Health and Quality of Life Outcomes

Research

Health-related quality of life improves with treatment-related GERD symptom resolution after adjusting for baseline severity

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Published: 29 November 2003

Health and Quality of Life Outcomes 2003, **1**:73

Received: 11 August 2003
Accepted: 29 November 2003

This article is available from: http://www.hqlo.com/content/1/1/73

Abstract

Severity and frequency of gastroesophageal reflux disease (GERD) related symptoms are associated with impaired health-related quality of life (HRQL). This study evaluated the association between baseline heartburn severity and endpoint HRQL of patients treated for heartburn and the relationship between complete resolution of heartburn symptoms and HRQL outcomes after controlling for baseline severity. We completed a secondary analysis of clinical symptom and HRQL data from three clinical trials in adult patients receiving either omeprazole or ranitidine treatment for GERD. HRQL was assessed using the Psychological General Well-Being Index (PGWB) in each of the three clinical trials, and two of the trials also included the Medical Outcomes Study Sleep disturbance scale. Gastrointestinal symptoms were evaluated using either the Gastrointestinal Symptom Rating Scale or a modified version of the scale. Baseline heartburn severity (none/minor, mild, moderate or severe) was defined based on patient-reported symptoms. Analysis of covariance (ANCOVA) models were used to compare mean HRQL scores by baseline level of heartburn symptom severity and whether or not patients experienced complete heartburn resolution. At baseline, PGWB scores were significantly worse ($p < 0.05$) for patients with more severe heartburn symptoms. There were no statistically significant baseline severity by symptom resolution interactions in any of the ANCOVA models. For all three trials and across all follow-up assessments, mean PGWB scores were statistically significantly higher for patients with completely resolved heartburn symptoms versus those whose symptoms were unresolved (all p-values < 0.05). Few significant effects were observed for sleep disturbance scores. While the severity of heartburn symptoms at the start of medical treatment for GERD is not associated with improvements in HRQL in subsequent weeks of treatment, complete resolution of symptoms is associated with improvements in psychological well-being.

Introduction

Gastroesophageal reflux disease (GERD) is common in the general population and represents a frequent reason for visits in primary care practices [1-4]. The spectrum of

disease manifestations associated with GERD ranges from mild heartburn to erosive esophagitis and, less commonly, may generally include more serious medical conditions such as esophageal ulcer, esophageal stricture, and a pre-cancerous condition known as Barrett's esophagus [1]. Effective treatment of GERD is necessary to heal the esophagus and to provide symptom relief. The frequency and severity of symptoms associated with GERD have been demonstrated to diminish patient health-related quality of life (HRQL) [5-8]. Studies have shown that medical intervention in the treatment of GERD provides improvement in GERD-related symptoms and in turn, an improvement in well-being and functioning (i.e., HRQL) [5,9-14]. Revicki et al. have demonstrated an association between the complete resolution of heartburn symptoms and improvements in measures of HRQL [15]. Few studies have been published relating the severity of GERD symptoms at the start of treatment with HRQL outcomes throughout the course of treatment. Of further interest is whether complete resolution of heartburn symptoms has the same effect on patients in terms of HRQL given more or less severe symptoms at the start of treatment.

The primary objectives of this study were to evaluate the association between baseline heartburn severity and endpoint HRQL in patients treated for heartburn; and to examine the relationship between complete resolution of heartburn symptoms, while controlling for baseline severity, and HRQL outcomes. Previous research indicates that baseline severity of disease and health status scores may be associated with changes in HRQL outcomes [16,17] where patients with very severe disease (and worse HRQL) may demonstrate differential impact of effective medical therapy than those with milder disease. Since the diagnosis of GERD and related treatment decisions are based on severity of symptoms and the reported interference of GERD symptoms with patient well-being [18], clinicians treating patients with GERD are concerned about differential effects of treatment by initial disease severity. It is therefore useful to evaluate whether the association between symptom resolution and HRQL varies by baseline disease severity, since there may be differences in proportion of patients who experience symptom resolution, depending on pre-treatment disease severity. We performed a secondary analysis of three clinical trials comparing omeprazole and ranitidine to evaluate the relationship between severity of heartburn symptoms at the start of treatment and HRQL at subsequent weeks of treatment. A secondary objective was to evaluate whether complete resolution of heartburn symptoms, while controlling for baseline severity, results in improved well-being and functioning. The latter objective extends previous work that demonstrated complete resolution of these symptoms improves HRQL [15].

