# Health-related quality of life and utilities in primary-care patients with generalized anxiety disorder

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## Abstract

*Background* Generalized anxiety disorder (GAD) is prevalent and significantly impacts patient health-related quality of life (HRQL) and disability.

*Purpose* This study evaluated the effect of GAD and anxiety symptom severity on the HRQL of primary-care patients with GAD.

*Methods* Patients 18 years or older with GAD were recruited from an integrated health care delivery system. Clinical assessments included the Hamilton Anxiety Rating Scale (HAM-A), GAD Questionnaire-IV (GAD-Q-IV), and the Patient Health Questionnaire depression module (PHQ). HRQL was assessed by the Quality of Life Enjoyment and Satisfaction Questionnaire—Short Form (Q-LES-Q-SF), Sheehan Disability Scale (SDS), SF-12 Health Survey (SF-6D), and the Health Utilities Index (HUI2, HUI3).

*Results* The sample included 297 patients, 72% women with mean ± standard deviation (SD) age of 47.6 ± 13.7 years. At baseline, the mean HAM-A score was 16.8 ± 7.6 (suggesting the presence of moderate anxiety symptoms). Anxiety and depression symptoms were significantly correlated with mental component summary (MCS), Q-LES-Q-SF, SDS, SF-6D, HUI2, and HUI3 scores (all $P < 0.001$). The mean HRQL and all of the preference-based measures varied significantly by anxiety severity groups (all $P < 0.001$). Anxiety and depression symptoms significantly predicted HRQL and preference-based scores ($R^2$ values ranged from 0.22 to 0.57).

*Conclusions* Anxiety symptoms reported by GAD patients resulted in significant impairment to HRQL and functional outcomes.

**Keyword** Generalized anxiety disorder · Health-related quality of life · Anxiety symptoms · Health utility · Health utilities index · Primary-care patients

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## Introduction

Generalized anxiety disorder (GAD) is a common disorder characterized by periods of at least 6 months that include excessive worry and anxiety [1]. Epidemiological studies have found that the lifetime prevalence rate for GAD ranges from 4 to 6% [2–6]. Among patients seeking ambulatory care, GAD is even more common, with a reported 8–10% prevalence rate [7–9]. In the Kaiser Permanente Northwest Region (KPNW) primary care population, 29% of GAD patients also had a major depressive disorder diagnosis and 13% had a dysthymia diagnosis.

GAD is associated with increased self-reported disability days, as well as impairments in psychosocial functioning, role functioning, work productivity, and health-related quality of life (HRQL) [2, 9–13]. GAD is associated with psychological and functional impairment, even when controlling for comorbidity, such as depression [13]. Furthermore, GAD with no concomitant depression has been

shown to be associated with HRQL impairment comparable to that of major depressive disorder [2, 10, 11]. However, a more recent study found that the impact of GAD on HRQL and utility scores was significantly attenuated when comorbid depression was entered into the analyses [14].

Health utilities are measures of preferences for various health states and clinical conditions, and are summary, preference-based measures of health, and are considered within the broader family of HRQL measures [15]. Preference-based HRQL instruments provide information on the value of different health states and can be used to estimate health outcomes for cost-effectiveness analyses. Although there have been studies examining health utilities in patients with depression [16–18], we are not aware of any studies that have directly measured utilities in patients with GAD. Mittal et al. [16] found that, in patients with depression, a GAD diagnosis and depression symptoms were significant predictors of Quality of Well-Being Scale-Self Administered (QWB-SA) preference scores, but GAD was not associated with physical or mental component summary (MCS) scores. Sullivan et al. [19] provided a preference score for anxiety disorders (0.76) based on the data collected in the Medical Expenditure Panel Survey during 2001, but this utility estimate is not specific to GAD. Utilities, which are considered to be an index of HRQL, are anchored to scores of 0 (representing dead) and 1.0 (representing perfect health), although it is possible to have states rated as worse than dead [18, 20]. Utilities can be measured directly, using standard gamble or time trade-off methods, or indirectly, using multi-attribute health state classification systems [19–22]. Utility estimates are needed to calculate quality-adjusted life years (QALYs), which are recommended as the most appropriate effectiveness measure for economic evaluations because they incorporate survival and HRQL into a single index [23].

This study examined the relationship between HRQL outcomes and clinical severity and symptom ratings in primary-care patients with a diagnosis of GAD recruited in an integrated health care setting. We expected a moderate and consistent relationship between the severity of anxiety and depressive symptoms and HRQL.

