens removed and with intact spleens holding expectations prior to beginning ET.

F. Expectations met following ET: participants with spleens versus without spleens

A comparison was made between participants with their spleens removed and participants with their spleens intact to determine if there was a statistically significant difference between the proportions of groups that had their expectations met. There were no statistically significant differences identified for any of the expectation statements.

Table 6: Expectations held prior to ET: participants with spleens versus participants without spleens

Expectation	With Spleen	%	Without Spleen	%
A. Hematologic Response				
number of bleeding episodes to decrease	15/33	45.5	6/27	22.2
length of bleeding episodes to decrease	15/32	46.9	6/23	26.1
to bruise less easily	21/33	63.6	14/27	51.9
anemia to improve	24/32	75.0	19/27	70.4
frequency of feelings of fatigue to decrease	24/33	72.7	20/27	74.1
B. Organomegaly Response				
size of spleen to decrease	27/31	87.1	N/A	N/A
size of liver to decrease	24/33	72.7	23/27	85.2
to have little difficulty eating regular meals	8/33	24.2	2/26	7.7
to have less abdominal pain after eating	9/33	27.3	4/27	14.8
C. Bone Response				
amount of bone pain to decrease	17/33	51.5	24/27	88.9
frequency of bone pain crises to decrease	8/33	24.2	19/26	73.1
intensity of bone pain crises to decrease	9/33	27.3	17/26	65.4
osteoporosis to improve	14/33	42.4	13/27	48.1
to have no bone fractures	13/33	39.4	13/27	48.1
to have no joints replaced	14/33	42.4	11/27	40.7
D. Social Quality of Life				
to feel down in the dumps less often	11/33	33.3	7/26	26.9
to feel anxious less often	8/33	24.2	9/26	34.6
to have fewer mood swings	6/32	18.8	5/26	19.2
to be able to take part in more social activities	19/33	57.6	8/26	30.8
E. Physical Quality of Life				
weight to remain relatively constant	18/33	54.5	13/27	48.1
to be able to resume vigorous activities (e.g., running, lifting heavy objects, participating in strenuous sports)	14/33	42.4	7/26	26.9
to be able to resume moderate activities (e.g., moving a table, a vacuum cleaner, playing golf)	19/33	57.6	10/26	38.5
number of times feeling short-of-breath to decrease	7/33	21.2	5/27	18.5
to be able to accomplish more	16/33	48.5	15/26	57.7
to have no side-effects from ET	20/31	64.5	21/26	80.8
F. general health to improve	27/33	81.8	26/26	100

Severity

Of the 62 participants, 19 (30.6%) met criteria for having severe disease. These participants reported being diagnosed at less than age 18, plus reported one of the following prior to receiving ET: (1) spleen size greater than fifteen times normal, (2) liver size greater than four times normal, (3) joint replacements due to complications of GD type 1, (4) major bone fracture due to complications of GD type 1, or (5) vertebrae collapse due to GD type 1. The remaining 43/62 (69.4%) of respondents did not meet the above criteria and were classified as having non-severe disease.

Fisher's exact test showed that participants with severe disease were found to be significantly more likely than non-severe participants to have received ET for seven or more years ($P = 0.002$) and to have had their spleen removed prior to receiving ET ($P = 0.002$). There were no significant differences in gender, ethnicity, marital status, child status, income, schooling, or ability to work between the severe and non-severe groups.

A. Expectations held: severe versus non-severe participants

A statistical comparison was made between the severe and non-severe participants who were in agreement with each expectation statement prior to beginning ET. Fisher's exact test detected a significant difference in the proportion of severe and non-severe participants that held one expectation statement. Severe participants were significantly more likely than non-severe participants to expect the frequency of their bone pain crises to decrease after receiving ET ($P = 0.021$). Although not statistically significant, there was also a trend for non-severe participants to be more likely than severe participants to expect their spleen size to decrease after receiving ET ($P = 0.074$) and to expect their

