

The humanistic burden of hereditary angioedema: Impact on health-related quality of life, productivity, and depression

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ABSTRACT

Hereditary angioedema (HAE) is a rare, autosomal dominant disorder characterized by recurrent acute attacks of swelling of the larynx, abdomen, and periphery. This study was designed to assess the humanistic burden of illness associated with HAE. HAE burden was assessed via a web-based survey of patients that solicited information on attack characterization, treatment, side effects, pain, and functional and emotional burden of disease management. In addition to HAE-specific sections, the survey used three standardized instruments to compare HAE patient data to normative (healthy) and chronic disease populations: the 12-Item Short Form (SF-12) Health Survey, the Work Productivity and Activity Impairment–General Health (WPAI-GH) questionnaire, and the Hamilton Depression Inventory–Short Form (HDI-SF). A total of 457 HAE patients responded to the survey (response rate, ~19%). Patients reported significantly poorer health-related quality of life versus population norms, based on the SF-12 Physical Component Summary (mean, 43.7 versus 49.6; $p < 0.001$) and Mental Component Summary (mean, 42.6 versus 49.4; $p < 0.001$). HAE patients also had higher mean HDI-SF scores than population norms (8.1 ± 6.5 versus 3.1 ± 3.0 ; $p < 0.001$), with 42.5% of HAE patients scoring >8.5 , indicative of depressive symptomatology. Productivity was also markedly impaired in all WPAI-GH categories, including 34% overall work impairment. Because of their most recent HAE attack, workers lost a mean of 3.3 days; students lost a mean of 1.9 days. HAE results in considerable humanistic burden to patients across physical and mental health domains; negatively impacts education, career, and work productivity; and compounds the substantial economic burdens that are reported separately.

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Hereditary angioedema (HAE) is a rare, debilitating, life-altering, and potentially life-threatening autosomal dominant disease resulting from mutations in the C1-esterase inhibitor (C1-INH) gene. The estimated incidence is ~1 in 50,000 people worldwide.¹

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The survey, consent form, and recruitment methodology used in this study were approved by the Essex Institutional Review Board, Inc., Lebanon, New Jersey

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HAE is characterized by acute attacks of pain and edema that may involve nearly every body area—most notably the larynx, oropharynx, face, gastrointestinal mucosa, limbs, or genitalia.^{2–5} Laryngeal attacks pose the greatest risk, with variable speed and degree of progression and the potential for asphyxiation.^{6,7} Abdominal attacks may mimic acute abdominal emergencies, prompting unnecessary surgery.^{2,8} Peripheral attacks can be painful, debilitating, and disfiguring.^{4,9} Improper diagnosis, unnecessary treatments and surgeries, and delay to timely therapy all contribute to a very real and substantial burden for HAE patients.

HAE attacks are highly variable and unpredictable and can be induced by a variety of stimuli including stress, medical and dental procedures, and hormonal changes¹⁰; however, many attacks occur without a known precipitating factor.⁸ Prodromal symptoms before HAE attacks are common, with unusual fatigue, rash, and muscle aches occurring most frequently.^{11,12} The frequency of attacks ranges from <1 /year to >26 /year on average, with rare patients reporting >100 HAE attacks per year.^{8,13} Attacks can last up to 5 days.³ The frequent need for medical intervention and time away from normal activities can be very costly both in

terms of direct medical costs and in terms of impact on patients' health-related quality of life (HRQL).¹³⁻¹⁵

Several clinical reviews of HAE include mention of HRQL impacts^{9,15-18} but do not provide detailed, quantitative information about the specific economic consequences and humanistic burdens of HAE. In 2004, Huang reported the results of an online survey of HAE patients, noting that 46% of patients were dissatisfied with the current management of HAE, 85% had a constant fear of airway closure, and 65% had a fear of pain.¹⁹ More recently, Bygum *et al.* quantified HRQL both before and after participation in a program of self-administration of C1-INH, but only included seven patients.²⁰ The study presented here was conducted to comprehensively assess the economic and HRQL (humanistic) burden of illness associated with both acute HAE attacks and the chronic management of this episodic disease. This article reports the impact of HAE on HRQL. The results of the economic burden are reported separately.²¹