## Methods

Participants were identified and recruited from KPNW for a longitudinal study examining the clinical, HRQL, utilization of health care services, and cost outcomes of GAD in an integrated care setting. KPNW provides comprehensive health care services, including mental health care, to about 17% of the population of the greater Portland, Oregon, metropolitan area (over 486,000 members). The KPNW mental health department provides a full range of pharmacotherapy, group psychotherapy, and brief individual psychotherapy services. The demographic and socioeconomic characteristics of its members are similar to those of the population in its service area, except for the under-representation of Oregon Medicaid enrollees. Most members are covered through employer-purchased plans, but approximately 18–20% are covered via contracts with Medicare, Medicaid, or other subsidized health insurance programs for low-income persons.

A total of 297 patients with GAD, currently enrolled in KPNW for at least 12 months, were recruited between June 2005 and June 2006. Potential study patients were initially identified through medical encounter records and were only contacted if their physician agreed to permit a recruiting contact. All study participants had at least two medical care encounters with diagnoses of GAD (300.02) and/or anxiety state unspecified (300.00), confirmed Diagnostic and Statistical Manual of Mental Disorders—IV Text Revision (DSM-IV-TR) diagnosis of GAD based on the Structured Clinical Interview for DSM-IV-TR (SCID), were 18 years or older, were able to speak and read English, and provided written informed consent. Patients were excluded from the study if they had a diagnosis of psychosis, bipolar disorder, organic psychotic disorder, or mental retardation within the past 12 months, or had current cognitive impairment (memory loss and temporal disorientation), as demonstrated during a telephone contact or as reported by a family member. The study was approved by KPNW's institutional review board and was approved as complying with HIPAA requirements.

Data collection procedures and measures

The clinical and HRQL measures were collected by telephone, with experienced and trained interviewers administering the questionnaires. All baseline, 3-month follow-up (10–14 weeks after baseline) and 6-month follow-up (22–26 weeks after baseline) interviews were scheduled at times most convenient for participants. Participants received a token of appreciation of a $20 merchandise certificate for the completion of each interview. The baseline and follow-up interviews included the Structured Interview Guide for the Hamilton Anxiety Scale (SIGH-A), Generalized Anxiety Disorder Questionnaire-IV (GAD-Q-IV), Quality of Life Enjoyment and Satisfaction Questionnaire—Short Form (Q-LES-Q-SF), Patient Health Questionnaire (PHQ) depression questions, SF-12 Health Survey version 2 (SF-12v2), Health Utilities Index Mark 2/Mark 3 (HUI2, HUI3), and the Sheehan Disability Scale (SDS). At baseline, demographic data on gender, age, race/ethnicity, education, employment status, and household income were collected.

## SCID anxiety module

The Structured Clinical Interview for DSM Disorders (SCID) is an interviewer-administered, semi-structured interview used for the diagnosis of Axis I and Axis II disorders, as defined by DSM-IV-TR [1]. In this study, only the anxiety module was administered to confirm a GAD diagnosis. The SCID is highly reliable [24, 25] and has good inter-rater reliability in anxiety disorder patients [26] and for telephone interviews [27, 28].

## Structured Interview Guide for the Hamilton Anxiety Scale

The Hamilton Anxiety Scale (HAM-A) was developed to evaluate the severity of anxiety symptoms [29]. The instrument consists of 14 items rated over the past week. This study used the interview-administered SIGH-A [30], which has been validated for telephone administration [31]. We defined anxiety severity as asymptomatic ($\leq 9$), mild (10–15), moderate (16–24), or severe ($\geq 25$) using the HAM-A.

## Generalized Anxiety Disorder Questionnaire-IV

The GAD-Q-IV is a nine-item self-reported diagnostic measure of GAD revised from the original GAD-Q. The instrument is based on the fourth edition of the Diagnostic and Statistical Manual (DSM-IV) [32]. The first part of the measure is designed to evaluate the occurrence of excessive and uncontrollable worry using a checklist of five yes/no items and one "please list" item. Only if the participant answers "Yes" to the question, "During the *last six months*, have you been bothered by excessive and uncontrollable worries more days than not," was the participant asked the final three questions on the GAD-Q-IV. The remaining items include: the checklist of six DSM-IV symptoms and two items on worry and its physical symptoms that are rated using a nine-point Likert scale ranging from 0 = none to 8 = very severe.

## Quality Of Life Enjoyment and Satisfaction Questionnaire—Short Form

The Q-LES-Q-SF is a participant-rated scale designed to measure the degree of enjoyment and satisfaction experienced by them in their general activities of daily functioning [33]. The Q-LES-Q-SF is comprised of 15 general activity items and one overall life satisfaction item. A summary score is calculated for the general activities items and for the overall life satisfaction item. Higher scores indicate greater enjoyment or satisfaction.