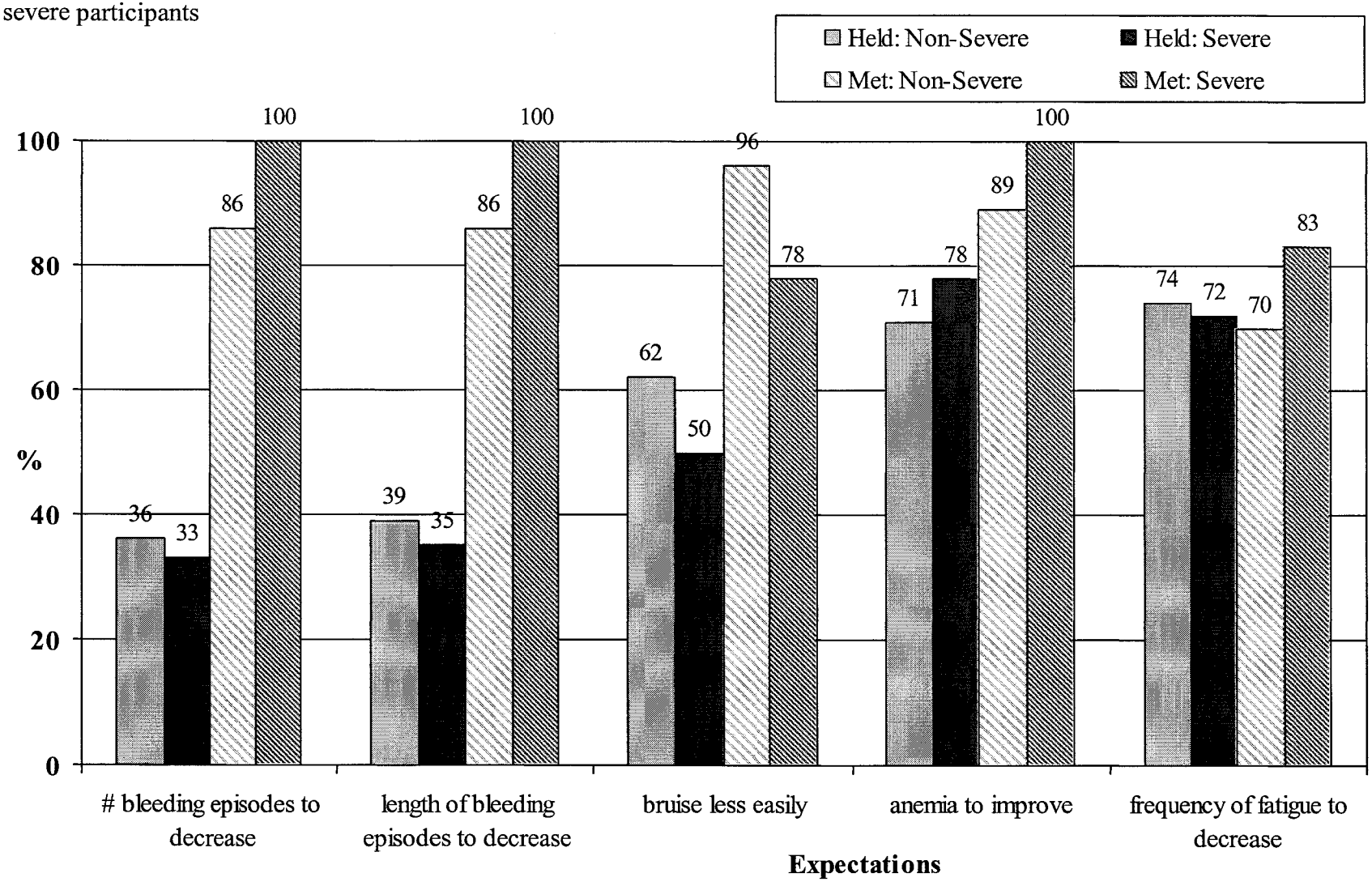
liver size to decrease after receiving ET (P = 0.084). There were no significant differences detected between the severity groups for holding the remaining expectation statements. A non-significant trend showed that a greater proportion of severe participants than non-severe participants tended to hold expectations. 16 of 26 expectation statements were held by a greater proportion of severe participants than non-severe participants.