Methods

Data sources

Data from three clinical trials were used to evaluate the relationship between baseline level of heartburn symptom severity and HRQL. Each of the three trials was originally designed to compare the effectiveness of omeprazole versus ranitidine in the treatment of patients with symptoms of GERD.

Clinical Trial 1

This two-phase multi-center trial was designed to compare omeprazole and ranitidine in the treatment of patients with at least moderate to severe heartburn symptoms and to evaluate HRQL in patients with poorly responsive symptomatic GERD [5,13]. Phase 1 (open label) enrolled 533 patients with a 6 month or longer history of heartburn, including moderate to severe heartburn during four out of the last 7 days prior to the start of the phase. Patients enrolled in the open label phase were started on ranitidine 150 mg twice daily for 6 weeks. Patients who experienced one or more episodes of moderate to severe heartburn during Week 6 and who had taken at least nine ranitidine tablets during Week 6 were classified as non-responsive. These patients were eligible for Phase 2 (double-blind) and were randomized to receive either omeprazole 20 mg once daily or ranitidine 150 mg twice daily for 8 weeks. Three hundred sixteen patients (59%) were randomized in the double blind phase of the trial; baseline and 8-week data were included in this secondary analysis.

Clinical Trial 2

The second study was a multi-center, double-blind, randomized clinical trial designed to compare omeprazole and ranitidine in the treatment of heartburn and included baseline and follow-up data (weeks 4, 8, 12, and 16) [14]. Eligible subjects were drawn from four large managed care health plans and were under the care of a primary care physician. To be enrolled, patients had to be at least 18 years of age, have heartburn, and have their physician consider them appropriate candidates for treatment of suspected GERD. Heartburn was defined as a rising, uncomfortable burning feeling in the chest behind the breastbone. Patients were randomly assigned to receive either omeprazole 20 mg once daily or ranitidine 150 mg twice daily. Six hundred eighty-five patients were enrolled in this study.

Clinical Trial 3

This clinical trial was a prospective, multi-center, open-label, randomized trial designed to evaluate the effectiveness of omeprazole versus ranitidine in the initial treatment of patients with GERD [8,19]. Patients were enrolled over a 24-month period from five family practice clinics in the Charleston, West Virginia area. All enrolled patients were at least 18 years of age, were clinically diagnosed as

having GERD, and were determined to need pharmaceutical intervention in the treatment of GERD based on frequency of heartburn / acid regurgitation. Patients were randomly assigned to receive either omeprazole 20 mg once daily or ranitidine 150 mg twice daily. This study population had a higher level of chronic illness than the other two study populations with 61% of the patients reporting one or more medical co-morbidities. Secondary analyses included data collected at baseline, 4-, 12-, and 24-week follow-up from 251 patients.

Health-Related Quality of Life Measures

The Psychological General Well-Being Index (PGWB) was used to evaluate health-related quality of life in each of the three clinical trials. The Medical Outcomes Study (MOS) Sleep Disturbance scale was also included in Clinical Trial 1 and Clinical Trial 3.

The PGWB measures psychological well-being and distress [20,21]. The instrument is composed of 22-items which, when scored, constitute 6 subscales and one total score with higher scores indicating better health status and psychological well-being. Subscale scores include anxiety, depression, self control, positive well-being, general health, and vitality. Normal values for the total score are considered to fall in the range of 100–105, with women generally reporting lower well-being than men [6]. The PGWB has good evidence supporting internal consistency, test-retest reliability and validity, and has been shown to be sensitive to gastrointestinal disease occurrences [6,7,9,13,21-23]. For the purposes of this study only the PGWB total score was examined.

The MOS Sleep Disturbance scale [24], included in Clinical Trials 1 and 3, is composed of four items pertaining to sleep initiation and maintenance. The sleep scale ranges from 0 to 100 with higher scores indicating better sleep quality (i.e., less sleep disturbance). The MOS Sleep Disturbance score has been evaluated and demonstrates good reliability and validity [24].

