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ORIGINAL ARTICLE

Association of gastrointestinal events with quality of life and treatment satisfaction in osteoporosis patients: results from the Medication Use Patterns, Treatment Satisfaction, and Inadequate Control of Osteoporosis Study (MUSIC OS)

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Abstract
Summary The purpose of this study was to assess the association of GI events with HRQoL and treatment satisfaction. The effect of baseline GI events persisted through 1 year of follow-up, as indicated by lower EQ-5D, OPAQ-SV, and treatment satisfaction scores among patients with vs without baseline GI events. The presence of GI events is an independent predictor of decreased HRQoL and treatment satisfaction in patients being treated for osteoporosis.
Introduction The goal of this study was to assess the association of gastrointestinal (GI) events with health-related quality of life (HRQoL) and treatment satisfaction in patients being treated for osteoporosis.
Methods MUSIC OS was a multinational, prospective, observational study examining the impact of GI events on osteoporosis management in postmenopausal women. In this analysis, HRQoL and treatment satisfaction were assessed at baseline, 6, and 12 months and compared between patients with and without GI events. Covariate-adjusted scores were calculated using multivariate least-squares regression analysis, and differences between the mean scores of patients with and without baseline and post-baseline GI events were determined.
Results Among the 2959 patients in the analysis, unadjusted scores at each time point were lower (i.e., worse) for patients with GI events than patients without GI events. In adjusted analyses, the effect of baseline GI events persisted through 1 year of follow-up, as indicated by lower EQ-5D and OPAQ-SV scores at 12 months among patients with vs without baseline GI events (−0.04 for the EQ-5D utility score, −5.07 for the EQ-5D visual analog scale, −3.35 for OPAQ physical function, −4.60 for OPAQ emotional status, and −8.50 for OPAQ back pain; $P \leq 0.001$ for all values). Decrements in month 12 treatment satisfaction scores were −6.46 for patients with baseline GI events and −7.88 for patients with post-baseline GI events.
Conclusions The presence of GI events is an independent predictor of decreased HRQoL and treatment satisfaction in patients being treated for osteoporosis.

S. Adami and S. Sajjan are recently deceased.

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Keywords Gastrointestinal diseases · Osteoporosis · Patient satisfaction · Postmenopausal · Quality of life

Introduction

Approximately 20% of European women and 11% of Canadian women aged 50 or older have osteoporosis [1, 2]. Fully one third of the world's osteoporotic hip and vertebral fractures occur in Europe, resulting in approximately two million disability-adjusted life-years lost in the year 2000 [3]. This places the burden of osteoporosis in Europe above that of asthma, hypertensive heart disease, and most types of cancer [3].

Many studies have shown that osteoporosis-related fractures are associated with decreased health-related quality of life (HRQoL) [4–11]. A recent meta-analysis found that health state utility values of osteoporosis patients were reduced by 17–19% after a fracture [12]. Evidence is mixed on whether and how much osteoporosis itself (i.e., in the absence of fracture) reduces quality of life [13], but some studies have found that femoral bone mineral density is associated with HRQoL [14, 15].

Pharmacologic treatment of osteoporosis is associated with improved HRQoL [7, 16–19]. However, global adherence to osteoporosis therapies is low [20]. This may be due to a variety of clinical- and patient-based factors, including gastrointestinal (GI) events, which are experienced by up to 52% of treated European osteoporosis patients [21–23]. GI events have been shown to affect HRQoL and treatment satisfaction in studies of US osteoporosis patients [24, 25]. However, there is limited evidence of this association in European patients.

The objective of this study was to determine the association of GI events with HRQoL and treatment satisfaction in osteoporosis patients in Europe and Canada, using data from the Medication Use Patterns, Treatment Satisfaction, and Inadequate Control of Osteoporosis Study (MUSIC OS).

Methods

Study design

The MUSIC OS-EU study was a prospective observational study conducted to examine the effect of GI symptoms on osteoporosis treatment, treatment satisfaction, and HRQoL in postmenopausal women in Europe and Canada [26]. The study was conducted in six countries—France, Italy, the Netherlands, Sweden, the UK, and Canada in accordance with the Declaration of Helsinki. Patient recruitment occurred between March 2012 and June 2013, and participants were followed for 12 months with outcomes recorded at baseline, 3, 6, and 12 months.

Study sample

Study participants were postmenopausal women ≥55 years of age enrolled in physician clinics in one of the participating sites, which encompassed both primary care (58.3%) and specialist (41.7%) settings [26]. Each had a physician diagnosis of osteoporosis, was literate, was willing and able to follow the study protocol and complete all scheduled assessments, and provided informed consent.

