Burden of illness in fibromyalgia patients with comorbid depression

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ABSTRACT

Objective. *To assess the burden of fibromyalgia (FM) in patients with FM taking antidepressant medication for comorbid depression.*

Methods. *Symptom burden, impact on work and activity, and healthcare resource utilisation (HCRU) was examined at randomisation in patients enrolled in a clinical trial. Symptom burden was estimated based on self-reported health status measures. The Work Productivity and Activity Impairment: Specific Health Problem scale adapted to FM and a separate HCRU questionnaire were completed. The relationship between FM severity and burden was evaluated.*

Results. *The total population analysed comprised 193 patients; 71 (36.8%) had moderate FM and 119 (61.7%) severe FM. Patients had moderate pain, severe impairment in functioning due to FM, sleep disruption, mild anxiety, and mild depression. In the 7 days preceding randomisation, an average of 58.0% overall work impairment was reported, with 15.2% of working hours missed and 54.0% productivity while at work. In the 3 months preceding randomisation, on average, 5.0 visits per patient were made to healthcare professionals. Physical treatments were used by 34.7% and supplements by 31.6% of patients. Prescription and non-prescription medications, as well as professional services providing help with activities of daily living (ADL) that are impacted by FM, were used by >75% of patients. In addition, 50.4 hours of unpaid help was provided for ADL assistance. Total out-of-pocket expenditures were US$307.1, €410.4, or C$211.3, depending on location. FM burden worsened with increasing FM severity.*

Conclusion. *This study demonstrates the significant burden of FM in patients with comorbid depression treated with an antidepressant.*

Introduction

Fibromyalgia (FM) in the general population occurs primarily in women, with estimates of 75-90% (1, 2) based on diagnosis using the 1990 American College of Rheumatology (ACR) criteria (3). It is characterised by chronic widespread pain and tenderness, often accompanied by sleep disruption, fatigue, anxiety, depression, limitations in physical function, cognitive difficulties, including poor concentration and forgetfulness, and impaired quality of life (1, 4-6). These symptoms lead to a significant burden of illness for the individual (7-9) and society, including negative impact on work productivity (7, 10-13) and increases in healthcare utilisation (12-16), with associated costs. The burden of FM worsens with increasing FM severity (7, 9, 13, 14).

Depression and FM are closely associated. A lifetime history of major depression in FM patients may be as high as 50-70% (1, 5, 17, 18), ~20–40% of FM patients have current depression (1,17-19), and ~25–60% of FM patients with comorbid depression take an antidepressant for depression (1, 19). Pathophysiological links between FM and depression have been postulated (5), and FM has been shown to coaggregate with depressive disorders, suggesting that FM and depression share some familial factor or group of factors (20). Patients with FM are 3-5 times more likely to exhibit depressive symptoms than those without FM (1, 19, 21), and depression may be associated with younger age, female gender, number of chronic comorbidities, and limited activity in FM patients (19). Moreover, a bidirectional association exists between FM and depression, such that FM patients are at an increased risk of developing subsequent depression, and patients with depression are at an increased risk of developing subsequent

FM (22). Nonetheless, data indicate that not every FM patient has or will experience depression (1, 5, 17-19), and improvements in FM pain following treatment with antidepressants may be independent of changes in depression (5). Despite the close association between FM and depression, FM patients taking an antidepressant for comorbid depression are a population that has not been extensively studied in a controlled clinical environment. The burden of FM and the impact of FM severity in this population are largely unknown.

Recently, a clinical trial evaluated pregabalin efficacy and safety in FM patients taking either a selective serotonin reuptake inhibitor (SSRI) or a serotonin/norepinephrine reuptake inhibitor (SNRI) for comorbid depression (23). Compared with placebo, pregabalin significantly improved the primary efficacy endpoint of mean pain score (treatment difference, -0.61 on an 11-point numeric rating scale [NRS]; p=0.0001), as well as secondary efficacy endpoints including scores for Hospital Anxiety and Depression Scale-Anxiety (HADS-A) and -Depression (HADS-D), Fibromyalgia Impact Questionnaire (FIQ), Patient Global Impression of Change, and sleep quality (23). The participants in this trial provide an opportunity to examine the burden of FM in this patient population with comorbid depression, because previous trials of pregabalin efficacy and safety excluded patients with current depression symptoms, or who were taking antidepressants (24-27).