Clinical Measures

To evaluate the gastrointestinal symptoms of patients, Clinical Trial 1 used both diary cards and the Gastrointestinal Symptom Rating Scale (GSRS). Diary cards were completed by patients each day for a 1-week period prior to both the baseline and the 8-week HRQL assessment [13]. Ninety-seven percent of patients provided complete diary data during the study. The GSRS is a 15-item, disease specific instrument used to evaluate common gastrointestinal symptoms [23,25]. The items are measured on a 7-point Likert-type scale ranging from 1 = 'no discomfort' to 7 = 'very severe discomfort'. The GSRS was administered at baseline and 8-week follow-up. To assess the gastrointestinal symptoms in Clinical Trial 2, patients were asked about how much of the time during the past 7 days they were bothered by each of three symptoms: heartburn, regurgitation, and difficulty swallowing. These three questions were asked at baseline and follow-up weeks 4, 8, 12, and 16 and were measured on a 6-point response scale: from 1 = 'none of the time' to 6 = 'all of the time' [14]. Clinical Trial 3 used the GSRS to assess gastrointestinal symptoms of patients at baseline and follow-up weeks 4, 12, and 24.

Baseline Heartburn Severity

Baseline heartburn severity (i.e., none/minor, mild, moderate, severe) was defined based on their level of heartburn symptoms. For Clinical Trial 1 and Clinical Trial 3 baseline severity was determined using the GSRS heartburn item: *Have you been bothered by HEARTBURN during the past week? (by heartburn we mean a burning pain or discomfort behind the breastbone in your chest)*. For Clinical Trial 2 severity was determined based on the patients' indicated frequency (i.e., 'none of the time' to 'all of the time') of bothersome heartburn during the 7 days prior to baseline assessment.

Complete Symptom Resolution

For Clinical Trial 1 diary data were used to define whether or not patients were experiencing complete resolution of heartburn symptoms. Using these data, complete resolution of heartburn symptoms was defined for persons who specified no episodes of heartburn during the 7 days prior to the follow-up visit [15]. For Clinical Trial 2, patients indicating that they were bothered by heartburn 'none of the time' during the 7 days prior to the follow-up visit were classified as completely resolved [15]. For Clinical Trial 3, completely resolved patients were identified using the GSRS heartburn item. Complete resolution status was determined at each follow-up period across each of the three studies [15].

Statistical Analyses

PGWB total and MOS Sleep Disturbance scores were compared between patients classified as having none/minor, mild, moderate, or severe heartburn symptoms at start of treatment. Comparisons were conducted for each of the three clinical trials and were performed independent of treatment group assignment. To evaluate whether baseline heartburn severity is associated with endpoint HRQL scores, we focused on the interaction between baseline symptom severity and complete resolution status at follow-up, based on an analysis of covariance (ANCOVA) model. This ANCOVA model included the interaction term and main effects for baseline symptom severity and complete resolution. The covariates included in the models were age, gender, relevant baseline HRQL measure. A separate ANCOVA model was fit for each follow-up assessment for each of the three trials. Patients with

Table 1: Patient demographics and baseline HRQL.

	Clinical Trial 1	Clinical Trial 2	Clinical Trial 3
N	316	685	251
Male%	43%	38%	39%
Caucasian%	89%	69%	91%
Age, mean (s.d.)	45.5 (13.0)	47.9 (14.1)	45.1 (14.1)
Omeprazole%	49%	50%	52%
Heartburn Severity%[1]			
None/Minor	21%	37%	17%
Mild	53%	34%	8%
Moderate	20%	24%	36%
Severe	4%	5%	39%
Missing	2%	0%	0%
Heartburn-related symtoms[2]	3.1 (0.8)	3.9 (1.0)	4.5 (1.8)
PGWB Total, mean (s.d.)	76.3 (16.4)	73.0 (18.2)	58.0 (21.8)
MOS Sleep, mean (s.d.)	67.7 (25.7)	NA	55.5 (29.2)

[1]Based on the diary data, all patients randomized in Phase 2 of Clinical Trial 1 had at least one episode of moderate to severe heartburn (Phase 2 enrollment criteria). Patient responses to the GSRS heartburn item varied compared to the diary data. Hence, a proportion of the population is indicated as having heartburn (during the week previous to the baseline assessment) that was of less than moderate discomfort. [2]GSRS heartburn item (1–7) scale for Clinical Trials 1 and 3 and heartburn item (1–6 scale) for Clinical Trial 2.

missing data for any of the variables included in the models were dropped from the analyses. A second set of ANCOVAs evaluated mean PGWB total scores and Sleep Disturbance scores by symptom resolution status, controlling for baseline symptom severity, age, gender and baseline score. Standard errors (SE) for the covariate adjusted follow-up scores are reported. All statistical tests were two-sided with p-values ≥ 0.05 considered to be statistically significant. Analyses were performed using SAS System Software Package, Version 8.0.