B. Expectations met: severe versus non-severe participants

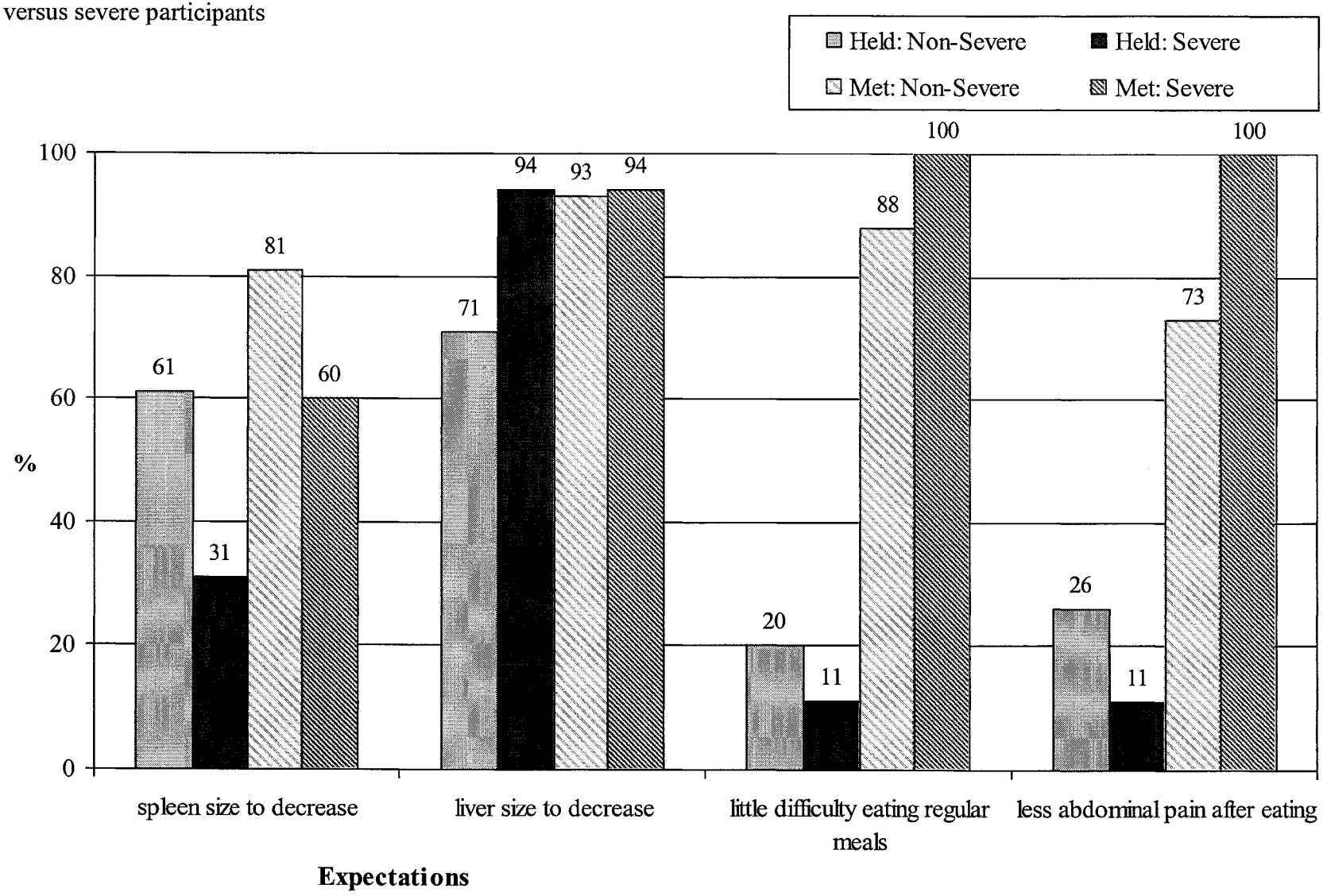
A statistical comparison was made between the severe and non-severe participants who either agreed or strongly agreed that their expectations had been met following ET. These two responses were grouped together in order to gain more power for the statistical test. Fisher's exact test detected no significant differences between the groups for any of the expectation statements. A comparison between severe and non-severe participants who had the expectation of decreased intensity of bone pain crises met resulted in the lowest p-value obtained. Severely affected participants were more likely to have this expectation met than non-severe participants (P = 0.087). A non-significant trend showed that severe participants were more likely than non-severe participants to either agree or strongly agree that an expectation had been met. 18 of 26 expectation statements were reportedly met by a greater proportion of severe participants than non-severe participants.

Graphs 1 though 5 summarize the proportion of severely and non-severely affected participants who (1) held an expectation prior to beginning ET, and (2) either agreed or strongly agreed that an expectation had been met after receiving ET.