The objective of this study was to examine FM-related symptom burden, impact on work and activity, and healthcare resource utilisation (HCRU) in FM patients taking an SSRI or an SNRI for comorbid depression. Patients were stratified by FM severity to determine its impact on FM-related burden.

Materials and methods

Clinical trial design and participants

Patients from 38 centers in the United States, Europe (Italy and Spain), and Canada were enrolled in a Phase 3b, randomised, placebo-controlled, double-blind, 2-period, 2-way crossover trial (ClinicalTrials.gov identifier: NCT01432236). Inclusion and exclusion criteria have been described previously (23). Briefly, male or female patients aged ≥18 years had a diagnosis of FM, based on the 1990 ACR criteria (3), and a diagnosis of major depressive disorder (MDD), dysthymia, or depression not otherwise specified (NOS) documented in medical records. Those patients not diagnosed with one of these three conditions were excluded from the trial. Patients were taking either a single SSRI or SNRI specifically for the treatment of depression for ≥3 months with no change in depression medication type, and at a stable dose for the 2 months preceding randomisation. Therefore, depression would have been pre-existing at the time of entry into the study. Patients with severe depression, based on a HADS-D score ≥15 or in the judgement of the investigator, were excluded from the trial. At screening and randomisation, eligible patients had a mean pain score ≥4 on an 11-point NRS (0=no pain, 10=worst possible pain). Informed consent was obtained in writing from each patient prior to inclusion in the trial. At each participating site, the informed consent documents and the trial protocol were reviewed and approved by an institutional review board or independent ethics committee. The trial was conducted in accordance with the Declaration of Helsinki, the Council for International Organisations of Medical Sciences International Ethical Guidelines for Biomedical Research Involving Human Subjects, and the International Conference on Harmonisation Good Clinical Practice guidelines.

Assessment of symptom burden, work productivity and activity impairment, and healthcare resource utilisation

FM-related symptom burden, impact on work and activity, and HCRU were assessed at randomisation. Clinical characteristics were used to assess symptom burden based upon self-reported measures of pain, mood, FM health status, global ratings of disease, health utility, and sleep. Mean pain score for the past week on an 11-point NRS was used to assess pain severity. Scores were calculated as the mean of the last 7 daily entries and at least 4 entries were required to calculate a mean. Patients with scores <4 at screening or randomisation were not eligible for inclusion in the study. Severity categorisations for mean pain score are as follows: mild, 0–<4; moderate, 4–<7; severe, 7–10 (28, 29). The HADS-A and HADS-D subscales measured anxiety and depression severity, respectively, at the time of assessment. Each measure comprised 7 items scored on a 4-point response scale, producing final scores ranging from 0–21 (30, 31). Higher scores indicate worse anxiety/depression. Severity categorisations for each HADS subscale are as follows: normal, 0-7; mild, 8-10; moderate, 11-14; severe, 15-21 (30). The FIQ assessed areas of patient function, pain, fatigue, and psychological distress at the time of assessment. The 10 subscales were each scored from 0–10 and were summed to generate a total score from 0–100 (32, 33). Higher scores indicate greater impairment. The self-rated Patient Static Global Assessment (PSGA) measured overall status, with a recall period of 1 week, on an 11-point NRS (0=very poor, 10=very good) (23). Higher scores indicate better status. The EuroQol 5-Dimensions 3 level version (EQ-5D-3L) measured health utility at the time of assessment. The 5 dimensions of mobility, self-care, usual activities, pain/discomfort, and anxiety/depression were each rated on a 3-point response scale, and scores were combined to form a single index value ranging from 0–1 (34). Higher scores indicate better status. The self-reported Subjective Sleep Questionnaire (SSQ) captured subjective sleep behaviours and was completed on awakening each day. The SSQ captured sleep quality, scored on an 11-point NRS, with higher scores indicating better sleep quality (0=very poor, 10=excellent); subjective wake after sleep onset (sWASO), in minutes; subjective latency to sleep onset (sLSO), in minutes; subjective number of awakenings after sleep onset (sNAASO); and subjective total sleep time (sTST), in minutes (23). Mean values were calculated as the mean of the last 7 days.