## Patient Health Questionnaire depression questions

The PHQ is a self-administered version of the Primary Care Evaluation of Mental Disorders (PRIME-MD) instrument. The nine-item depression scale of the PHQ is used to measure the severity of depression and consists of the nine DSM-IV criteria used to diagnose major depressive disorder [34]. The current study used the PHQ-8, which excludes the suicide item of the PHQ-9. Higher scores indicate greater depression severity.

## SF-12 Health Survey version 2

The SF-12v2 was developed as a shorter version of the SF-36 Health Survey version 2 based on regression methods [35] and provides physical component summary (PCS) and mental component summary (MCS) scores. The SF-12 instrument has proven to be useful in comparing general and specific study samples, comparing the relative burden of diseases, differentiating the health benefits produced by a wide range of different treatments, and screening individual patients [35]. The interview administration version of the SF-12v2 was used in this study.

## SF-6D index

The SF-6D is a preference-based measure derived from selected items in the SF-12 [36]. The scoring algorithm for the index was generated based on standard gamble methods in a United Kingdom general population sample. SF-6D cores range from 0.30 to 1.0, and higher scores indicate better health status.

## Health Utilities Index Mark 2 and Mark 3 interview (HUI2/HUI3)

The HUI was used as a measure of health utilities in this study. The HUI is a preference-based measure of HRQL which can be administered in an in-person or telephone interview [37–39]. The combined interviewer-administered HUI2/HUI3 is comprised of the minimum number of questions required to classify a participant's health status according to the classification systems of both HUI2 and HUI3 [37–39]. This version of the questionnaire is phrased to capture responses from a broad range of participants about their health status. The recall period used in the study was the past 4 weeks. HUI2 and HUI3 have some overlap, but are often used together because the two measures complement each other. For example, the concepts related to the emotion domain in HUI2 are referred to as "worry" and "anxiety," whereas in HUI3, emotion is "happiness" versus "depression." Both measures evaluate pain severity,

but HUI2 focuses on the use of analgesia, while HUI3 targets the disruption of activities. Self-care is only addressed in HUI2, and dexterity is only available in HUI3. HUI2 and HUI3 have been widely used in clinical studies, providing valuable benchmark results for comparisons. HUI3 has been used in four major Canadian population health surveys, generating extensive data on population norms [21]. Recently, HUI3 (and in one case for HUI2) was included in a nationally representative population health survey of community-dwelling subjects in the United States, so population norm data for HUI is available for the US [40, 41].

### Sheehan Disability Scale

The Sheehan Disability Scale (SDS) is a patient-reported three-item questionnaire that was designed to assess mental health-related functional impairment [42]. The three scale questions are phrased, "To what extent have emotional symptoms disrupted your (work, family, or social) life in the past month?" Participants are asked to respond to each question on a ten-point scale from 0 (Not at all) to 10 (Extremely). A "Not applicable" response option is offered for the first question pertaining to work. The total score for the scale ranges from 0 to 30, with higher scores indicating greater impairment.

### Statistical analyses

Descriptive statistics are summarized for patient demographic and clinical characteristics, and for the patient-reported outcomes and the clinical rating scales. Pearson correlations were examined between the HAM-A, GAD-Q-IV, and PHQ scores and the SF-12 PCS and MCS, Q-LES-Q, SDS, HUI2, HUI3, and SF-6D scores at the baseline visit. We expected that greater anxiety symptom severity and greater depression symptom severity would be associated with greater impairment to HRQL (i.e., PCS, MCS, Q-LES-Q), more disability (i.e., SDS), and lower health utility (i.e., HUI, SF-6D) scores.

Analysis of variance (ANOVA) models were used to evaluate the mean HRQL, disability, and utility scores by levels of anxiety severity at baseline and at 3 months. Anxiety severity was based on the HAM-A and patients were categorized as asymptomatic ($\leq 9$), mild (10–15), moderate (16–24), or severe ($\geq 25$). The ANOVA models compared the mean HUI2, HUI3, SF-6D, PCS, MCS, Q-LES-Q, and SDS scores by anxiety severity groups. Statistically significant overall effects ($P < 0.05$) were followed by post-hoc group comparisons by Scheffe's test.

Ordinary least squares regression analysis was used to examine the relationship between the clinical measures (i.e., HAM-A, PHQ, GAD-Q-IV) and the HRQL measures. The

regression models also included age, gender (1 = female), and education (college vs. <college).