METHODS

Study Design

The survey was conducted from November 2007 to January 2008. Participants were recruited *via* the United States Hereditary Angioedema Association (HAEA) and were required to complete a voluntary, cross-sectional, one-time, web-based survey. Eligible participants were ≥ 18 years of age (19 years old in Alabama and Nebraska) with a diagnosis of HAE who were able to participate in a web-based survey administered in English. The HAEA recruited participants from its database of patients who had contacted the HAEA, identified themselves as HAE patients, and requested information on HAEA membership. These patients were e-mailed an introduction to the study along with the web link for the survey; patients were sent an initial invitation and one reminder. The survey, consent form, and recruitment methodology were approved by the Essex Institutional Review Board, Inc. (Lebanon, NJ). The survey responses were completely anonymous, and all participants provided electronic informed consent before completing it.

Survey Components

The survey included four overall components, including one disease-specific Burden of Illness survey and three standardized instruments: the 12-Item Short Form (SF-12) Health Survey, the Hamilton Depression Inventory–Short Form (HDI-SF), and the Work Productivity and Activity Impairment–General Health (WPAI-GH) questionnaire.

The HAE-specific Burden of Illness survey was designed to capture information about disease and attack characteristics, medical care, and the humanistic bur-

den of HAE and contained five sections that focused on informed consent, the respondent's most recent HAE attack, general disease information, the humanistic burden of HAE, and sociodemographic and clinical information.

The SF-12 is a generic HRQL survey consisting of 12 questions about various aspects of health-related functioning over the prior 4 weeks. The survey measures eight health profile components and outcomes consist of scores for each of these components plus two summary scores: a Mental Component Summary (MCS-12) and a Physical Component Summary (PCS-12).²² For each of the components and the summary scores, higher scores indicate better functioning.

The HDI-SF is a nine-item measure designed to capture symptoms of depression over the prior 2 weeks.²³ The possible range of scores is 0–33, with higher scores indicating more depression symptoms. Scores > 8.5 are indicative of clinically significant levels of at least mild depressive symptomatology and suggest a need for further evaluation for clinical depression.^{23,24}

The WPAI-GH includes six questions about work and activity impairment due to health problems over the previous 7 days.²⁵ Outcomes are expressed as impairment percentages, with higher numbers indicating greater impairment and less work or activity productivity.

Statistical Methods

All available data from the survey were used for the analysis; no data were imputed. Descriptive statistics were used to characterize sociodemographic and clinical characteristics and disease experience. The impact of HAE on HRQL, emotional functioning, and depression was assessed by comparing results from the SF-12 and the HDI-SF to population norms using *t*-tests, assuming a normal distribution.

A linear z-score transformation was used to calculate the HRQL outcomes of the SF-12, per the SF-12 Version 2 scoring guidelines.²² The PCS-12 and MCS-12 summary scores were aggregated from the transformed component scores.

For analyses based on average severity, the criteria used to classify attack severity as mild, moderate, or severe were defined as follows:

- Mild—"Noticeable symptoms but does not impact activities of daily living. (*Example*: Hand is swollen, but you can still hold a pencil or grip a utensil.)"
- Moderate—"Intervention is highly desirable for symptoms; activities of daily living are affected. (*Example*: Hands are swollen and you cannot button your shirt, or your feet are swollen and wearing shoes is uncomfortable.)"
- Severe—"Treatment or intervention required; unable to perform activities of daily living. (*Example*: Your throat is

Table 1 Demographic characteristics and hereditary angioedema (HAE) attack characteristics