The impact of FM on work productivity and activity in the 7 days preceding randomisation was assessed using the self-reported Work Productivity and

Activity Impairment: Specific Health Problem scale (35) adapted to FM (WPAI:FM). The questionnaire consisted of 6 questions, and responses were used to calculate the following 4 scores: absenteeism, a measure of work time missed, calculated as work time missed due to FM as a proportion of hours actually worked; presenteeism, a measure of impairment while working, the degree to which FM impacted work; overall work impairment, a measure of overall work productivity loss due to FM, combining absenteeism plus presenteeism; and activity impairment, a measure of the degree to which FM affected the ability to do regular activities other than work. Scores are expressed as a percentage, with higher scores indicating less productivity and greater impairment. Absenteeism, presenteeism, and overall work productivity impairment were assessed in employed individuals only, whereas activity impairment was assessed in all individuals.

HCRU relating to FM in the 3 months preceding randomisation was assessed using a self-reported HCRU assessment questionnaire. The questionnaire captured the number of office visits by healthcare professional specialty; the number of hospitalisations; the number of emergency room (ER) visits; use of physical treatments, such as physical therapy/massage, acupressure/acupuncture, or chiropractic care; use of supplements, such as herbs, vitamins, or other supplements; the amount of time in hours other people spent providing unpaid help with activities of daily living (ADL); and out-of-pocket expenses for physical treatments, supplements, prescription and non-prescription (over-the-counter) medications, and professional services to assist with ADL that were impacted by FM. Out-of-pocket expenses were captured using the currency of each participating country, i.e. US$ (United States), € (Italy and Spain), and C$ (Canada).

Stratification by fibromyalgia severity

Patients were stratified by FM severity based on FIQ total score at randomisation (36). Those with an FIQ total score of 0-<39 were categorised as having mild FM, those with a score of 39-<59 moderate FM, and those with a score of 59-100 severe FM.

Statistical analysis

Descriptive statistics were captured for symptom burden, work and activity, and HCRU at randomisation in the total population, and by FM severity. Statistically significant differences for symptom burden between FM severity categories were determined using a general linear model with scores at randomisation for pain severity, HADS-A, HADS-D, PSGA, EQ-5D-3L, and SSQ measures as variables, and significance for pairwise comparison between FM severity categories set at $p<0.05$.

Results

Study sample

As described previously (23), 318 patients were screened for participation in the original trial and 197 were randomised to treatment, 124 (62.9%) from the United States, 39 (19.8%) from Spain, 22 (11.2%) from Canada, and 12 (6.1%) from Italy. Four patients who were randomised did not receive any treatment. The total population analysed in the current study consists of the 193 patients at randomisation who went on to receive at least 1 dose of treatment.

The demographic and clinical characteristics of the total population at randomisation have been described previously (23). Briefly, 180 patients (93.3%) were female, 181 (93.8%) were white, and the mean (standard deviation [SD]) age was 50.1 (10.0) years. The mean (range) durations of FM and depression since diagnosis were 6.1 (0.0–32.7) and 12.3 (0.3–45.8) years, respectively. Eighty-four patients (43.5%) had MDD, 8 (4.2%) dysthymia, and 101 (52.3%) depression NOS. The mean (range) duration of depression since diagnosis was 10.6 (0.3–41.7) years for MDD, 6.6 (0.4–22.4) years for dysthymia, and 14.1 (0.4–45.8) years for depression NOS. Of the total population, 101 patients (52.3%) were taking an SSRI and 92 (47.7%) an SNRI for depression.

Based on FIQ total score at randomisation (36), 190 patients (98.4%) had moderate or severe FM; 71 (36.8%) had moderate FM, and 119 (61.7%) severe FM. Two patients (1.0%) had mild FM and were not analysed further because of the small sample size. One patient was not stratified because of a missing FIQ total score at randomisation.

Fibromyalgia-related symptom burden

Self-reported clinical characteristics at randomisation were used as an indicator of FM-related symptom burden (Table I) (23). In the total population, patients on average had moderate pain (mean pain score, 6.7) (28,29), mild anxiety (mean HADS-A score, 8.3) (30), mild depression (mean HADS-D score, 8.0) (30), and were severely impaired by FM (mean FIQ total score, 63.3) (36). FIQ subscale scores, SSQ scores, and scores for PSGA and EQ-5D-3L are also shown in Table I.

When analysed by FM severity, scores for mean pain, HADS-A, HADS-D, PSGA, EQ-5D-3L, sleep quality, sLSO, and sTST were all significantly ($p<0.05$) worse in patients with severe FM than in those with moderate FM (Table I). FIQ total and subscale scores were all greater in patients with severe FM, but statistical comparisons were not made because stratification by FM severity was based on FIQ total score.