The mean PCS and MCS scores for the GAD sample were compared with the mean SF-12 PCS and MCS scores collected from the Medical Expenditures Panel Survey (MEPS), a nationally representative sample of the non-institutionalized US civilian population [43] and the SF-12 manual [35]. In addition, we compared the mean PCS and MCS scores, based on the SF-36, with those from a sample of primary-care patients with major depressive disorder reported in a previously completed study [44]. Previous research has indicated that PCS and MCS scores from either the SF-12 or SF-36 are comparable [35]. t-tests for independent groups were used for comparisons of the mean SF-12 summary scores between the GAD and MEPS samples and between the GAD and the depression samples. In addition, the mean HUI2 and HUI3 scores were compared to the mean HUI2 and HUI3 scores from the US general population data reported in Luo et al. [41]. t-tests for independent groups were used for comparisons of the mean HUI scores between the GAD and Luo et al. [41] samples.

For all statistical tests, a P-value of 0.05 was used to evaluate statistical significance. There was no formal adjustment for multiple statistical tests, but the interpretation of significance tests took into account the number of comparisons.

## Results

A total of 297 patients with GAD completed the baseline interview. The sample was primarily female (72%) and Caucasian (92%), with a mean age of 47.6 years (standard deviation [SD] = 13.7) (Table 1). About 43% were employed full-time and most completed some college education (38%) or had college degrees (37%).

At baseline, the mean HAM-A score was 16.7 (SD = 7.2). About 34% of the patients reported HAM-A scores between 16 and 24, and 16% had scores greater than or equal to 25. The mean GAD-Q-IV scores was 6.0 (SD = 3.0) and the mean PHQ score was 11.0 (SD = 0.6). The mean HRQL scores at baseline are reported in Table 2.

### Relationship between clinical and HRQL outcomes

At baseline, the HAM-A scores were significantly correlated with PCS, MCS, Q-LES-Q-SF, SDS, SF-6D, and HUI scores (Table 2). Greater anxiety symptoms were associated with greater impaired HRQL, more disability, and lower health utility scores. Anxiety symptoms, as assessed by the GAD-Q-IV, were also moderately and significantly correlated with all of the HRQL measures, except for the

**Table 1** Demographic characteristics for the generalized anxiety disorder (GAD) patient sample ($n = 297$)

| | |
|---|---|
| Age, years, mean (SD) | 47.6 (13.7) |
| Female, % | 72.4 |
| Caucasian, % | 91.9 |
| Education, % | |
|     Elementary school | 3.4 |
|     High school | 20.9 |
|     Some college | 38.4 |
|     College degree | 37.1 |
| Employment status, % | |
|     Employed full-time | 43.1 |
|     Employed part-time | 13.5 |
|     Retired | 17.5 |
|     Unemployed | 8.8 |
|     Homemaker | 6.7 |
|     Disabled | 6.4 |
|     Other | 4.0 |

**Table 2** Baseline mean health-related quality of life (HRQL) scores and correlations with clinical measures

| HRQL score | Mean (SD) | Correlations | | |
|---|---|---|---|---|
| | | HAM-A | GAD-Q-IV | PHQ |
| SF-12 PCS | 45.0 (10.3) | −0.39** | −0.13* | −0.32** |
| SF-12 MCS | 43.1 (8.3) | −0.40** | −0.49** | −0.64** |
| Q-LES-Q-SF | 55.8 (16.5) | −0.60** | −0.42** | −0.72** |
| SDS | 13.7 (7.7) | 0.41** | 0.49** | 0.58** |
| HUI2 | 0.54 (0.2) | −0.52** | −0.43** | −0.52** |
| HUI3 | 0.46 (0.3) | −0.54** | −0.44** | −0.57** |
| SF-6D | 0.62 (0.1) | −0.52** | −0.38** | −0.64** |

\* $P < 0.05$; \*\* $P < 0.0001$

HAM-A, Hamilton Anxiety Scale; GAD-Q-IV, Generalized Anxiety Disorder Questionnaire-IV; PHQ, Patient Health Questionnaire depression; SF-12, Short-Form 12 Health Survey; PCS, physical component summary score; MCS, mental component summary score; Q-LES-Q-SF, Quality of Life Enjoyment and Satisfaction Questionnaire—Short Form; SDS, Sheehan Disability Scale; HUI2, Health Utilities Index Mark 2; HUI3, Health Utilities Index Mark 3

PCS ($r = -0.13$, $P < 0.05$). Depression symptom severity, as assessed by the PHQ, was significantly correlated with the HRQL scores, where greater depression severity was associated with more impaired HRQL and greater reported disability. Comparable correlations were observed at the 3-month and 6-month follow-up visits (data not shown).