Results

Baseline Characteristics

Patient demographic data and baseline HRQL measures are presented in Table 1. The age distribution of patients was similar across the three trials. The mean age ranged from 45.1 years (SD = 13.0) (Clinical Trial 1) to 47.9 (SD = 14.1) (Clinical Trial 2). The proportion of male patients enrolled in each trial ranged from 38% to 43%. The proportion of Caucasian subjects ranged from 69% to 91% and was less in Clinical Trial 2 compared with the other studies.

The proportion of patients classified as having moderate or severe heartburn symptoms at baseline was substantially greater for Clinical Trial 3 (75%) compared to Clinical Trials 1 (24%) and 2 (29%). The defined level of symptom severity is reflective of the heartburn items used to classify the patients. For example, patients in Clinical Trial 3, when responding to "*Have you been bothered by HEARTBURN during the past week?*" had an average response of 4.5 (on a 7-point scale) compared to 3.1 (based on the same 7-point scale) and 3.9 (6-point scale) for Clinical Trial 1 and Clinical Trial 2, respectively. Baseline HRQL measures were also lower for Clinical Trial 3 reflecting greater impairment at baseline (Table 1).

Relationship Between Baseline Heartburn Severity and HRQL

Table 2 presents mean baseline HRQL measures by baseline severity of heartburn symptoms. Patients experiencing more severe heartburn symptoms reported lower (more impaired) PGWB scores in all three studies ($p < 0.05$) and more sleep disturbance in clinical trials 1 and 3 ($p < 0.05$). For example, patients from Clinical Trial 1 who were classified as having no or minor heartburn symptoms at baseline had a mean baseline Sleep Disturbance score of 74.1 (s.e. = 3.0) while patients classified as having severe heartburn symptoms had a mean baseline Sleep Disturbance score of 36.4 (s.e. = 6.7) ($p < 0.0001$). This indicates that patients with more severe heartburn symptoms also report more problems with their sleep.

Relationship Between Baseline Severity, Symptom Resolution Status, and Endpoint HRQL Outcomes

The ANCOVA models were run using endpoint PGWB total or Sleep Disturbance scores as the dependent variable and including factors for baseline symptom severity and complete resolution status, with adjustment for age, gender and baseline score. The interaction effect of baseline severity of heartburn symptoms and heartburn resolution status was statistically significant in only one of twelve ANCOVA models. Because of very small sample

Table 2: Baseline HRQL by baseline measure of heartburn severity

Baseline level of heartburn severity	Clinical Trial 1			Clinical Trial 2			Clinical Trial 3		
	n[1]	PGWB Total, mean (s.e.)	MOS Sleep, mean (s.e.)	n[1]	PGWB Total, mean (s.e.)	MOS Sleep, mean (s.e.)	n	PGWB Total, mean (s.e.)	MOS Sleep, mean (s.e.)
None/Minor	65	81.0 (1.9) *	74.1 (3.0) *	250	74.5 (1.1) *	NA	43	71.4 (3.1) *	64.1 (4.4) *
Mild	166	77.8 (1.2)	70.3 (1.9)	232	74.9 (1.2)	NA	21	63.0 (4.5)	60.8 (6.4)
Moderate	63	71.0 (2.0)	61.3 (3.1)	165	69.6 (1.4)	NA	90	58.8 (2.2)	58.0 (3.1)
Severe	13	60.1 (4.3)	36.4 (6.7)	36	66.6 (3.0)	NA	97	50.1 (2.1)	48.2 (2.9)

[1]Due to missing data points Ns may not sum to total trial sample size. *p < 0.05 for test of overall differences in means from one-way ANCOVA model.