Patients were excluded if they had been diagnosed with Parkinson's disease, any other neuromuscular diseases, or Paget's disease; were currently treated with any injected medication for osteoporosis; were considered by the investigator to be unwilling or unable to complete the study or comply with the protocol; were involved in any active litigation or compensation issues, including disability dispute cases with government; or were currently enrolled in a clinical trial or had participated in a clinical trial within the past 90 days.

Osteoporosis treatment

All patients had been prescribed treatment for their osteoporosis, which included bisphosphonates (e.g., alendronate, risedronate, and ibandronate), calcitonin, strontium ranelate, or selective estrogen-receptor modulators (raloxifene and bazedoxifene). Patients may also have been receiving calcium with or without vitamin D, estrogen, or hormone replacement therapy in addition to pharmacologic therapy for osteoporosis, but these agents were not by themselves considered pharmacologic treatment for this disorder.

Patients were classified as new users or experienced users of pharmacologic osteoporosis therapy. New users were defined as patients who had been receiving oral pharmacologic therapy for <3 months at the time of enrollment, with no prior history of any pharmacologic therapy for osteoporosis. Experienced users were defined as patients receiving the same oral pharmacologic therapy for ≥3 months and continuing that treatment at the time of enrollment.

Gastrointestinal symptoms

GI events were self-selected from a list of symptoms which included heartburn/acid reflux, upset stomach/indigestion, nausea/vomiting, pain behind the breastbone, pain on swallowing or food sticking, stomach pain above or below the navel, diarrhea or constipation, and bloating. GI events were assessed by asking patients whether they had experienced any of the listed symptoms in the past 6 months (past 3 months at the 6-month time point). Answers were indicated with yes/no check boxes for each symptom.

Outcome measures

Generic HRQoL was measured with the EuroQol 5-dimension questionnaire (EQ-5D) [27]. The EQ-5D has two components: a utility score (scale 0 to 1.0), where 1.0 is defined as full health, and a visual analog scale (VAS; scale 0–100), where 100 is the best imaginable health. The utility score comprises five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and is not bounded by a time frame, and the VAS assesses the patient's quality of life "today." The minimal clinically important difference (MCID) in the utility score, defined as the smallest change which patients perceive as beneficial and which would mandate a change in disease management, has been reported alternatively as 0.074 [28] and 0.03 [29].

Osteoporosis-specific quality of life was measured with the short version of the Osteoporosis Assessment Questionnaire (OPAQ-SV) [30]. The OPAQ-SV consists of 34 items in three domains (physical function, emotional status, and back pain), each with a scale of 0–100. Higher scores indicate better quality of life. The time frame of the questionnaire is the previous 2 weeks.

Treatment satisfaction was measured with the Osteoporosis Patient Treatment Satisfaction Questionnaire (OPSAT-Q) [31]. The OPSAT-Q consists of 16 items on four subscales (convenience, confidence with daily functioning, overall satisfaction, and side effects). Subscale scores are used to create a composite satisfaction score that ranges from 0 to 100, with higher scores indicating greater treatment satisfaction. The questions have no time frame of reference.

Statistical analysis

The study sample size was calculated to permit a final evaluable population of approximately 2700 subjects for the descriptive and exploratory analyses to permit comparisons between patients with and without GI events. Analyses of patient attrition at each time point showed that GI events did not influence the attrition rates.

Descriptive summaries of unadjusted scores for quality of life and treatment satisfaction were compiled at baseline, 6 months, and 12 months, and multiple linear regression analysis with backwards elimination was used to adjust for principal covariates. Covariates included in the full regression model, in addition to GI events, were age, body mass index (BMI), duration of treatment for osteoporosis at baseline, duration of osteoporosis at baseline, history of previous fractures, history of falls, concomitant medication use, comorbidities (including cardiac, endocrine, and GI disorders, metabolic and nutrition disorders, musculoskeletal diseases, vascular disorders, and malignant or benign neoplasms), pharmacologic treatment class (bisphosphonates or non-bisphosphonates), and, for analyses of all patients, user group (new or experienced).

GI events were categorized as (i) baseline, meaning they were reported on the baseline questionnaire, or (ii) post-baseline, meaning they were reported on either the month 6 or month 12 questionnaires, or both. Interaction terms were included for baseline and post-baseline GI events. Multivariate analyses of treatment satisfaction at baseline were not performed for new users since many were prescribed their first treatment at the baseline visit and thus could not complete these questions. The baseline results for "all patients" include the new users who were able to complete this component.