	HAE Patients (n = 457)
Age (yr), mean $\pm$ SD	41.4 $\pm$ 13.3
Gender, n (%)	
Female	345 (75.5%)
Male	112 (24.5%)
Race/Ethnicity, n (%)	
White	421 (92.1%)
Black or African American	11 (2.4%)
Asian	8 (1.8%)
Other	17 (3.7%)
Ethnicity: Hispanic or Latino, n (%)	29 (6.3%)
Overall HAE attack characteristics:	
No. of attacks per year*	
Mean $\pm$ SD	26.9 $\pm$ 43.1
Median (range)	12.0 (0, 350)
Duration of attacks, hr, mean (range)	61.3 (1.0–360)
Age of diagnosis, yr, mean (range)	22.2 (1.0–72.0)
Average attack severity over the last 12 mo, n (%)	
Mild	71 (15.5%)
Moderate	256 (56.0%)
Severe	130 (28.4%)
Most recent HAE attack characteristics	
Length of time since most recent attack, days	
Mean $\pm$ SD	81.7 $\pm$ 247.9
Median (range)	12.0 (0–3804)
Severity, n (%)	
Mild	121 (26.5%)
Moderate	212 (46.4%)
Severe	124 (27.1%)
Body sites affected, n (%)	
Internal head/neck (laryngeal)	112 (24.5%)
Stomach/GI (abdominal)	258 (56.5%)
Genitals/buttocks (peripheral)	73 (16.0%)
External head/neck (peripheral)	70 (15.3%)
Cutaneous (peripheral)	197 (43.1%)
Worst pain experienced during attack, mean (range)#	
Mild attack	2.9 (0.0–8.7)
Moderate attack	5.7 (0.4–10.0)
Severe attack	7.1 (0.2–10.0)

*A total of 399 patients responded to this question.

#Pain reported on a visual analog scale of 0 (no pain) to 10 (worst possible pain).

GI = gastrointestinal; SD = standard deviation.

swollen and you are having difficulty breathing, or your lips are swollen and you cannot eat.)"

The burden specifically associated with chronic androgen therapy was assessed using an analysis of variance (ANOVA) to compare "bother" caused by side effects for patients taking androgens versus those patients receiving therapy other than androgens. The impact of androgen therapy on both work productivity and depression scores was

assessed using analysis of covariance (ANCOVA). All statistical tests used a significance level of 0.05.

RESULTS

Patient Demographics and HAE Attack Characteristics

Approximately 2400 HAE patients were invited to participate. A total of 457 (~19%) patients (112 male

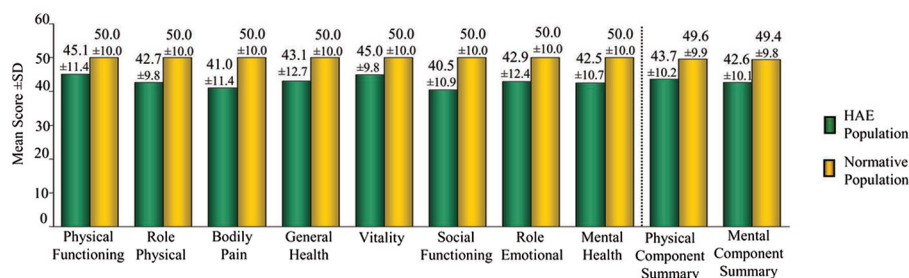


Figure 1. Health-related quality of life (HRQL; 12-Item Short Form [SF-12] scores. Standardized (z-score transformed) SF-12 values are shown. Normative population values based on Ware et al.¹⁹ Patients with HAE reported decreased physical and mental health versus the normative population ($p < 0.001$) for all subscales and overall summary components, based on t-tests.

and 345 female patients) responded to the study and met the inclusion criteria. Patient demographics and overall HAE attack characteristics are provided in Table 1. The mean age at diagnosis was 22 years, although the age of diagnosis ranged from 1 to 72 years. Patients experienced a mean of 26.9 HAE attacks annually (median, 12.0); the majority of attacks were typically moderate in severity, but more than one-quarter were noted as severe. Female patients reported more HAE attacks per year than male patients (mean, 29.8 versus 17.9; median, 15.0 versus 8.5); however, attacks typically last for a similar mean duration in both genders (female patients, 60.8 hours; male patients, 62.6 hours).