Fibromyalgia-related work and activity impairment

WPAI:FM scores in the 7 days preceding randomisation are shown in Figure 1. In the total population, 47.2% (91/193 patients) were employed. In employed individuals, there was a considerable impact of FM on work, as shown by scores for overall work impairment, absenteeism, and presenteeism. Regular activities other than work were also considerably impaired.

WPAI:FM scores were also assessed by FM severity. A smaller percentage of patients with severe FM were employed (41.2%; 49/119 patients) compared with those with moderate FM (57.7%; 41/71 patients). For employed individuals, overall work impairment was greater, more work time was missed, and productivity while at work was worse in patients with severe FM than in those with moderate FM (Fig. 1). Regular activities other than work were also affected more in patients with severe FM than in those with moderate FM.

Table I. Clinical characteristics at randomization.

Clinical characteristic	Total population (n=193)	FM severity[a]		
		Moderate (n=71)	Severe (n=119)	*p*-value[b]
Mean pain score	6.7 (1.2)	6.0 (1.0)	7.2 (1.1)	<0.0001
HADS-A score	8.3 (3.9)	6.5 (3.0)	9.4 (3.9)	<0.0001
HADS-D score	8.0 (3.6)	6.3 (3.2)	9.1 (3.5)	<0.0001
FIQ total score	63.3 (12.0)	51.0 (4.9)	71.1 (7.4)	n/a
FIQ subscale scores				
Physical impairment	4.5 (2.1)	3.3 (2.0)	5.3 (1.8)	n/a
Feel good	7.6 (2.4)	6.3 (2.5)	8.4 (1.9)	n/a
Work missed	3.4 (3.0)	2.0 (2.4)	4.4 (3.0)	n/a
Do job	6.5 (2.1)	5.1 (1.9)	7.4 (1.7)	n/a
Pain	7.0 (1.3)	6.2 (1.1)	7.6 (1.1)	n/a
Fatigue	8.1 (1.5)	7.3 (1.6)	8.7 (1.1)	n/a
Rested	7.9 (1.7)	6.9 (1.9)	8.5 (1.3)	n/a
Stiffness	7.6 (1.7)	6.8 (1.7)	8.1 (1.4)	n/a
Anxiety	5.6 (2.7)	3.8 (2.3)	6.7 (2.3)	n/a
Depression	5.0 (2.6)	3.4 (2.2)	6.0 (2.3)	n/a
PSGA score	4.4 (2.0)	5.2 (1.2)	3.9 (2.2)	<0.0001
EQ-5D score	0.4 (0.3)	0.6 (0.2)	0.3 (0.3)	<0.0001
SSQ scores				
Sleep quality	4.7 (1.7)	5.3 (1.4)	4.4 (1.8)	0.0012
sWASO	71.1 (64.9)	62.2 (63.7)	77.4 (65.7)	0.1195
sLSO	53.1 (43.9)	44.6 (37.4)	58.6 (47.2)	0.0341
sNAASO	2.6 (1.5)	2.8 (1.7)	2.5 (1.3)	0.2736
sTST	392.7 (83.4)	414.0 (81.9)	378.5 (82.4)	0.0044

Data are presented as mean (standard deviation).
[a]FM severity categorised as moderate or severe based on FIQ total score (moderate, 39–<59; severe, 59–100).
[b]Calculated for moderate versus severe categories. *p*-values for FIQ total and subscale scores were n/a because FM severity was based on FIQ total score.
EQ-5D-3L: EuroQol 5-Dimensions 3 level version; FIQ: Fibromyalgia Impact Questionnaire; FM: fibromyalgia; HADS-A: Hospital Anxiety and Depression Scale-Anxiety; HADS-D: Hospital Anxiety and Depression Scale-Depression; n/a: not applicable; PSGA: Patient Static Global Assessment; sLSO: subjective latency to sleep onset; sNAASO: subjective number of awakenings after sleep onset; SSQ: Subjective Sleep Questionnaire; sTST: subjective total sleep time; sWASO: subjective wake after sleep onset.

Fibromyalgia-related healthcare resource utilisation

HCRU related to FM was assessed for the 3 months prior to randomisation. No hospitalisations were reported. Twelve patients (6.2%) in the total population reported having visited the ER. Ten patients (8.4%) with severe FM had visited the ER, compared with 2 patients (2.8%) with moderate FM.