Results

Baseline characteristics of study participants

A total of 2959 patients were eligible for analysis at study entry, of which 684 were new users and 2275 were experienced users. Of these, 2545 patients remained eligible for analysis at month 12 of whom 535 were new users and 2010 were experienced users. The baseline demographic and clinical characteristics of the study sample have been reported elsewhere [32]. Briefly, the mean age of the study population was 69.4 years, and about half the patients (49.4%) had a history of osteoporotic fracture. Overall, 79.9% of patients were taking bisphosphonates. A total of 2015 subjects (68.1%) reported GI symptoms at baseline (new users 64.6%; experienced users 69.1%; $P = 0.03$) [32], and the cumulative frequency of subjects reporting GI events rose throughout the study, reaching 79.0% at month 6 (new users 79.6%; experienced users 78.9%) and 81.1% at month 12 (new users 81.5%; experienced users 81.1%) (manuscript in preparation). A total of 737 subjects (25%) reported having one or more falls at baseline, with 39% reporting falls between baseline and month 12, and 1457 subjects (49.5%) reported fractures at baseline with a further 1.8% between baseline and month 12.

Generic health-related quality of life: EQ-5D

Mean unadjusted EQ-5D utility and VAS scores for all subjects were 0.81 ± 0.18 and 73.0 ± 19.1, respectively, at baseline, with no clinically important differences in either value between new and experienced users (EQ-5D score 0.81 ± 0.18 vs 0.80 ± 17; VAS 72.8 ± 20.3 vs 73.0 ± 18.9; data not shown). EQ-5D utility and VAS scores at baseline were lower by a clinically meaningful difference in both new users and experienced users with GI events than in those without GI problems and remained consistently lower throughout the 12-month period of follow-up in both patient groups (Table 1).

When adjusted for influential variables, the baseline differences in the least-squares mean values between patients with and without GI events were highly significant (−0.05 for the

EQ-5D utility score, $P < 0.001$, and −5.61 for the VAS, $P < 0.001$; Table 2). The effect of baseline GI events persisted through the entire year of follow-up, as indicated by the significant difference at both 6 and 12 months of patients with vs without baseline GI events (−0.05 and −0.04 for utility scores and −5.22 and −5.07 for VAS; $P < 0.001$ for all values; Table 2).

The occurrence of GI events after baseline was also an important predictor of reduced quality of life. Adjusted EQ-5D utility scores at 6 and 12 months (−0.05 and −0.05, respectively, $P < 0.001$) and VAS scores at 6 and 12 months (−3.49 and −4.14, respectively, $P < 0.001$) were significantly lower in patients who developed GI events during these intervals. Interaction terms (Table 2) indicated that reduction in the two EQ-5D measures was greatest in patients who reported GI events both prior to baseline and during the period of follow-up (utility score −0.08 and −0.07 at months 6 and 12, $P < 0.001$; VAS score −7.11 and 7.44 at months 6 and 12, $P < 0.001$).

Osteoporosis Assessment Questionnaire: OPAQ-SV

Mean unadjusted OPAQ-SV scores for all subjects at baseline were 79.8 ± 19.9 for physical function (new users 80.9 ± 19.5, experienced users 79.5 ± 20.0), 68.5 ± 20.7 for emotional status (new users 71.4 ± 20.5; experienced users 67.6 ± 20.7), and 62.8 ± 27.7 for back pain (new users 63.9 ± 27.8; experienced users 62.5 ± 27.7; data not shown). Physical function scores were marginally lower, while emotional status scores and back pain scores were more markedly reduced, in patients with GI events than in those without GI problems. Reported values remained consistently lower throughout the 12-month period of follow-up and appeared numerically greater among experienced than among new users (Table 1).

When adjusted for influential variables, the baseline differences in the least-squares mean values between patients with and without GI events were highly significant (−3.53 for physical function, −5.55 for emotional status, and −10.11 for back pain, all $P < 0.001$; Table 3). The effect of baseline GI events

Table 1 Unadjusted quality of life and treatment satisfaction scores at baseline, month 6, and month 12 in patients with and without GI events at baseline