A total of 94% of respondents had at least one HAE attack in the 12 months before the survey. Table 1 presents the characteristics of the most recent attack. The median time since the patients' most recent HAE attack was 12.0 days. Overall, the majority of attacks (56.5%) were abdominal, and 24.5% were laryngeal. Approximately 74% of patients reported that their most recent HAE attack was moderate or severe. Using a visual analog pain scale of 0 (no pain) to 10 (worst possible pain), patients whose attack was moderate reported a mean pain score of 5.7; patients whose attack was severe reported a mean pain score of 7.1.

Impact of HAE on HRQL and Depression

HAE patients reported significant decrements in HRQL. Mean scores for every component of the SF-12 Health Survey were significantly lower for HAE patients compared with population norms, with a mean overall PCS-12 score of 43.7 for HAE patients versus 49.6 for population norms and a mean overall MCS-12 score of 42.6 for HAE patients versus 49.4 for population norms ($p < 0.001$ for both; Fig. 1).

Figure 2 presents depression scores from the HDI-SF survey. HAE patients showed higher mean score on the HDI-SF survey than population norms (8.1 versus 3.1; $p < 0.001$), suggesting that HAE patients are more likely to exhibit depressive symptoms than the general population. Increased average attack severity resulted in higher HDI-SF scores, suggesting an increased level of depressive symptomatology in patients who typically experience severe attacks (mean HDI-SF score =

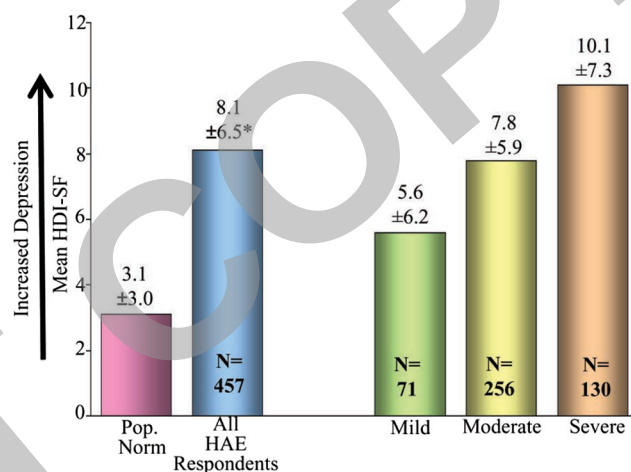


Figure 2. Depression (Hamilton Depression Inventory–Short Form [HDI-SF]) scores. Numbers presented are mean $\pm$ standard deviation. Normative population value based on Reynolds and Koback.²¹ Hereditary angioedema (HAE) patients are more likely to experience symptoms of depression than population norms (* $p < 0.0001$), based on t-test. Depression increases with attack severity.

10.1) compared with those whose attacks are generally mild (mean HDI-SF score = 5.6). Furthermore, 42.5% of HAE patients reported an HDI-SF score > 8.5 , indicative of at least mild symptoms of depression.²³ A total of 19.5% of the HAE patients who responded to the survey reported that they were taking psychotropic or antidepressant medication, which is nearly double the national average of 11.1%.²⁶

Reduced Productivity and Missed Opportunities due to HAE

Survey respondents reported that HAE significantly impacted their ability to work and attain an education. A total of 50.6% of all patients who identified themselves primarily as full- or part-time workers missed at least 1 day of work because of their most recent HAE attack, and 44.4% of students missed at least 1 school day (Fig. 3). Furthermore, 59.3% of respondents reported that they missed at least 1 day of leisure activities as a result of their most recent HAE attack (Fig. 3).