Table 3: Adjusted mean PGWB total scores by baseline severity of heartburn symptoms

Trial/Follow-up		n	Mean (s.e.)
Clinical Trial 1			
8 Weeks	None/Minor	59	80.5 (1.6)
	Mild	159	80.3 (1.0)
	Moderate	59	82.0 (1.6)
	Severe	13	87.5 (3.5)
Clinical Trial 2			
4 Weeks	None/Minor	237	82.4 (0.8)
	Mild	219	81.8 (0.9)
	Moderate	160	82.5 (1.0)
	Severe	33	82.3 (2.2)
8 Weeks	None/Minor	234	83.4 (0.9)
	Mild	219	82.1 (0.9)
	Moderate	155	83.7 (1.1)
	Severe	35	82.3 (2.3)
12 Weeks	None/Minor	231	84.4 (0.9)
	Mild	217	83.1 (1.0)
	Moderate	151	85.8 (1.2)
	Severe	34	82.5 (2.4)
16 Weeks	None/Minor	229	86.0 (0.9)
	Mild	211	84.8 (1.0)
	Moderate	153	88.4 (1.2)
	Severe	32	86.8 (2.5)
Clinical Trial 3			
4 Weeks	None/Minor	40	76.0 (3.0)
	Mild	21	73.7 (3.9)
	Moderate	79	72.8 (2.0)
	Severe	84	70.9 (2.0)
12 Weeks	None/Minor	37	76.9 (3.2) *
	Mild	17	71.9 (4.5)
	Moderate	71	74.0 (2.3)
	Severe	69	64.3 (2.4)
24 Weeks	None/Minor	37	74.5 (3.5)
	Mild	18	69.6 (4.8)
	Moderate	68	72.4 (2.5)
	Severe	74	67.4 (2.4)

*p < 0.05 for test of overall differences in least square means from ANCOVA model, adjusted for gender, age, relevant baseline PGWB total score, and symptom resolution status.

Table 4: Adjusted mean Sleep Disturbance scores by baseline severity of heartburn symptoms

Trial/Follow-up		N	Mean (s.e.)
Clinical Trial 1			
8 Weeks	None/Minor	59	75.0 (2.3)
	Mild	158	73.9 (1.5)
	Moderate	58	77.3 (2.4)
	Severe	13	74.3 (5.1)
Clinical Trial 3			
4 Weeks	None/Minor	39	75.7 (3.8)
	Mild	20	69.2 (5.1)
	Moderate	72	72.4 (2.7)
	Severe	79	66.4 (2.6)
12 Weeks	None/Minor	36	75.0 (3.8) *
	Mild	16	70.8 (5.6)
	Moderate	66	71.3 (2.9)
	Severe	65	62.8 (2.9)
24 Weeks	None/Minor	33	75.6 (4.3)
	Mild	14	73.3 (6.4)
	Moderate	63	70.0 (3.1)
	Severe	69	66.3 (3.0)

*$p < 0.05$ for test of overall differences in least square means from ANCOVA model, adjusted for gender, age, relevant baseline sleep disturbance score, and symptom resolution status.

sizes for the severe group in this ANCOVA, these findings may not be meaningful. There was no evidence for significant interactions between baseline heartburn severity and complete symptom resolution in any of the models evaluated.

For Clinical Trials 1 and 2, baseline symptom severity was not associated with endpoint PGWB total scores. Covariate adjusted mean PGWB total scores by baseline severity level are presented in Table 3. For example in Clinical Trial 2, severity of baseline heartburn symptoms was not statistically significantly associated with PGWB total score at any follow-up point (Table 3; weeks 4, 8, 12, or 16; all $p > 0.05$). In Clinical Trial 3, baseline severity of heartburn symptoms was a statistically significant factor in the ANCOVA models for PGWB total score at week 12 (Table 3; $p = 0.006$). Adjusted mean PGWB total scores at week 12 were higher for patients classified as having none/minor heartburn symptoms (mean = 76.9; SE = 3.2) and moderate heartburn symptoms (mean = 74.0; SE = 2.3) compared to patients classified as having severe heartburn symptoms (mean = 64.3; SE = 2.4) ($p = 0.0025$ and $p = 0.0031$ respectively).

Baseline symptom severity was not statistically significantly associated with Sleep Disturbance scores in Clinical Trial 1 (see Table 4). In Clinical Trial 3, the overall effect of baseline heartburn severity on week 12 Sleep Disturbance scores was statistically significant ($p = 0.0471$). The adjusted mean Sleep Disturbance scores were higher for patients with none/minor heartburn symptoms (men = 75.0; SE = 3.8) and moderate heartburn symptoms (mean = 71.3; SE = 2.9) compared to those with severe symptoms (mean = 62.8; SE = 2.9) ($p = 0.0113$ and $p = 0.0315$ respectively).