	GI events at baseline			No GI events at baseline		
	Baseline	Month 6	Month 12	Baseline	Month 6	Month 12
EQ-5D utility score						
All patients	0.79 (0.18)	0.80 (0.18)	0.80 (0.18)	0.85 (0.17)	0.86 (0.16)	0.85 (0.18)
New users	0.79 (0.18)	0.81 (0.19)	0.81 (0.17)	0.84 (0.17)	0.86 (0.15)	0.86 (0.17)
Experienced users	0.78 (0.17)	0.79 (0.18)	0.80 (0.18)	0.85 (0.17)	0.86 (0.17)	0.85 (0.18)
EQ-5D VAS score						
All patients	71.0 (19.2)	71.9 (17.3)	72.2 (17.1)	77.2 (18.2)	78.4 (16.9)	78.6 (16.2)
New users	69.9 (20.4)	72.7 (17.4)	73.1 (16.8)	77.8 (18.1)	79.8 (15.8)	81.0 (15.6)
Experienced users	71.3 (18.8)	71.7 (17.3)	72.0 (17.2)	77.0 (18.2)	77.9 (17.3)	77.9 (16.3)
OPAQ physical function						
All patients	78.2 (20.3)	78.1 (21.3)	77.8 (21.5)	83.2 (18.6)	84.2 (18.5)	83.2 (19.9)
New users	80.0 (19.2)	80.4 (20.0)	79.6 (20.6)	82.6 (19.9)	84.0 (18.1)	84.3 (19.7)
Experienced users	77.7 (20.6)	77.5 (21.6)	77.3 (21.7)	83.4 (18.2)	84.2 (18.7)	82.9 (19.9)
OPAQ emotional status						
All patients	66.1 (20.7)	65.8 (21.8)	65.5 (22.0)	73.6 (19.9)	73.1 (20.6)	72.3 (21.4)
New users	69.5 (20.1)	68.5 (20.9)	67.9 (21.2)	75.0 (20.6)	75.3 (19.2)	75.1 (20.4)
Experienced users	65.1 (20.7)	65.1 (21.9)	65.0 (22.1)	73.1 (19.7)	72.3 (21.0)	71.4 (21.7)
OPAQ back pain						
All patients	59.1 (27.2)	59.8 (27.1)	60.8 (27.3)	70.8 (27.0)	70.4 (25.8)	71.7 (25.3)
New users	61.1 (26.8)	61.7 (26.0)	62.8 (26.0)	68.9 (28.9)	70.0 (25.7)	71.8 (25.0)
Experienced users	58.5 (27.3)	59.3 (27.4)	60.3 (27.7)	71.5 (26.4)	70.6 (25.8)	71.7 (25.4)
OPSAT composite score						
All patients	78.6 (15.1)	78.0 (15.6)	77.3 (16.3)	84.6 (13.4)	84.2 (13.5)	84.4 (13.7)
New users	75.0 (16.0)	76.7 (16.4)	77.3 (15.4)	82.0 (12.2)	83.0 (13.9)	84.6 (13.3)
Experienced users	78.9 (15.0)	78.4 (15.4)	77.3 (16.6)	84.9 (13.5)	84.6 (13.3)	84.3 (13.8)

Scores are mean (SD) values. GI event status is at baseline. There were 2943 patients in the analysis, 672 new users and 2271 experienced users

EQ-5D EuroQol 5 dimension questionnaire, *OPAQ-SV* Osteoporosis Assessment Questionnaire (short version), *OPSAT* Osteoporosis Patient Treatment Satisfaction Questionnaire, *VAS* visual analog scale

Table 2 Least-squares mean differences in EQ-5D between patients with and without GI events at baseline, month 6, and month 12

	Baseline		Month 6		Month 12	
	LS mean difference (95% CI)	*P*	LS mean difference (95% CI)	*P*	LS mean difference (95% CI)	*P*
EQ-5D utility						
Baseline GI problems vs no baseline GI problems	−0.05 (−0.065, −0.039)	<0.001	−0.05 (−0.062, −0.034)	<0.001	−0.04 (−0.055, −0.026)	<0.001
GI event BL to M6	–	–	−0.05 (−0.064, −0.033)	<0.001	−0.05 (−0.066, −0.034)	<0.001
GI (BL to M6)*GI (BL = Y)	–	–	−0.08 (−0.092, −0.059)	<0.001	−0.07 (−0.086, −0.052)	<0.001
GI (BL to M6)*GI (BL = N)	–	–	−0.04 (−0.067, −0.019)	<0.001	−0.04 (−0.067, −0.018)	<0.001
GI event BL to M12	–	–	–	–	−0.05 (−0.068, −0.035)	<0.001
GI (BL to M12)*GI (BL = Y)	–	–	–	–	−0.07 (−0.088, −0.053)	<0.001
GI (BL to M12)*GI (BL = N)	–	–	–	–	−0.05 (−0.074, −0.026)	<0.001
EQ-5D VAS						
Baseline GI problems vs no baseline GI problems	−5.61 (−7.076, −4.146)	<0.001	−5.22 (−6.613, −3.823)	<0.001	−5.07 (−6.437, −3.705)	<0.001
GI event BL to M6	–	–	−3.49 (−5.034, −1.942)	<0.001	−4.31 (−5.817, −2.797)	<0.001
GI (BL to M6)*GI (BL = Y)	–	–	−7.11 (−8.784, −5.437)	<0.001	−7.44 (−9.075, −5.811)	<0.001
GI (BL to M6)*GI (BL = N)	–	–	−1.99 (−4.386, 0.401)	0.103	−3.44 (−5.780, −1.102)	0.004
GI event BL to M12	–	–	–	–	−4.14 (−5.705, −2.567)	<0.001
GI (BL to M12)*GI (BL = Y)	–	–	–	–	−7.29 (−8.985, −5.603)	<0.001
GI (BL to M12)*GI (BL = N)	–	–	–	–	−3.41 (−5.669, −1.156)	0.003