HRQL outcomes by anxiety severity

The mean HRQL and utility scores varied significantly by anxiety severity at baseline (Table 3) and after 3 months of follow-up, except for differentiating between the

asymptomatic and mild groups (Table 4). At baseline, the Q-LES-Q-SF, SDS, HUI2, HUI3, and SF-6D were most sensitive to differences in HAM-A-based severity. For example, the Q-LES-Q scores differentiated between each level of anxiety severity, with the least impaired Q-LES-Q-SF scores observed in the asymptomatic and mildly symptomatic groups. Compared with the HUI2, the mean HUI3 scores were more sensitive to increasing anxiety severity, with mean scores of 0.39 and 0.17 in the moderate and severe anxiety groups, respectively. The mean SF-6D scores varied with anxiety severity from 0.53 for the severe to 0.72 for the asymptomatic groups (Table 3).

Similar results were seen at 3 months, with the Q-LES-Q-SF, SDS, SF-6D, HUI2, and HUI3 differentiating among the anxiety severity groups (Table 4). At 3 months, the HUI2 and HUI3 scores were not significantly different between the asymptomatic and mild severity groups ($P > 0.05$). The mean SF-6D scores varied significantly between all of the anxiety severity groups. Those patients with more severe anxiety symptoms reported more impaired physical functioning and well-being and psychological well-being, and quality of life, greater disability in their everyday lives, and lower health preference scores.

Regression analyses

The results of the regression analyses are summarized in Table 5. MCS scores were more closely associated with depression and GAD-related symptoms than PCS scores. The SDS was significantly associated with GAD and depressive symptoms, and the Q-LES-Q was significantly associated with all three symptom scales. The symptom measures explained 38% (HUI2) to 46% (SF-6D) of the variance in the preference-based measures (Table 5). The HAM-A, PHQ, and GAD-Q-IV were all significant predictors of the preference-based scores.

Normative comparisons of HRQL measures

The mean baseline SF-12 PCS and MCS scores were significantly lower in the GAD study sample than in the SF-12 normative data or in the MEPS data (all $P < 0.001$; Table 6). Compared to MEPS, the GAD patients reported mean PCS scores that were 3.9 points lower and mean MCS scores that were 7.0 points lower. The GAD group reported significantly more impaired mean PCS scores compared with the depressed sample (45.0 vs. 51.0, $P < 0.001$), but the depressed sample reported significantly worse mean MCS scores (28.3 vs. 43.1, $P < 0.001$).

The GAD patients had mean HUI2 scores that were substantially more impaired than those reported by the US general population (0.50 vs. 0.86, $P < 0.05$) or the US general population aged 45–64 years (0.50 vs. 0.83,

**Table 3** Mean HRQL outcomes by anxiety severity at baseline

| Measure | Asymptomatic HAM-A ≤ 9 Mean (SD) (n = 47) | Mild 10 ≤ HAM-A ≤ 15 Mean (SD) (n = 101) | Moderate 16 ≤ HAM-A ≤ 24 Mean (SD) (n = 102) | Severe HAM-A ≥ 25 Mean (SD) (n = 46) | Overall test[a] | P-value[b] |
|---|---|---|---|---|---|---|
| SF12-PCS | 49.80 (7.1) | 47.48 (8.5) | 43.56 (10.4) | 37.56 (12.2) | <0.0001 | 2:** 3:* 4:* 5:*** 6:*** |
| SF12-MCS | 49.65 (6.8) | 43.88 (7.1) | 41.42 (8.1) | 38.43 (8.6) | <0.0001 | 1:*** 2:*** 3:*** 5:*** |
| Q-LES-Q-SF | 72.43 (10.7) | 59.17 (13.4) | 51.41 (13.5) | 40.83 (16.4) | <0.0001 | 1:*** 2:*** 3:*** 4:*** 5:*** 6:*** |
| SDS | 7.24 (5.5) | 12.77 (7.1) | 15.64 (7.7) | 17.93 (6.8) | <0.0001 | 1:*** 2:*** 3:*** 4:* 5:*** |
| HUI2 | 0.70 (0.2) | 0.59 (0.2) | 0.50 (0.2) | 0.36 (0.2) | <0.0001 | 1:* 2:*** 3:*** 4:* 5:*** 6:*** |
| HUI3 | 0.68 (0.2) | 0.54 (0.3) | 0.39 (0.3) | 0.17 (0.3) | <0.0001 | 1:* 2:*** 3:*** 4:*** 5:*** 6:*** |
| SF-6D | 0.72 (0.1) | 0.64 (0.1) | 0.60 (0.1) | 0.53 (0.1) | <0.0001 | 1:*** 2:*** 3:*** 4:*** 5:*** 6:** |