For all three clinical trials, complete heartburn symptom resolution was associated with improved PGWB total scores (see Table 5). In Clinical Trial 1, complete heartburn symptom resolution was a statistically significant factor associated with 8-week PGWB total score ($p = 0.0329$). The adjusted mean PGWB total score at 8-week follow-up was 84.2 (SE = 1.5) for completely resolved patients compared to 80.9 (SE = 1.2) for patients not resolved. In Clinical trial 2, at each follow-up assessment adjusted mean PGWB total scores were consistently higher for patients who experienced complete resolution of heartburn symptoms versus those without heartburn resolution. For weeks 4, 8, and 12 adjusted mean PGWB total scores were 3 points higher for patients experiencing complete resolution of heartburn symptoms compared to those not resolved ($p = 0.0034$, $p = 0.0105$, and $p= 0.0098$ respectively). At week 16, patients who were completely resolved had an adjusted mean PGWB total score 7 points higher than patients who were not resolved ($p < 0.0001$). For Clinical Trial 3, resolution status was statistically significantly associated with differences in adjusted mean PGWB total scores at each follow-up period (see Table 5). The observed difference in adjusted mean PGWB total scores between completely resolved patients and non-

Table 5: Adjusted mean PGWB total score by complete heartburn resolution status

Trial/Follow-up	Resolution Status	n	Mean (s.e.)
Clinical Trial 1			
8 Weeks	Completely resolved	97	84.2 (1.5)*
	Not resolved	193	80.9 (1.2)
Clinical Trial 2			
4 Weeks	Completely resolved	263	83.7 (0.9)*
	Not resolved	386	80.8 (0.8)
8 Weeks	Completely resolved	257	84.3 (1.0)*
	Not resolved	386	81.4 (0.9)
12 Weeks	Completely resolved	250	85.5 (1.0)*
	Not resolved	383	82.4 (0.9)
16 Weeks	Completely resolved	235	90.0 (1.1)*
	Not resolved	390	82.9 (0.9)
Clinical Trial 3			
4 Weeks	Completely resolved	116	77.5 (1.8)*
	Not resolved	108	69.2 (1.9)
12 Weeks	Completely resolved	73	76.2 (2.3)*
	Not resolved	121	67.4 (2.0)
24 Weeks	Completely resolved	72	78.6 (2.5)*
	Not resolved	125	63.3 (2.1)

*$p < 0.05$ for test of overall differences in least square means from ANCOVA model, adjusted for gender, age, relevant baseline PGWB total score, and baseline severity.

Table 6: Adjusted mean Sleep Disturbance scores by complete heartburn resolution status

Trial/Follow-up	Resolution Status	n	Mean (s.e.)
Clinical Trial 1			
8 Weeks	Completely resolved	97	76.3 (2.1)
	Not resolved	191	74.0 (1.7)
Clinical Trial 3			
4 Weeks	Completely resolved	103	72.4 (2.3)
	Not resolved	107	69.5 (2.5)
12 Weeks	Completely resolved	116	72.0 (2.9)
	Not resolved	67	67.9 (2.4)
24 Weeks	Completely resolved	114	74.4 (3.2)
	Not resolved	65	68.1 (2.7)

*$p < 0.05$ for test of overall differences in least square means from ANCOVA model, adjusted for gender, age, relevant baseline sleep disturbance score, and baseline severity.

resolved patients at week 4 and week 12 was 8.3 ($p = 0.0007$) and 8.8 ($p = 0.0021$) respectively. At Week 24 the mean adjusted PGWB total score was approximately 15 points higher for resolved patients compared to non-resolved patients ($p < 0.0001$).

There were no statistically significant differences observed by heartburn symptom resolution on mean Sleep Disturbance scores in the ANCOVA models (see Table 6).

Discussion

This secondary analysis was designed to evaluate the relationship between baseline level of heartburn symptom severity, resolution of heartburn symptoms, and HRQL outcomes assessed at various time-points during pharmaceutical treatment for GERD. This study failed to find evidence supporting the interaction between baseline symptom severity and complete resolution of heartburn symptoms on PGWB total or Sleep Disturbance scores. However, baseline symptom severity was significantly associated with psychological well-being, as measured by

the PGWB, and sleep problems. Those patients reporting greater severity in heartburn symptoms were more likely to report psychological distress and impaired well-being compared with those who reported no or milder symptoms. Heartburn severity was also associated with greater reports of sleep problems in these GERD patients.