Results are for new users and experienced users combined

BL baseline, *EQ-5D* EuroQol 5-dimension questionnaire, *GI* gastrointestinal, *M6* month 6, *M12* month 12, *VAS* visual analog scale

persisted through the entire year of follow-up (Table 3), as shown by the significant difference at both 6 and 12 months of patients with vs those without baseline GI events (−4.55 and −3.35 for physical function, −5.55 and −4.60 for emotional status, and −8.66 and −8.50 for back pain; all $P < 0.001$).

The occurrence of GI events after baseline was also an important predictor of reduced quality of life measured by OPAQ-SV (Table 3). Adjusted scores for physical function (6 months −3.85, $P < 0.001$; 12 months −2.98, $P < 0.002$), emotional status (6 months −5.20, $P < 0.001$; 12 months −5.35, $P < 0.001$), and back pain (6 months −7.01, $P < 0.001$; 12 months −6.93, $P < 0.001$) were significantly lower in patients who developed GI events during these intervals. The differences in all three OPAQ-SV measures were greatest among patients who reported GI events both prior to baseline and during the period of follow-up (physical function −6.80 and −4.83 at months 6 and 12, $P < 0.001$; emotional status −8.33 and −7.38 at months 6 and 12, $P < 0.001$; and back pain −12.55 and −12.27 at months 6 and 12, $P < 0.001$).

Osteoporosis Patient Treatment Satisfaction Questionnaire

The mean unadjusted composite treatment satisfaction score for all subjects at baseline was 80.5 ± 14.9 (new users 77.6 ± 15.0 and experienced users 80.8 ± 14.8; data not shown). As shown in Table 1, the score was lower in patients with than in those without GI events at baseline and remained so throughout follow-up (78.6 vs 84.6 at baseline, 78.0 vs 84.2 at 6 months, and 77.3 vs 84.4 at 12 months).

When adjusted for influential variables, the baseline difference in the least-squares mean values between patients with and without GI events was highly significant (−5.88, $P < 0.001$; Table 4). The effect of baseline GI events persisted throughout follow-up (Table 4), with a significant difference at both 6 and 12 months between patients with or without baseline GI events (−5.89 and −6.46, both $P < 0.001$).

As observed with the other measures, adjusted scores were also significantly lower in patients who reported GI events after baseline (6 months −6.83, $P < 0.001$; 12 months −7.88, $P < 0.001$). The differences were greatest among patients who reported GI events both prior to baseline and during the period of follow-up (−9.21 and −10.59 at months 6 and 12, both $P < 0.001$) (Table 4).

Other covariates influencing health outcome measures

Certain demographic and clinical factors other than GI events also influenced the health outcome measures recorded (Online Resource Tables 1, 2, 3, 4, 5, 6).

Table 3 Least-squares mean differences in OPAQ-SV between patients with and without GI events at baseline, month 6, and month 12