In the total population, on average, 5.0 visits per patient were made to healthcare professionals in the 3 months prior to randomisation. Primary care physicians, massage therapists, and rheumatologists were the most often visited specialties (Table II). More visits were made by patients with severe FM than those with moderate FM. The healthcare providers most often visited were similar for patients with moderate or severe FM. While primary care physicians were the most frequently visited healthcare professionals overall, those patients who reported visiting massage therapists, physical therapists, psychologists, chiropractors, acupuncturists, occupational therapists, or rehabilitation specialists reported more visits on average in the previous 3 months than those reporting visits to primary care physicians (Table II).

Table III shows the use of physical treatments, supplements, prescription and non-prescription medicines, and professional services to help with ADL. Supplements, prescription and non-prescription medicines, and professional services to help with ADL impacted by FM were used in similar proportions of patients with severe FM and moderate FM. A smaller proportion of patients with severe FM used physical treatments compared with patients with moderate FM.

The mean (SD) estimated time other people spent providing unpaid help with ADL in the total population was 50.4 (98.1) hours in the 3 months prior to randomisation. Other people spent more time providing unpaid help for patients with severe FM (56.8 [111.0] hours) than for patients with moderate FM (41.1 [73.4] hours).

Out-of-pocket expenditure in the 3 months prior to randomisation was calculated for the use of physical treatments, supplements, prescription and non-prescription medicines, and professional services for ADL (Table III). Fewer patients entered the study from Italy/Spain and Canada compared with the United States, which may prevent definitive conclusions based on location. In the United States, the use of physical treatments was the largest single expense, compared with professional services in Italy/Spain and prescription medicines in Canada. There was no clear pattern of differences in expenditure among patients with different FM severity. Only expenditure on prescription or non-prescription medicines was consistently higher in patients with severe FM compared with those with moderate FM, irrespective of location.

Discussion

This study assessed the burden of FM in patients with FM taking an SSRI or SNRI for comorbid depression. The results of the analysis show that in these patients, FM-related symptom burden, work and activity impairment, and the use of healthcare resources are considerable, and worsen with increasing FM severity.

The degree of FM-related symptom burden in the current study was similar to that seen in previous studies of FM. In a cross-sectional, observational study in the United States, scores for pain, depression and anxiety severity, patient function, and patient status were similar to the current study (7), and subjects with worse FM reported significantly worse pain, health status, fatigue, sleep disturbance, and anxiety and depressive symptoms. In a similarly designed study in France and Germany (8), relatively consistent results were shown and a similar pattern of increasing pain severity, sleep disturbance, anxiety, and