* $P \leq 0.05$; ** $P < 0.01$; *** $P < 0.001$

[a] Proc GLM was performed to compare groups

[b] Pairwise comparisons between means were performed using Scheffe's method to adjust the P-values for multiple comparisons. 1, Asymptomatic vs. Mild; 2, Asymptomatic vs. Moderate; 3, Asymptomatic vs. Severe; 4, Mild vs. Moderate; 5, Mild vs. Severe; 6, Moderate vs. Severe

**Table 4** Mean HRQL outcomes by anxiety severity at 3 months

| Measure | Asymptomatic HAM-A ≤ 9 Mean (SD) (n = 68) | Mild 10 ≤ HAM-A ≤ 15 Mean (SD) (n = 76) | Moderate 16 ≤ HAM-A ≤ 24 Mean (SD) (n = 71) | Severe HAM-A ≥ 25 Mean (SD) (n = 31) | Overall test[a] | P-value[b] |
|---|---|---|---|---|---|---|
| SF12-PCS | 48.65 (6.8) | 44.97 (10.1) | 43.37 (9.2) | 36.81 (9.6) | <0.0001 | 2:** 3:*** 5:*** 6:** |
| SF12-MCS | 50.21 (6.3) | 46.90 (6.7) | 42.93 (7.0) | 36.02 (9.2) | <0.0001 | 2:*** 3:*** 4:* 5:*** 6:*** |
| Q-LES-Q-SF | 70.82 (14.5) | 61.89 (13.1) | 53.89 (14.6) | 38.65 (14.8) | <0.0001 | 1:** 2:*** 3:*** 4:*** 5:*** 6:*** |
| SDS | 5.68 (5.0) | 10.65 (6.4) | 14.12 (6.9) | 18.79 (7.8) | <0.0001 | 1:*** 2:*** 3:*** 4:*** 5:*** 6:* |
| HUI2 | 0.71 (0.2) | 0.63 (0.2) | 0.50 (0.2) | 0.32 (0.1) | <0.0001 | 2:*** 3:*** 4:** 5:*** 6:*** |
| HUI3 | 0.68 (0.2) | 0.56 (0.3) | 0.41 (0.3) | 0.07 (0.2) | <0.0001 | 2:*** 3:*** 4:** 5:*** 6:*** |
| SF-6D | 0.71 (0.1) | 0.65 (0.1) | 0.59 (0.1) | 0.50 (0.1) | <0.0001 | 1:** 2:*** 3:*** 4:** 5:*** 6:** |

* $P \leq 0.05$; ** $P < 0.01$; *** $P < 0.001$

[a] Proc GLM was performed to compare groups

[b] Pairwise comparisons between means were performed using Scheffe's method to adjust the P-values for multiple comparisons. 1, Asymptomatic vs. Mild; 2, Asymptomatic vs. Moderate; 3, Asymptomatic vs. Severe; 4, Mild vs. Moderate; 5, Mild vs. Severe; 6, Moderate vs. Severe

**Table 5** Relationship between anxiety and depression symptoms and HRQL measures (unstandardized regression coefficients)

| | HRQL measures | | | | | | |
|---|---|---|---|---|---|---|---|
| | PCS | MCS | Q-LES-Q-SF | SDS | HUI2 | HUI3 | SF-6D |
| Intercept | 63.2*** | 52.6*** | 84.8*** | 4.2* | 0.97*** | 1.05*** | 0.82*** |
| Age (years) | −0.167*** | 0.063* | −0.007 | −0.049 | −0.001 | −0.002 | −0.000 |
| Gender (1 = female) | −0.629 | 0.164 | 1.018 | 0.204 | −0.001 | −0.013 | −0.019 |
| Education (1 = college) | 0.698 | 0.074 | 1.272 | 0.101 | −0.023 | −0.001 | 0.004 |
| HAM-A | −0.437*** | 0.027 | −0.539*** | 0.047 | −0.008*** | −0.011*** | −0.003** |
| GAD-Q-IV | 0.119 | −0.746*** | −0.618* | 0.732*** | −0.015*** | −0.020*** | −0.004* |
| PHQ | −0.318* | −0.792*** | −1.575*** | 0.589*** | −0.012*** | −0.020*** | −0.010*** |
| $R^2$ | 0.22 | 0.47 | 0.57 | 0.41 | 0.38 | 0.42 | 0.46 |