Results from the WPAI-GH are shown in Fig. 4. HAE patients reported a mean of 33.6% overall work impairment (a weighted combination of missed work and

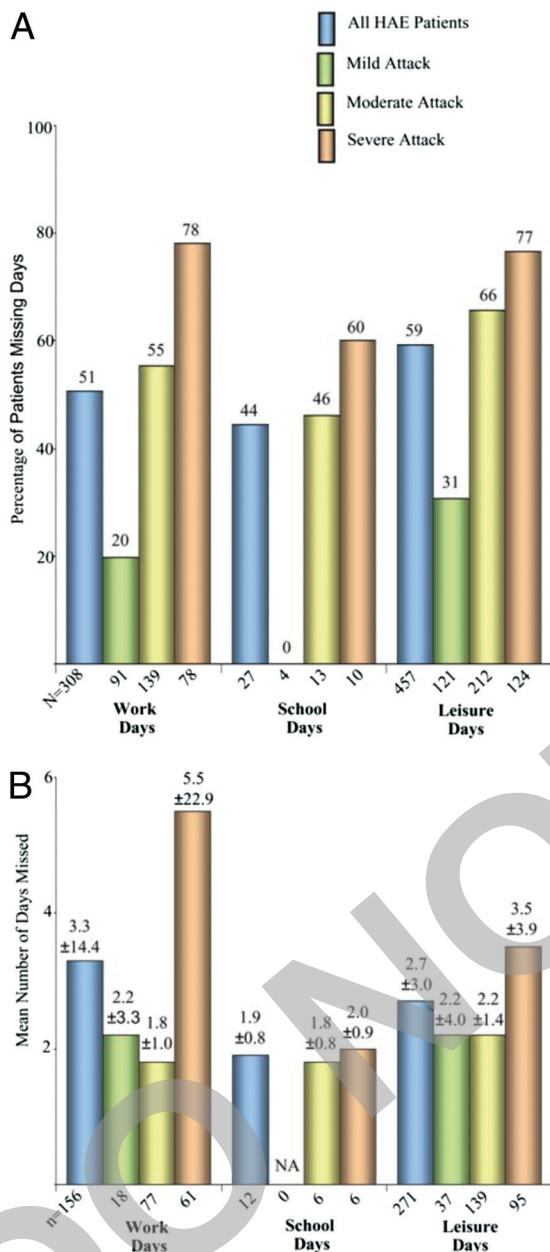


Figure 3. (A) Percentage of patients with missed days due to hereditary angioedema (HAE) attack by most recent attack severity. Missed workdays calculated for employed patients; missed school days calculated for students; missed leisure days included all respondents. (B) Number of missed days due to HAE Attack by most recent attack severity. Means $\pm$ standard deviation calculated for patients who reported missing ≥ 1 day.

reduced productivity while working) and 45.0% non-work activity impairment because of health. The work and activity impairment suffered by HAE patients is comparable with the impairments suffered by patients with severe asthma and Crohn's disease.^{27,28} Furthermore, as shown in Fig. 5, 40.5% of all respondents felt that HAE had prevented them from going as far in school as they would have liked, and 69.1% said they

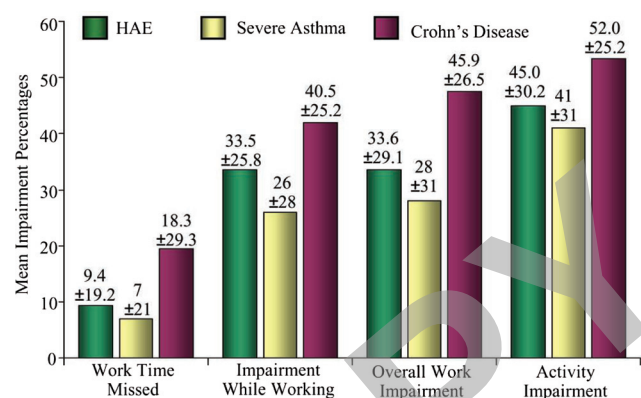


Figure 4. Impact of hereditary angioedema (HAE) on productivity. Mean impairment percentages ($\pm$ standard deviation) as determined by the Work Productivity and Activity in Impairment-General Health (WPAI-GH) questionnaire are presented. The reduced productivity experienced by HAE patients is comparable with that experienced by patients with severe asthma or Crohn's disease, as reported in the literature.^{23,25}

could not consider certain jobs because of HAE. HAE impacted the career advancement of 57.5% of respondents and hindered the educational attainment of 48.4% of respondents. A total of 16.4% of patients said they were working less than full time as a direct result of their HAE.