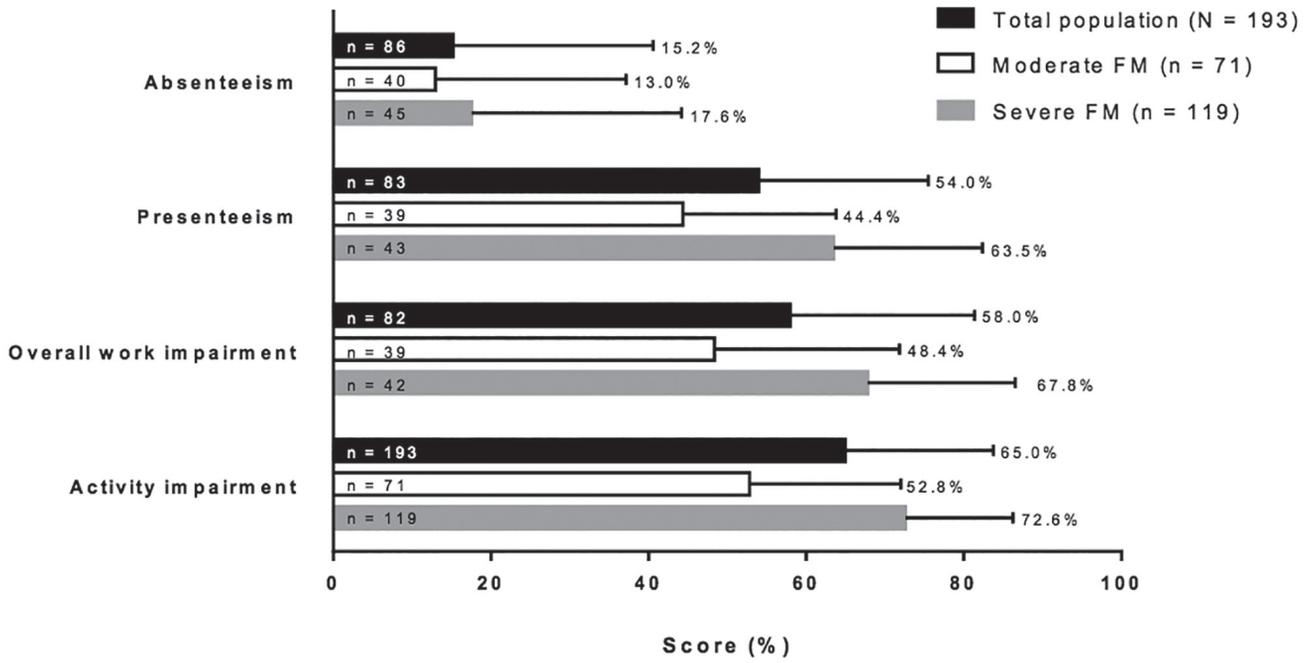

Fig. 1. Work productivity and activity impairment scores in the 7 days preceding randomisation.
Error bars represent standard deviation. Number of patients for each score is indicated. FM severity was categorised as moderate or severe based on FIQ total score (moderate, 39 to <59; severe, 59–100). Absenteeism is a measure of work time missed, calculated as work time missed due to FM as a proportion of hours actually worked. Presenteeism is a measure of impairment while working, the degree to which FM impacted work. Overall work impairment is a measure of overall work productivity loss due to FM, combining absenteeism plus presenteeism. Activity impairment is a measure of the degree to which FM affected the ability to do regular activities other than work. FIQ: Fibromyalgia Impact Questionnaire; FM: fibromyalgia.

Table II. Mean number of office visits in the 3 months preceding randomisation.

Healthcare profession by specialty	FM severity[a]				
	Total population (n=193)	Moderate (n=71)	Severe (n=119)	Patients reporting ≥1 visit (n=183)	
				n (%)	Number of visits
Primary care physician	1.4 (1.9)	1.0 (1.1)	1.8 (2.2)	115 (62.8)	2.4 (1.9)
Massage therapist	0.7 (2.2)	0.9 (2.8)	0.5 (1.8)	35 (19.1)	3.7 (4.0)
Rheumatologist	0.6 (1.1)	0.4 (0.8)	0.8 (1.3)	61 (33.3)	1.9 (1.2)
Psychiatrist	0.5 (1.1)	0.2 (0.8)	0.6 (1.2)	41 (22.4)	2.1 (1.4)
Physical therapist	0.4 (1.9)	0.2 (1.3)	0.6 (2.2)	14 (7.7)	6.1 (4.0)
Psychologist	0.4 (1.2)	0.2 (0.6)	0.5 (1.5)	30 (16.4)	2.5 (2.1)
Chiropractor	0.2 (1.1)	0.3 (0.9)	0.2 (1.3)	15 (8.2)	3.0 (3.0)
Acupuncturist	0.2 (1.1)	0.3 (1.5)	0.1 (0.7)	6 (3.3)	5.5 (3.3)
Occupational therapist	0.1 (0.8)	<0.1 (0.4)	0.2 (1.0)	7 (3.8)	3.9 (1.8)
Neurologist	0.1 (0.5)	<0.1 (0.1)	0.2 (0.6)	15 (8.2)	1.5 (0.7)
Counselor	0.1 (0.5)	0.0 (0.0)	0.2 (0.6)	9 (4.9)	2.1 (0.6)
Physician assistant or nurse practitioner	0.1 (0.3)	<0.1 (0.1)	0.1 (0.4)	10 (5.5)	1.3 (0.5)
Rehabilitation specialist	0.1 (0.5)	0.1 (0.8)	<0.1 (0.2)	5 (2.7)	2.6 (2.1)
Psychiatric social worker	0.1 (0.5)	0.0 (0.0)	0.1 (0.6)	5 (2.7)	2.4 (2.1)
Nutritionist/dietitian	<0.1 (0.2)	<0.1 (0.1)	<0.1 (0.2)	4 (2.2)	1.3 (0.5)
Alternative medicine or therapy	<0.1 (0.2)	<0.1 (0.2)	<0.1 (0.1)	2 (1.1)	1.5 (0.7)
Other	<0.1 (0.2)	0.0 (0.0)	<0.1 (0.3)	2 (1.1)	2.0 (1.4)
Total	5.0 (6.6)	3.6 (5.1)	5.9 (7.4)		6.2 (6.9)