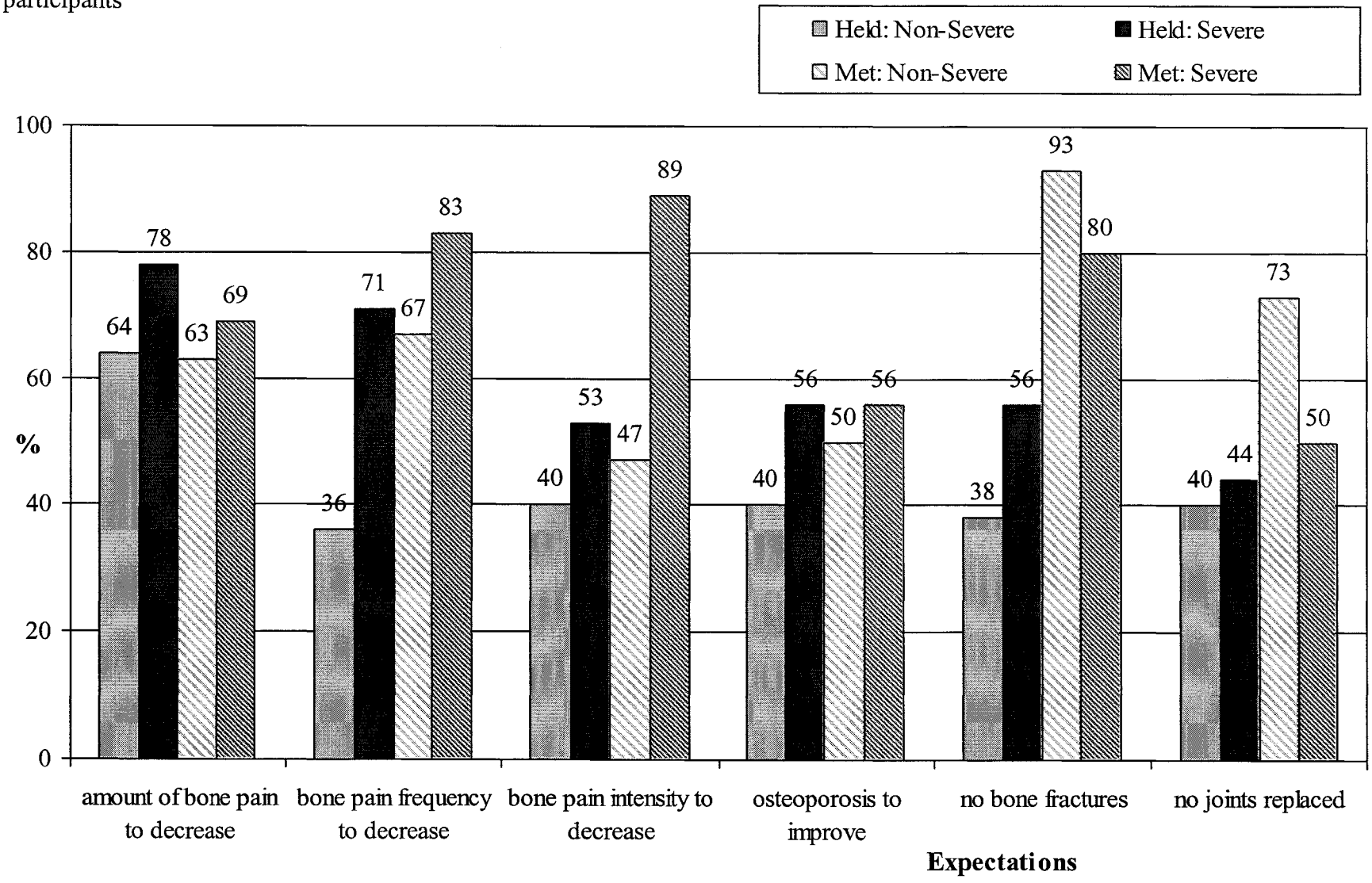
Graph 1: Hematalogic response expectations (1) held prior to beginning ET and (2) met following ET: non-severe participants versus severe participants



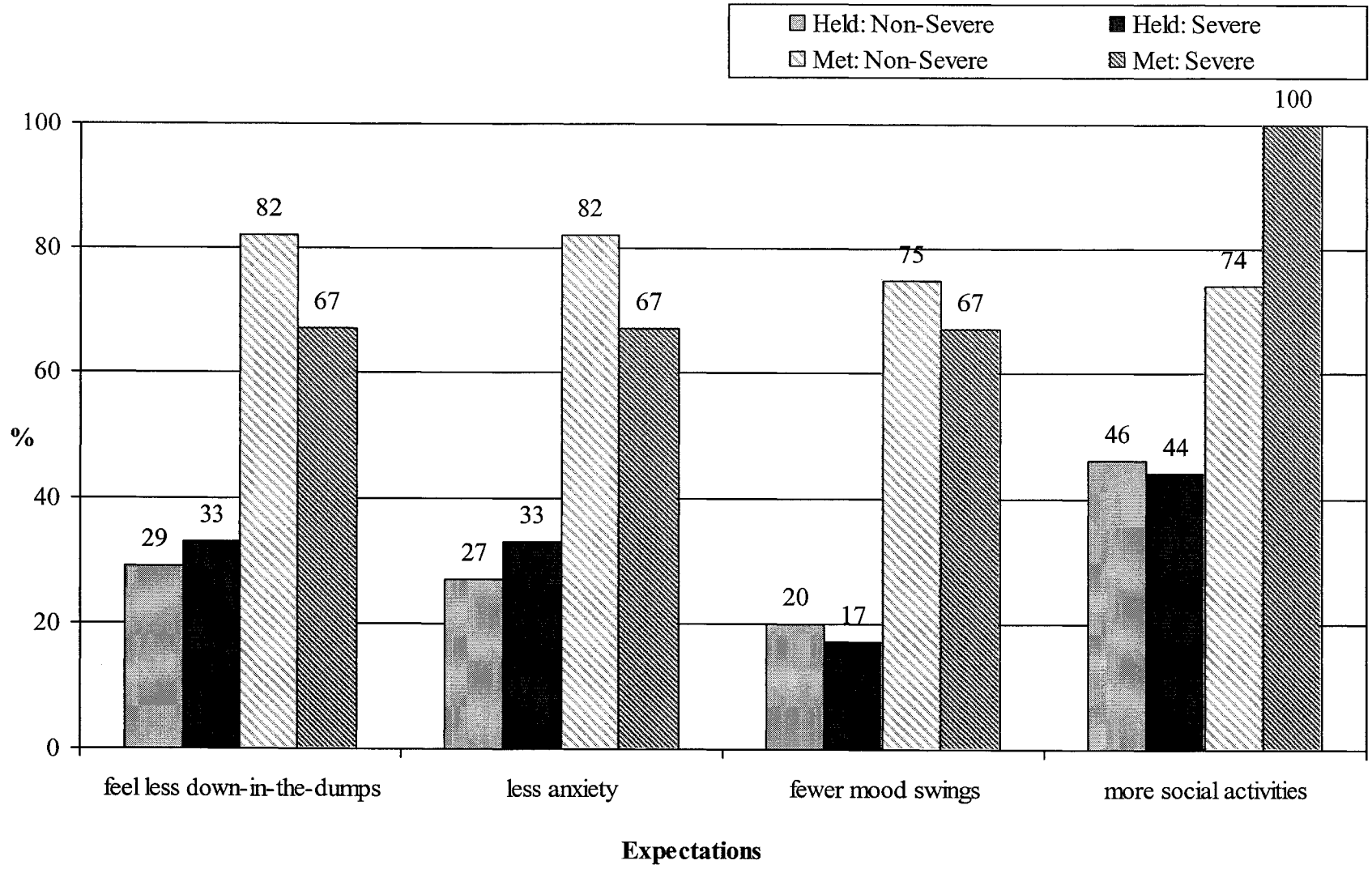
Graph 2: Organomegaly response expectations (1) held prior to beginning ET and (2) met following ET: non-severe participants versus severe participants