* $P \leq 0.05$; ** $P < 0.01$; *** $P < 0.001$

HAM-A, Hamilton Anxiety Scale; GAD-Q-IV, Generalized Anxiety Disorder Questionnaire-IV; PHQ, Patient Health Questionnaire depression; SF-12, Short-Form 12 Health Survey; PCS, physical component summary score; MCS, mental component summary score; Q-LES-Q-SF, Quality of Life Enjoyment and Satisfaction Questionnaire—Short Form; SDS, Sheehan Disability Scale; HUI2, Health Utilities Index Mark 2; HUI3, Health Utilities Index Mark 3

**Table 6** Mean SF-12 physical component and mental component summary scores for GAD, SF-36 normative, MEPS, and depression study samples

| SF-12 summary score | GAD study ($n = 297$) Mean (SD) | SF-12 norms[a] ($n = 6,917$) | MEPS[b] ($n = 20,761$) | Depression[c] ($n = 536$) |
|---|---|---|---|---|
| Physical component summary score | 45.0 (10.3) | 49.6 (9.9) | 48.9 (11.1) | 51.0 (10.9) |
| Comparison with GAD sample, $P$-value[d] | | $P < 0.001$ | $P < 0.001$ | $P < 0.001$ |
| Mental component summary score | 43.1 (8.3) | 49.4 (9.8) | 50.1 (10.3) | 28.3 (10.4) |
| Comparison with GAD sample, $P$-value[d] | | $P < 0.001$ | $P < 0.001$ | $P < 0.001$ |

[a] Reported in [35], summary scores based on SF-12

[b] From [43], summary scores based on SF-12

[c] Reported in [44], summary scores based on SF-36

[d] $P$-value from $t$-test for independent groups

$P < 0.05$). The mean HUI3 scores were also significantly more impaired compared with the US general population (0.50 vs. 0.81, $P < 0.05$) or the US general population aged 45–64 years (0.50 vs. 0.78, $P < 0.05$).

## Discussion

This study demonstrated that anxiety severity is associated with significant impairments in psychological well-being, physical functioning, and disease-specific quality of life and increased disability in everyday life in patients with GAD. Patients with GAD also demonstrated significant impairments in general health status and health utilities compared with the general US population. GAD symptoms impact patient HRQL and functioning, and increasing anxiety symptom severity is related to greater impairment of HRQL.

Anxiety symptoms, as assessed by the HAM-A or GAD-Q-IV, were moderately related to measures of generic

health status, disease-specific quality of life, disability, and health utilities. Symptom severity and frequency were associated with greater impairments to generic measures of physical functioning and well-being and psychological well-being. As expected, the psychiatric disease-specific quality of life measure (i.e., Q-LES-Q-SF) was more strongly related to anxiety symptoms than the generic health status measures. These findings further support and extend previous research on the burden of GAD and anxiety on HRQL outcomes [2, 9–13]. The health utility measures were also moderately correlated with both anxiety and depression symptom measures, indicating that greater symptomatology was associated with lower health utility scores. The greater impairment in HUI3 scores may be due, in part, to the content of the emotional domain focus on happiness and depression, and may be more sensitive to comorbid GAD and depression, whereas the HUI2 emotional domain assesses worry and anxiety.

Depressive symptoms were also significantly associated with the HRQL measures in this primary-care GAD

sample. The strongest relationships were seen between measures of depression and the MCS, Q-LES-Q-SF, SDS, SF-6D, and the HUI measures. In all cases, greater depression symptoms were associated with more impairment in HRQL, greater disability, and lower health utility scores. These findings were not unexpected, given that previous research demonstrated the impact of GAD and depression on HRQL outcomes [2, 10, 11], although some research suggests that the impact may be mostly due to depression severity [14]. Future studies need to more clearly delineate the severity of GAD and the severity of depression to determine the burden on patient HRQL and functioning.

The regression analyses indicated that anxiety and depressive symptoms predicted about 22% (PCS) to 57% (Q-LES-Q) of the variance in the HRQL measures. For the health preference-based measures, anxiety and depressive symptoms were significant predictors, indicating that preference scores were more impaired in those patients reporting greater depression or anxiety severity. Clearly, patients with both GAD and depressive symptoms have more impaired HRQL.