	Baseline		Month 6		Month 12	
	LS mean difference (95% CI)	*P*	LS mean difference (95% CI)	*P*	LS mean difference (95% CI)	*P*
Physical function						
Baseline GI problems vs no baseline GI problems	−3.53 (−4.953, −2.102)	<0.001	−4.55 (−6.125, −2.965)	<0.001	−3.35 (−4.981, −1.712)	0.001
GI event BL to M6	–	–	−3.85 (−5.601, −2.098)	<0.001	−2.79 (−4.609, −0.981)	0.003
GI (BL to M6)*GI (BL = Y)	–	–	−6.80 (−8.695, −4.904)	<0.001	−4.95 (−6.905, −2.990)	<0.001
GI (BL to M6)*GI (BL = N)	–	–	−3.14 (−5.857, −0.416)	0.024	−1.96 (−4.780, 0.855)	0.172
GI event BL to M12	–	–	–	–	−2.98 (−4.867, −1.101)	0.002
GI (BL to M12)*GI (BL = Y)	–	–	–	–	−4.83 (−6.864, −2.805)	<0.001
GI (BL to M12)*GI (BL = N)	–	–	–	–	−1.99 (−4.704, 0.728)	0.151
Emotional status						
Baseline GI problems vs no baseline GI problems	−5.55 (−7.183, −3.915)	<0.001	−5.55 (−7.188, −3.912)	<0.001	−4.60 (−6.281, −2.914)	<0.001
GI event BL to M6	–	–	−5.20 (−7.008, −3.386)	<0.001	−5.37 (−7.223, −3.510)	<0.001
GI (BL to M6)*GI (BL = Y)	–	–	−8.33 (−10.287, −6.371)	<0.001	−7.47 (−9.476, −5.461)	<0.001
GI (BL to M6)*GI (BL = N)	–	–	−3.12 (−5.935, −0.308)	0.030	−3.84 (−6.720, −0.952)	0.009
GI event BL to M12	–	–	–	–	−5.35 (−7.282, −3.417)	<0.001
GI (BL to M12)*GI (BL = Y)	–	–	–	–	−7.38 (−9.459, −5.303)	<0.001
GI (BL to M12)*GI (BL = N)	–	–	–	–	−4.08 (−6.866, −1.296)	0.004
Back pain						
Baseline GI problems vs no baseline GI problems	−10.11 (−12.196, −8.014)	<0.001	−8.66 (−10.855, −6.467)	<0.001	−8.50 (−10.697, −6.298)	<0.001
GI event BL to M6	–	–	−7.01 (−9.438, −4.591)	<0.001	−7.19 (−9.618, −4.766)	<0.001
GI (BL to M6)*GI (BL = Y)	–	–	−12.55 (−15.174, −9.932)	<0.001	−12.51 (−15.133, −9.879)	<0.001
GI (BL to M6)*GI (BL = N)	–	–	−4.98 (−8.745, −1.220)	0.010	−4.71 (−8.474, −0.939)	0.014
GI event BL to M12	–	–	–	–	−6.93 (−9.452, −4.407)	<0.001
GI (BL to M12)*GI (BL = Y)	–	–	–	–	−12.27 (−14.994, −9.549)	<0.001
GI (BL to M12)*GI (BL = N)	–	–	–	–	−5.21 (−8.844, −1.570)	0.005

Results are for new users and experienced users combined. Scores were from the Osteoporosis Assessment Questionnaire (short version)

BL baseline, *GI* gastrointestinal, *M6* month 6, *M12* month 12

Increased age was an important predictor of reduced health quality (Online Resource Tables 1, 2, 3, 4, 5). Patients 80 years or older exhibited decreased scores for EQ-5D utility (−0.04 to −0.07, $P < 0.001$) and EQ-5D VAS (−5.80 to −8.87, $P < 0.001$) measures, and for the OPAQ physical function (−13.66 to −17.01, $P < 0.001$), emotional status (−13.50 to −16.86, $P < 0.001$), and back pain (−5.95 to −8.61, $P \leq 0.001$) domains, while subjects 70–80 years of age had significantly lower values on individual measures when compared to those aged 50–60 years of age.

Obese subjects (BMI ≥30) exhibited decreased EQ-5D utility (−0.06 to −0.07, $P < 0.001$) and EQ-5D VAS scores (−6.85 to −7.06, $P < 0.001$), along with reduced OPAQ physical function (−10.42 to −11.83, $P < 0.001$), emotional status (−9.08 to −10.42, $P < 0.001$), and back pain domain scores (−9.86 to −10.29, $P \leq 0.001$; Online Resource Tables 1, 2, 3, 4, 5), while overweight subjects (BMI 25–29.99) had significantly lower values on individual EQ-5D utility measures and OPAQ domains when compared with those of normal body weight (BMI 18.5–24.99).

Subjects with osteoporosis of long duration (>10 years) paradoxically demonstrated improved EQ-5D utility scores (0.03 to 0.04, $P = 0.037$–0.002) with improvement also in EQ-5D VAS and individual OPAQ domains at specific time points (Online Resource Tables 1, 2, 3, 4, 5), perhaps reflecting adaptation to their illness or milder disease expression. Prolonged duration of treatment for osteoporosis for more than 5 or 10 years was also associated with improved OPSAT-Q scores (5 years 2.51 to 3.45, $P = 0.036$–0.006; 10 years 3.41 to 4.09, $p = 0.017$–0.003; Online Resource Table 6).