We evaluated the relationship between complete resolution of heartburn symptoms and PGWB and Sleep Disturbance scores, after controlling for baseline levels of symptom severity. Baseline heartburn severity was significant in only one model for the PGWB and one model for Sleep Disturbance scores, both for Clinical Trial 3 at the 12 week follow-up. For most of the analyses, baseline symptom severity was not significantly associated with endpoint health outcomes. In general, complete resolution of heartburn symptoms resulted in reports of improved psychological well-being. Those patients reporting complete relief from their heartburn symptoms also reported better psychological well-being. The observed differences in mean PGWB total scores are clinically meaningful, since differences or changes of 4 to 5 points represent the minimally important difference for the PGWB [22,26]. Using a 4-point difference as the criteria for minimal important, 5 out of the 8 comparisons (63%) are clinically meaningful. No association between symptom resolution and Sleep Disturbance scores was observed in this secondary analysis. These results extend previously published results that demonstrated complete resolution of heartburn symptoms is associated with improved patient functioning and well-being [15]. Even after adjusting for baseline symptom severity, complete resolution of heartburn symptoms remains associated with improved psychological well-being. These findings were consistent across all three studies.

Other published research has reported an association between GERD-related gastrointestinal symptoms (e.g., heartburn, epigastric pain, regurgitation) and patient functioning and well-being [5-7,10,23]. An earlier study has shown that the complete resolution of these symptoms results in greater patient functioning and well-being compared to continued symptoms and to an overall improvement in functioning and well-being over the course of medical treatment [15]. While these analyses did not demonstrate significant differences in HRQL by baseline severity of heartburn symptoms, they did provide further support for the association between complete resolution of these symptoms and improvement in HRQL.

Recently published work by Farup, et al. reported that measures of nocturnal GERD, such as discomfort with nocturnal GERD symptoms, frustration with sleep loss, and worry and concern about symptoms were associated with impaired HRQL [27]. Earlier work by Revicki et al. demonstrated a negative and statistically significant correlation between both the continuous measures of number and severity of heartburn episodes and the sleep disturbance scores [13]. Others have reported that there are no statistically significant associations between measures of symptom severity and the sleep disturbance scores [8]. Analyses presented in this report failed to demonstrate that baseline severity of heartburn symptoms had an effect on measures of sleep disturbance during the course of medical treatment of GERD.

Limitations

Interpretation of the findings of this study should be moderated by several limitations. One limitation of the study is that the information used to generate the two primary study variables (i.e., baseline symptom severity, complete resolution of symptoms) was collected through patient self-report and that these self-reported outcomes were measured differently for each of the three studies. The patient diary reports used in Clinical Trial 1 collected information on symptom frequency and severity. Clinical Trials 2 and 3 collected information on discomfort or frequency of symptoms. Clinician assessments, patient diary data, and patient self-report data have been observed to be in general agreement when using the GSRS [23]. The patient reports of heartburn symptoms are believed to be reliable and valid.

A second limitation is the means by which the baseline heartburn severity measure was defined across all three clinical trials. The severity measure was defined based on physician consultation following an examination of the distribution of responses to heartburn symptom items for each of the three studies. It is uncertain as to the extent that modifications in this measure would impact the results. However, examination of mean HRQL scores at baseline has demonstrated a clear association between symptom severity and HRQL scores.

In conclusion, this secondary analysis of clinical and HRQL data from three clinical trials demonstrated that complete resolution of heartburn symptoms is associated with improved psychological well-being in patients with GERD. No significant association was seen between complete resolution of heartburn symptoms and sleep problems. Adjusting for baseline heartburn severity did not affect the relationship between symptom resolution and psychological well-being. In general, the severity of heartburn symptoms at the start of medical treatment for GERD does not modify the association between complete symptom resolution and follow-up HRQL outcomes. Complete resolution of heartburn symptoms is associated with improvements in overall psychological well-being, but not sleep disturbance outcomes. Medical and surgical

treatment of GERD is focused on relief and complete resolution of heartburn, and other, symptoms and in improving patient HRQL. These findings confirm that relief of GERD-related symptoms is associated with significant improvements in patient-reported psychological well-being.

Competing Interests

None declared.

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