Subgroup Analysis: Patients Using Androgens

A total of 226 survey respondents (49.5%)—66 male (58.9% of male respondents) and 160 female (46.4% of female respondents) respondents—reported receiving attenuated androgens for prophylactic use during the 12 months before the survey. Androgen therapy results in significant side effects, as shown in Table 2. Nearly one-half of the HAE patients on chronic androgen therapy experience sleeplessness (45.6%), agitation (45.6%), and increased hair growth (42.0%); 59.7% experience mood changes, and 70.8% experience weight gain; 6.2% reported that they suffered no side effects.

The chronic use of androgen therapy for HAE is associated with further decreases in HRQL when compared with the overall HAE population (Table 3). An assessment of both (the side effect burden of a therapy) showed that androgen-taking patients exhibit a statistically significantly greater burden from treatment side effects than those taking treatment other than androgen ($p < 0.001$). Androgen-receiving patients score higher on the HDI-SF than the remainder of the HAE population (8.7 versus 7.4; $p < 0.001$). Additionally, androgen-receiving patients show larger decrements in overall work impairment on the WPAI-GH than the remainder of the HAE population (35.4 versus 32.7; $p = 0.003$).

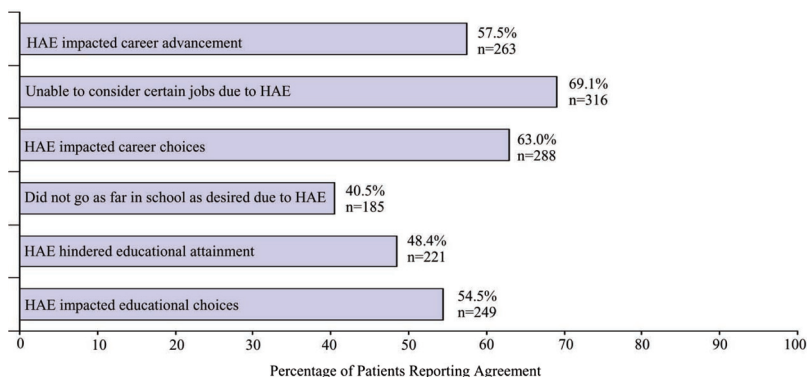


Figure 5. Missed opportunities due to hereditary angioedema (HAE). Percentage of patients reporting that HAE hindered their education and work opportunities, as indicated by their agreement with statements about their opportunities.

Table 2 Side effects associated with chronic medication use for hereditary angioedema (HAE)

Side Effects	HAE Patients Taking Androgens (n = 226)
Weight gain	160 (70.8%)
Changes in mood	135 (59.7%)
Agitation	103 (45.6%)
Sleeplessness/insomnia	103 (45.6%)
Increased hair growth	95 (42.0%)
Acne	91 (40.3%)
Sexual side effects	84 (37.2%)
Menstrual irregularities	83 (36.7%)
Cholesterol level increase	74 (32.7%)
Changes in attention span	59 (26.1%)
Liver function problems	42 (18.6%)
Long-term health problem	32 (14.2%)
Voice changes	31 (13.7%)
Blood clots	6 (2.7%)
Stunted growth	3 (1.3%)
Other	17 (7.5%)
None	14 (6.2%)

DISCUSSION

Patients with HAE experience considerable burden in many ways because of the unpredictable but recurring, debilitating, and potentially life-threatening attacks of edema that typically last for several days.^{8,9,14} This study provides the first comprehensive look at the overall burden of HAE. Patients who responded to the survey report a broad range and degree of suffering that results in significant declines in HRQL and productivity.