Fractures and falls were both associated with a significant reduction of health quality (Online Resource Tables 1, 3, 4) and, in both cases, events occurring prior to baseline and

Table 4 Least-squares mean differences in OPSAT-Q between patients with and without GI events at baseline, month 6, and month 12

Composite satisfaction	Baseline		Month 6		Month 12	
	LS mean difference (95% CI)	*P*	LS mean difference (95% CI)	*P*	LS mean difference (95% CI)	*P*
Baseline GI problems vs no baseline GI problems	−5.88 (−7.159, −4.601)	<0.001	−5.89 (−7.172, −4.612)	<0.001	−6.46 (−7.793, −5.120)	<0.001
GI event BL to M6	–	–	−6.83 (−8.241, −5.409)	<0.001	−7.07 (−8.539, −5.596)	<0.001
GI (BL to M6)*GI (BL = Y)	–	–	−9.21 (−10.706, −7.711)	<0.001	−10.20 (−11.757, −8.635)	<0.001
GI (BL to M6)*GI (BL = N)	–	–	−3.97 (−6.164, −1.778)	<0.001	−5.92 (−8.205, −3.644)	<0.001
GI event BL to M12	–	–	–	–	−7.88 (−9.407, −6.355)	<0.001
GI (BL to M12)*GI (BL = Y)	–	–	–	–	−10.59 (−12.201, −8.971)	<0.001
GI (BL to M12)*GI (BL = N)	–	–	–	–	−7.05 (−9.236, −4.857)	<0.001

Results are for new users and experienced users combined. Scores were from the Osteoporosis Patient Treatment Satisfaction Questionnaire

BL baseline, *GI* gastrointestinal, *M6* month 6, *M12* month 12

during follow-up combined to substantially reduce values across all measures (Online Resource Tables 1, 2, 3, 4, 5, 6). Fractures reduced quality of life measured by EQ-5D utility (−0.08, $P = 0.002$- < 0.001), OPAQ physical function (−7.26 to −10.85, $P = 0.003$- < 0.001), and OPAQ emotional status domains (−6.57 to −9.95, $P = 0.009$- < 0.001). The negative influence for falls was observed in EQ-5D utility (−0.06 to −0.08, $P < 0.001$), EQ-5D VAS (−7.87 to −9.01, $P < 0.001$), OPAQ physical function (−11.49 to −11.80, $P < 0.001$), emotional status (−11.81 to −13.15, $P < 0.001$), and back pain (−11.51 to −11.98, $P < 0.001$) domains, and in OPSAT-Q scores (−4.27 to −4.72, $P < 0.001$).

Health quality scores were also generally lower in subjects with other comorbidities, in those receiving non-bisphosphonates and in those with other co-medications (Online Resource Tables 1, 2, 3, 4, 5, 6). There was no significant difference, however, between new users or experienced users in this study.

Discussion

This analysis of survey responses from European and Canadian women receiving oral prescription treatment for osteoporosis showed that GI events are an independent predictor of reduced HRQoL and lower treatment satisfaction over 1 year of treatment. The results suggest that an ongoing experience of GI events produces a greater and more statistically significant reduction in HRQoL and treatment satisfaction than incident GI events.

Previous studies of the effect of GI events on HRQoL and treatment satisfaction have been conducted in the USA [24, 25]. Binkley et al. reported a subanalysis of an open-label, 6-month, multicenter trial in which postmenopausal women taking a weekly bisphosphonate were switched to 150 mg monthly oral ibandronate [25]. GI events were recorded under the new treatment regimen, and HRQoL and treatment satisfaction were assessed concurrently with the OPSAT questionnaire. Among patients reporting experiencing GI side effects at study entry ($N = 89$), 66 and 75% reported decreased frequency of heartburn/acid reflux and stomach upset, respectively, at month 6. Concurrently, the OPSAT quality of life and satisfaction domain scores increased (i.e., improved) by 15.4 and 24.1 points, respectively, in this subset of patients.

Also in the USA, the Prospective Observational Scientific Study Investigating Bone Loss Experience (POSSIBLE) enrolled 5015 postmenopausal women treated for osteoporosis in an ongoing survey [24]. GI side effects were reported by participants at baseline and at 6 and 12 months. EQ-5D utility scores measured at month 6 were not significantly different between patients with and without GI side effects, but global treatment satisfaction scores, measured by the Treatment Satisfaction Questionnaire for Medication at month 6, were significantly lower (i.e., worse) in patients with GI side effects.

One study from Europe has assessed GI events and treatment satisfaction in the same patient population. Turbi et al. examined compliance over 12 months with raloxifene and alendronate in 902 postmenopausal women in Spain [22]. GI adverse events that caused discontinuation of treatment were reported for each treatment group (3.4 and 9.9%, respectively; $P < 0.001$), and patient satisfaction was assessed with a single question. Significantly more raloxifene patients were satisfied or very satisfied with their treatment compared to patients taking alendronate (95.7 vs 85.4%; $P < 0.001$).