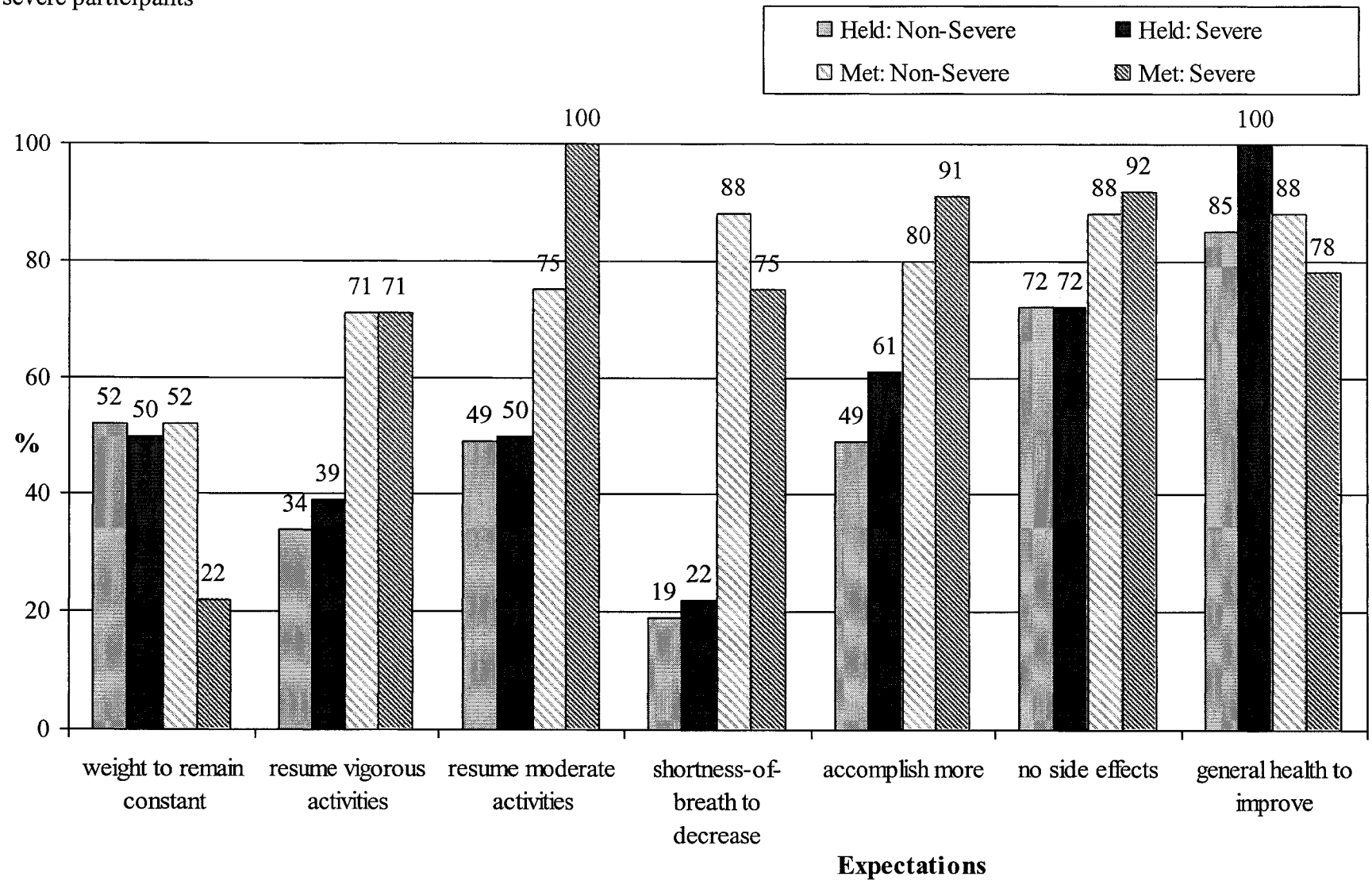
Graph 3: Bone response expectations (1) held prior to beginning ET and (2) met following ET: non-severe participants versus severe participants