The impact of moderate to severe anxiety symptoms was further demonstrated by the ANOVA analyses. We observed that the mean generic health status, Q-LES-Q-SF, SDS, and health utility scores varied significantly by anxiety severity groups based on the HAM-A. The patients categorized as having severe or moderate anxiety symptoms reported significantly more impaired psychological well-being, physical functioning and well-being, disease-specific quality of life, and health utility scores, and more disability compared with those in the asymptomatic and mild anxiety severity groups. There was a clear and consistent differentiation between the anxiety severity groups and the HRQL and disability measures. Further, it is important to note the differences in the mean overall HUI2, HUI3, and SF-6D scores by category based on the HAM-A (asymptomatic, mid, moderate, and severe) exceedance guidelines for clinically important differences in the overall scores of 0.03 for HUI2 and HUI3 [38] and 0.033 for SF-6D [45, 46].

More important for evaluations of the cost-effectiveness of new interventions for GAD, the health utility measures were very sensitive to varying anxiety severity. Both the HUI2 and HUI3 scores significantly discriminated among all of the anxiety severity groups at baseline and for all but the asymptomatic and mild severity groups at 3 months. Patients with moderate severity reported mean HUI2 and HUI3 scores of 0.50 and 0.39, respectively, while the severe group reported mean scores of 0.36 for HUI2 and 0.17 for HUI3. These HUI scores demonstrate very considerable impairments to preference-based HRQL and are significantly lower than the general population [41] or other chronic disease groups [40]. These results indicate

the burden of GAD and increasing symptom severity on patient HRQL. Effective treatments for GAD which alleviate anxiety symptoms may also be associated with large increases in QALYs and may result in favorable cost-effectiveness outcomes.

To our knowledge, the HUI2 or HUI3 has not been included in a study of patients with anxiety or major depressive disorder. However, these measures have been included in studies of patients with type 2 diabetes and research has demonstrated that comorbid depression in diabetes patients is associated with a −0.17 decrement in HUI3 scores, after adjusting for demographic characteristics and other medical conditions [47]. This suggests that the mean HUI3 scores are 0.51 in patients with both diabetes and depression. A GAD diagnosis comorbid to major depressive disorder was associated with a decrement of −0.30 in the Quality of Well-Being Scale scores [16], indicating added impairment to the utility scores.

The normative comparisons of PCS and MCS scores also demonstrate the impact of GAD on HRQL. Compared to the MEPS data, this primary-care GAD sample demonstrated significant impairments to both PCS and MCS scores. For PCS scores, the increased impairment was approximately 0.35 SD units and for MCS scores, the difference was approximately 0.68 SD units. Comparable differences were also seen between the GAD sample and the SF-36 normative sample. Although the GAD sample reported more impairment on PCS scores (45.0 vs. 51.0), they were less impaired on MCS scores (43.1 vs. 28.3) compared with a sample of primary-care patients with major depressive disorder who were beginning antidepressant treatment. Differences of 2.5–3.0 points on the MCS and PCS scores are considered to be clinically meaningful [35], and the observed differences are clearly clinically significant.

We compared the health utility scores for this GAD patient sample to those reported in a US national sample [41]. The mean HUI2 scores were 0.36 points lower than the HUI2 scores in the US general population and 0.33 points lower than those aged 45–65 years. For the mean HUI3 scores, the difference was 0.31 points for the general US population and 0.28 points lower for those aged 45–65 years. These represent very large differences, and suggest considerable HRQL burden associated with GAD. The HUI2 and HUI3 scores suggest that GAD is associated with comparable or greater impairments to health status compared with chronic medical conditions, such as diabetes, rheumatoid arthritis, and cardiovascular disease.

Several study limitations should be considered when reviewing these findings. First, the participating patients were all recruited from a managed care organization from a listing of patients with GAD or anxiety, and not otherwise specified diagnoses. While all patients met DSM-IV-TR

diagnostic criteria at study entry, differences between these patients and study non-participants and the general population of GAD patients may affect the generalizability of the study results. Second, the anxiety and depression symptom and HRQL assessments are based on telephone interviews and patient self-reporting. While directly asking the individual about their symptoms and the impact on functioning and well-being is the only way to obtain these data, patients may under- or over-estimate the impact on HRQL. However, the consistency of results across several HRQL measures would seem to obviate any self-reporting bias.

In conclusion, these findings indicate that anxiety symptoms in primary-care patients with GAD are associated with impairments in generic health status, disability, disease-specific quality of life, and preference-based measures of HRQL. The comparisons of HRQL outcomes for the GAD sample and different US general population samples suggest the significant impact on GAD on reducing patient-reported HRQL. The greatest impact on patient functioning and well-being was reported by those patients with moderate to severe anxiety symptoms. Significant and consistently decreased health utility scores observed in these GAD patients indicate that potential improvements in QALYs may be achieved with effective treatment strategies that significantly alleviate anxiety symptoms and depressive symptoms, given the frequent depressive comorbidity in GAD patients.

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