Our study showed that health quality scores were generally lower in subjects receiving non-bisphosphonates. These results vary from the findings of the POSSIBLE US study which reported that women who were new to bisphosphonate therapy at study entry had lower OPAQ-SV physical function scores at study entry than women new to non-bisphosphonate therapy (84.7 and 87.2, respectively; $P = 0.03$) [24]. However, the POSSIBLE US study reports that women stable on bisphosphonate therapy at study entry had no significant difference in

HRQoL scores compared with non-bisphosphonate users. It is possible that the differences reported here are a result of methodological differences between the two studies. We analyzed the effect of various covariates on HRQoL among the entire population of treated patients (new and experienced users were not separated for this analysis) while the effect of covariates on HRQoL was assessed separately for new and stable users in the POSSIBLE US manuscript.

The results of the current MUSIC OS-EU analysis are consistent with these previous studies of GI events, HRQoL, and treatment satisfaction, and they improve upon previous studies in several ways. First, MUSIC OS-EU assessed HRQoL and treatment satisfaction separately in patients with or without GI events, a design element missing from earlier studies [22, 25]. This inclusion of a comparator group strengthens the quality of the observed association. Second, our analyses were adjusted for demographic and clinical covariates, such that the results indicate an effect of GI events on HRQoL and treatment satisfaction independent of confounder variables. This effect was quantifiable to the point that differences between the effects of continuing and emergent GI events were observed. Specifically, post-baseline GI events occurring in patients with baseline GI events were associated with changes in the EQ-5D utility scores ≥0.07, the most stringent definition of the MCID [28]. In contrast, post-baseline events occurring in patients without baseline GI events did not produce this MCID (see Table 3). Third, our use of a disease-specific quality of life instrument produced the novel finding that, of the three dimensions of osteoporosis-specific quality of life, back pain is the one that is most affected by GI events. Finally, to our knowledge, MUSIC OS-EU is the first European study to assess the association of GI events with HRQoL in treated osteoporosis patients. Thus, the current study provides information about this association in a heretofore uncharacterized population.

Despite the strengths of the MUSIC OS study, the results of the current analyses are subject to several important limitations. First, due to the design of the study as a patient survey, the accuracy of the findings is limited by patient recall and potentially affected by reporting bias. Second, the least-squares mean differences were not adjusted for adherence, so some patients may have had GI events not associated with treatment. Third, data collection over the 12-month follow-up period was subject to attrition, so the results do not reflect the experience of patients who discontinued the study. However, the attrition rate was low (~10%) and, thus, would not be expected to significantly alter the results. Fourth, the data were pooled from culturally and demographically different countries and therefore reflect the average effect within potentially disparate data. Finally, lack of information about the minimal clinically important difference on the OPAQ and OPSAT questionnaires prevents assessment of the clinical relevance of the effect sizes reported here, and some of the observed differences in quality of life, although statistically significant, may not have been clinically important.

In conclusion, data from treated osteoporosis patients enrolled in MUSIC OS-EU showed that GI events are associated with lower HRQoL and lower satisfaction in osteoporosis patients treated with oral prescription medications. This association was observed at both baseline and 12 months and in both new users and experienced users of prescription treatments. Ongoing GI problems appeared to have a greater effect on HRQoL and treatment satisfaction than GI problems emerging during the study.

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Compliance with ethical standards

Conflicts of interest A. Modi and S. Sen are employees of Merck & Co., Inc. and own stock in the company. J.D. Adachi has received grant support and speaker honorarium from Actavis, Amgen, Eli Lilly, Merck & Co., Inc. and Novartis. J.D. Adachi is a consultant for Amgen, Eli Lilly, and Merck & Co., Inc. S. Adami has received consulting honorarium from Merck & Co., Inc. and served as a board member for Merck & Co., Inc. B. Cortet has received research grants, consulting honorarium, and/or speaker honorarium from Amgen, Expanscience, Ferring, Eli Lilly, Merck & Co., Inc., Merck Sharp & Dohme, Medtronic, and Roche diagnostics. A.L. Cooper has received research grants, advisory board and/or speaker honorarium from Consilient Health and Intemis Pharmaceuticals. P. Geusens has received research grants, advisory board and/or speaker honorarium from Pfizer, Abbott, Eli Lilly, Amgen, Merck Sharp & Dohme, Will Pharma, Roche, UCB pharmaceuticals, Bristol-Myers Squibb, and Novaritis. D. Mellström has received consulting honorarium from Merck Sharp & Dohme. J.P. Weaver is an employee of Merck & Co., Inc. J.P. van den Bergh is a paid consultant at Amgen

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