Graph 4: Social quality of life expectations (1) held prior to beginning ET and (2) met following ET: non-severe participants versus severe participants



Graph 5: Physical quality of life expectations (1) held prior to beginning ET and (2) met following ET: non-severe participants versus severe participants



DISCUSSION

This report summarizes the results of a retrospective study of individuals with GD type 1, 18 years of age or older, who have received ET for at least one year. Variation in symptom severity amongst patients with GD type 1 and individualized treatment regimens prompted the question: Have patients' expectations regarding ET been met? In order to address this question, it was first necessary to identify what expectations were held by patients with GD type 1 prior to receiving ET. Furthermore, participants were placed into severity groups to determine if the severity of disease was a significant factor influencing whether or not expectations were met following receipt of ET.

Demographic data was compared to the demographic data reported in the Gaucher Registry Reports (2000 and 2002) (15, 37). The current mean age of participants is 51.5 years (SD = 16.57 years). This is greater than the 2000 Gaucher Registry report, in which the average age was 34.7 years (SD = 19.5 years) (15). However, the 2000 Gaucher Registry included data from participants of all ages, whereas this study only included data from individuals age 18 and older. The current mean reported age at diagnosis was 26.0 ± 19.5 years, whereas the mean age of diagnosis for participants in the Gaucher Registry was 17 ± 17 years (37). Again, this variation is accounted for by the inclusion criteria of the current study. 27 of 62 (43.5%) of participants reported having their spleen removed prior to beginning ET, whereas 30% (N=308) of the participants in the Gaucher Registry report had their spleens removed (37). 35 of 62 (56.5%)

participants were women, compared with 52% of participants in the Gaucher Registry (37).

The significance of the current study is directly related to the care of patients with GD type 1. An evaluation of whether or not patients' expectations of ET have been met may lead to the provision of improved health care to patients with GD type 1. The need for effective information-giving, communication and monitoring strategies may be indicated in order to accurately anticipate and influence patients' expectations (11). The results of this study may potentially enable health care professionals to identify and address patients' expectations prior to beginning ET, thereby allowing patients to form more consistently reasonable and accurate expectations (20). As previous studies have found a correlation between the meeting of expectations and patient satisfaction and quality of life, the results of this study are particularly important (30, 39). The identification and analysis of the expectations held by GD patients may lead to a route by which patient satisfaction with ET and quality of life after receiving ET can be improved. This could have implications for future ET application not only in GD, but in other lysosomal storage diseases treated with ET.

The clinical parameters of patients with GD type 1 who receive ET have been shown to improve (15, 37), as has these patients' quality of life (10, 23). Measurement of these outcomes evaluates the ET experience of GD type 1 patients without necessarily taking the beginning of the entire process into account. Before a patient begins receiving ET, he must first decide, through consultation with his health care provider, whether or not he wishes to be placed upon ET. This decision-making process involves the

formulation of expectations of ET and the determination of whether these expectations can and will be met. This study is a first step in evaluating the experience of patients with GD type 1 from the beginning of this process through to the current stage of their treatment, including the impact of prior expectations upon treatment outcome.