Patient HRQL is significantly affected by the episodic and chronic nature of the disease. Overall mental and physical health scores are significantly lower for HAE patients than for the normative populations. Disruptive attacks also cause patients to miss opportunities for career and personal development. A large majority of HAE patients reported that HAE significantly impacted the direction of their educa-

tion and/or career, with a number of patients reporting that they worked less than full time as a direct result of HAE. Patients may be further inhibited from realizing their full potential by high levels of anxiety and depression. Respondents reported significantly higher levels of depressive symptomatology than population norms.

Although HAE is a rare disease, the patient burden reported here is similar to that of other, more common, chronic diseases. As shown by the WPAI results, the decrement in work productivity experienced by HAE patients is comparable with decrements experienced by patients with Crohn's disease or severe asthma. Additionally, HAE patients who work full or part time reported missing a mean of 1.7 days of work per attack. Considering that patients experience a mean of 26.9 attacks/year, the average HAE patient could miss a total of >40 workdays/year due to HAE, which exceeds the 2.5 days/worker per year reported as missed for diabetes.²⁹

Attenuated androgens are routinely used to manage and prevent the development of acute attacks of HAE.^{30,31} However, chronic androgen therapy results in significant side effects. As shown here, patients who reported taking androgens on a regular basis over the previous year had greater side effect burden compared with those taking treatments other than androgens. Additionally, patients taking androgens had higher levels of depressive symptoms and reduced levels of productivity when compared with patients not taking androgens. In considering these additional reductions in quality of life, it is important to keep in mind that androgens are often prescribed to patients with higher attack frequencies and more severe disease profile.⁸ Thus, it is unclear whether the demonstrated diminished quality of life is attributable to the side effects of androgens or to the severity of disease in these patients.

This study was conducted from November 2007 to January 2008, before the approval of prophylactic C1-INH therapy, which may help to alleviate some of the HRQL burdens of HAE.³² However, because prophy-

Table 3 Humanistic burden of chronic androgen therapy

	<i>n</i>	Mean (SE)	<i>F</i> -test	<i>p</i> Value
Assessment of bother*,#				
Androgen therapy	225	2.3 (0.1)	79.12	<0.001
Treatment other than androgen	81	3.7 (0.1)		
Depression scores (HDI-SF)§				
Androgen therapy	200	8.7 (0.5)	8.76	<0.001
No androgen therapy	199	7.4 (0.5)		
Overall work impairment (WPAI-GH)§				
Androgen therapy	143	35.4 (2.4)	5.85	0.003
No androgen therapy	139	32.7 (2.5)		

*The burden associated with treatment side effects. Lower scores indicate greater burden.

#Analysis of variance (ANOVA).

§Analysis of covariance (ANCOVA).

HDI-SF = Hamilton Depression Survey-Short Form; SE = standard error; WPAI-GH = Work Productivity and Activity Impairment-General Health questionnaire.

lactic C1-INH therapy appears to only prevent ~50% of HAE attacks,³³ the HRQL burden of HAE is still expected to be significant.

There are several limitations to this study. This study was a one-time survey that relied on patient-reported information; recall periods for questions related to patients' most recent attack varied from patient to patient; for other questions, recall periods ranged from a week to a year depending on the survey instrument or survey section. Additionally, representing ~20% of HAE patients who had contacted the HAEA for membership or information, this survey sample may not be entirely representative of the overall HAE patient population. The possibility that patients with more severe disease were more likely to respond to the survey can not be excluded. That a majority (75.5%) of respondents were female patients may also be indicative of a slight bias toward more severe disease, because female patients have been shown to experience more severe symptoms.⁴

CONCLUSIONS

Although it is a relatively rare disease, HAE results in a significant humanistic burden. The pain, discomfort, disfigurement, and life-threatening potential of acute attacks, compounded by the disease's unpredictability, all result in a significant chronic burden in the form of reduced HRQL, increased incidence of depressive symptoms, reduced productivity, and missed career and educational opportunities. There is a great unmet need for alternative therapies to manage acute HAE attacks to reduce the overall burden of this disease.

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