Expectations held by a patient are an important indicator of how that patient's satisfaction with treatment and quality of life will be affected following treatment (11, 18, 19, 30, 39). While it is important to measure satisfaction and quality of life as outcomes in and of themselves, it is also important to put them into the context of held expectations, met expectations, and unmet expectations. Patient expectations are likely to be in flux, changing as the patient's experience unfolds. Health care professionals do contribute to the development of patient expectations and therefore need to be aware of which expectations to anticipate and how those expectations evolve. It is true that some realities of ET may be unanticipated and patients therefore do not know what to expect before the experience itself. However, other realities, such as the slower response of bone parameters and potential weight gain, can be anticipated and dealt with. While it is possible to address patient dissatisfaction and low quality of life after receipt of ET, it makes more sense to anticipate these outcomes, using expectations as a measure. The patient's experience will thus be approached in a pro-active manner, before an expectation goes unmet and results in dissatisfaction and low quality of life.

Expectations Held

This study identified expectations held by participants prior to ET and evaluated whether or not patients believed those expectations had been met following ET. Greater

than 65% of participants agreed that they held 5 of 26 individual expectation statements, suggesting that these statements (improved anemia, decreased fatigue, decreased liver size, decrease bone pain, and no side effects) are topics that should be addressed by a health care professional prior to beginning ET. Helping patients to prepare realistic expectations regarding these topics could result in increased satisfaction and quality of life were these expectations to be met following receipt of ET. The 21 of 26 expectation statements that participants agreed with at a rate of less than 65% are no less important. Discussion of these expectations could lead to the development of a patient's own unique expectations and further elucidation of how that patient envisions his satisfaction being met and quality of life improving after receiving ET.

In general, the proportions of participants indicating that they held an expectation prior to receiving ET averaged highest in the "Hematologic Response" category (55.5%) and lowest in the "Social Quality of Life" category (31.0%). This could indicate that, prior to receiving ET, participants focused on the clinical success of ET as measured by therapeutic outcome, rather than on an improved social quality of life. However, patients could benefit from the formulation of realistic expectations regarding social quality of life, were health care professionals to initiate a discussion of such. For example, only 28.8% of participants reported that they expected to feel anxious less often following ET. However, of those who did report themselves as holding this expectation, 76.5% reported that the expectation was met. Should a patient, in the counseling process prior to receiving ET, be made aware that it is a possibility that they will feel anxious less often following ET? A patient could thus become aware of this possible expectation and

formulate his own expectation incorporating the knowledge he has gained. Should he decide that this expectation would not be pertinent to his situation, communication between health care professional and patient has still occurred and some of that patient's perceptions of ET revealed.

Since the level of participants reporting that their "Social Quality of Life" expectations had been met was generally high (average 76.8%), such a discussion could have the potential to increase patient satisfaction and quality of life. Formulating realistic expectations regarding social quality of life with patients prior to beginning ET could lead to those expectations being met. Health care professionals could indicate that many patients who hold these expectations prior to receiving ET find them to be met following ET, and could refer to studies that report better emotional and social well-being associated with longer duration of ET (10). Patients, with their health care providers, would thus generate their own realistic expectations regarding social quality of life and these expectations could impact the outcomes (satisfaction and quality of life) experienced by that patient.

Several groups within the participants were identified as having a significantly greater chance of holding expectations prior to beginning ET. First, women were found to be significantly more likely than men to hold seven expectations. Second, those participants who made less than $50,000 per year were significantly more likely than those who made more than $50,000 per year to hold five expectations. Participants receiving clinic infusions were significantly more likely than those receiving home infusions to hold two expectations, and participants infused at home were significantly more likely to hold one expectation. These results can have implications, depending

upon the demographics of the individual patient being counseled prior to receiving ET. For example, a female patient who makes less than $50,000 per year and who will be infused at a clinic may be significantly more likely than a male patient who makes more than $50,000 per year and who will receive home infusions to hold eleven different expectations. Recognition of a patient's demographic characteristics could initiate a discussion in which these expectations are addressed prior to beginning ET.

Determining if a patient has had a splenectomy prior to beginning ET could potentially help a health care professional anticipate the expectations that patient will hold. Participants who had splenectomies were significantly more likely to hold four of the twenty-six expectation statements. However, no significant differences were found between the groups when evaluating expectations that had been met. These findings are interesting because, although not used in the current study criteria to distinguish between severe and non-severe participants, spelenectomy has been suggested as an indication of more severe disease (9).

A non-significant trend indicated that a greater proportion of severe participants than non-severe participants held 16 of 26 expectations prior to beginning ET. This has implications for the counseling a patient receives prior to beginning treatment, depending upon disease severity and rate of progression.

Expectations Met

The overall proportion of participants agreeing that their expectations had been met was greater than 65% for 21 of 26 expectation statements. This relatively high level of agreement was not found for five expectation statements, four of which were in the

"Bone Response" category. Those participants who held expectations involving bone response found their expectations were met less often than expectations not involving bone response. Ideally, the issue of bone response would be addressed prior to a patient receiving ET, including the finding that bone symptoms have shown to respond at a slower rate than other symptoms, and that bone involvement prior to beginning ET may not be repairable (4, 12, 27, 33, 37). This could perhaps alleviate the lowered satisfaction and quality of life associated with unmet expectations (30, 39).

Male participants were found to be significantly more likely than female participants to have their expectation of maintaining a relatively constant weight met. Overall, this expectation was held by more than half of participants but only 43.3% (the lowest value obtained) of participants agreed that this expectation had been met. This illuminates an area which health care providers can attend to when counseling a patient prior to ET, before a patient (a) develops this expectation, (b) finds this expectation unmet, and (c) experiences low satisfaction with ET and a decreased quality of life as a result.

Those participants who expected the frequency of their feelings of fatigue to decrease and found this expectation to be met were significantly more likely than those who did not have this expectation met to also have their expectation of improved general health met (P=0.047). This indicates that participants value the outcome of decreased frequency of fatigue as an important factor when gauging their general health. Participants perceive their general health to improve if the frequency of their feelings of fatigue decreases. This is an issue upon which health care providers can capitalize, for the benefit of the patient, when discussing possible outcomes of ET.

Participants were grouped into severity groupings, severe and non-severe, for the purposes of statistical comparison. Prior to this study, no universally accepted criteria for categorizing patients into severe and non-severe disease groups had been developed. Contrary to our hypothesis, those participants with non-severe disease were not significantly more likely than participants with severe disease to have their expectations met. In fact, the analysis that most closely approached statistical significance ($P = 0.087$) indicated that severely affected participants were more likely than non-severely affected participants to have their expectation of decreased intensity of bone pain crises met. A non-significant trend also indicated that a greater proportion of severe participants than non-severe participants reported that 18 of 26 expectations had been met following ET. Again, this has implications for the counseling a patient should receive prior to beginning ET, depending upon disease severity and rate of progression.

Limitations

This study reports the expectations held prior to ET and met following ET by patients with GD type 1 for the first time. There were limitations in this study, primarily resulting from the small sample size surveyed. The small sample size resulted in data that were not necessarily representative of the population of patients with GD type 1 receiving ET as a whole. Response bias was a limiting factor, particularly in regards to the sample of participants responding from each center. The distribution of response was different from different treatment centers, suggesting a possible recruitment bias (i.e., participants mailed questionnaires versus those who received them when they attended their clinic infusion). The small sample size also affected the analysis of severe versus

non-severe participants, although adequate numbers were present to identify statistically significant differences between demographic groups. Statistical significance was reached when assessing only one expectation statement held prior to ET by severe versus non-severe participants. Despite grouping participants who both "agreed" and "strongly agreed" for more statistical power, statistical significance was not identified for any of the twenty-six expectation statements when evaluating those that had been met following ET.

This study was based strictly upon subjective participant report and did not incorporate objective clinical data in order to determine the extent of therapeutic gains. Neither did this study have control over the nature and quality of individual ET regimens prescribed by different physicians. Information regarding the dosage received by participants was not obtained. The doses patients receive are highly individualized and may contribute to the expectations they hold and whether or not they are met (1).

Participants who met eligibility criteria had received ET for at least one year, necessitating a retrospective study design. This increased the incidence of recall bias.

There is the potential for this study to have excluded those mildly affected patients who are not receiving ET. One study suggests that up to 60% of Ashkenazi patients who are homozygous for the N370S mutation do not come to medical attention (24). Since these patients would not have a diagnosis, they would not contribute to the findings reported here. This would affect the proportion of patients categorized as non-severe, since this proportion is likely to actually be greater than reported. Although the range of severity surveyed is therefore limited, this would be a limitation of any study involving the GD type 1 patient population.

The majority of the questionnaire was new and not validated. The criteria used to categorize participants into severity groups were also novel.

Future research in this area is warranted for several reasons. First, a prospective patient population would effectively reduce recall bias. Next, a study with a greater sample size would be better able to generate the power necessary for statistical analysis. Although there are some interesting trends indicated in the current data, greater numbers of participants are needed to determine if these trends are actually statistically significant. The data generated from future research has the potential to improve the ET experience for patients. A study collecting patient-reported information as well as clinically recorded data could allow for comparisons between patient expectations, patient reported outcomes, and objective clinical outcomes. It may be interesting to look for correlations between clinical improvement, held expectations, and met expectations.

Summary

The data reported suggest that certain groups of participants with GD type 1, including female participants, participants who make less than $50,000 per year, splenectomized participants, and participants who receive clinic infusions are significantly more likely to hold expectations prior to receiving ET. Certain groups are also more likely to report expectations as having been met following receipt of ET. Non-significant trends indicate that severe participants were more likely than non-severe participants to hold expectations prior to ET and to have their expectations met following ET. These findings have the potential to impact the clinical management of patients with GD type 1.

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