Data are presented as mean (standard deviation), except where indicated.
[a]FM severity categorised as moderate or severe based on FIQ total score (moderate, 39–<59; severe, 59–100).
FIQ: Fibromyalgia Impact Questionnaire; FM: fibromyalgia.

depression was associated with increasing FM severity. In comparison to the current analysis, subjects in these studies were not participating in a clinical trial and so were not subject to strict inclusion/exclusion criteria. In addition, subjects in these studies were not required to have a confirmed diagnosis of depression.

FM-related impact on work productivity and activity impairment was substantial. Less than half of the total population in the current analysis were employed, compared with 70.5% of women aged 45 to 54 years as reported

Table III. Healthcare resource utilisation and out-of-pocket expenditure in the 3 months preceding randomisation.

	Total population (n=193)		FM severity[a]			
			Moderate (n=71)		Severe (n=119)	
	n (%)	Expenditure	n (%)	Expenditure	n (%)	Expenditure
Physical treatments	67 (34.7)		29 (40.8)		37 (31.1)	
US$	37 (19.2)	167.4 (164.7)	17 (23.9)	136.5 (128.1)	19 (16.0)	196.1 (194.6)
€	23 (11.9)	116.5 (108.6)	7 (9.9)	155.7 (126.3)	16 (13.4)	99.4 (99.4)
C$	7 (3.6)	109.3 (96.9)	5 (7.0)	107.0 (116.0)	2 (1.7)	115.0 (49.5)
Supplements	61 (31.6)		20 (28.2)		40 (33.6)	
US$	41 (21.2)	93.5 (177.4)	16 (22.5)	60.1 (67.4)	24 (20.2)	117.2 (224.5)
€	14 (7.3)	90.1 (77.3)	2 (2.8)	35.0 (21.2)	12 (10.1)	99.3 (79.8)
C$	6 (3.1)	47.3 (31.2)	2 (2.8)	70.0 (42.4)	4 (3.4)	36.0 (22.4)
Prescription medicines	162 (83.9)		59 (83.1)		101 (84.9)	
US$	101 (52.3)	88.6 (202.4)	42 (59.2)	66.3 (91.5)	57 (47.9)	107.4 (257.1)
€	47 (24.4)	49.2 (60.9)	12 (16.9)	47.3 (53.6)	35 (29.4)	49.9 (63.9)
C$	14 (7.3)	111.6 (139.6)	5 (7.0)	71.6 (70.8)	9 (7.6)	133.9 (166.2)
Non-prescription medicines	168 (87.0)		61 (85.9)		104 (87.4)	
US$	103 (53.4)	41.2 (57.0)	43 (60.6)	34.4 (46.3)	57 (47.9)	46.8 (64.7)
€	46 (23.8)	61.2 (121.5)	12 (16.9)	18.0 (42.3)	34 (28.6)	76.5 (136.4)
C$	19 (9.8)	52.7 (53.8)	6 (8.5)	35.0 (26.8)	13 (10.9)	60.9 (61.7)
Professional services	145 (75.1)		52 (73.2)		91 (76.5)	
US$	92 (47.7)	114.8 (330.9)	38 (53.5)	60.0 (109.0)	52 (43.7)	157.4 (427.1)
€	40 (20.7)	276.0 (439.5)	10 (14.1)	430.0 (727.6)	30 (25.2)	224.7 (290.7)
C$	13 (6.7)	30.8 (83.1)	4 (5.6)	15.0 (30.0)	9 (7.6)	37.8 (99.2)
Total	177 (91.7)		65 (91.5)		109 (91.6)	
US$	110 (57.0)	307.1 (568.3)	47 (66.2)	209.1 (208.0)	60 (50.4)	391.9 (738.6)
€	49 (25.4)	410.4 (444.2)	13 (18.3)	480.3 (638.7)	36 (30.3)	385.2 (358.2)
C$	19 (9.8)	211.3 (251.9)	6 (8.5)	217.2 (180.7)	13 (10.9)	208.5 (285.6)

Expenditure is presented as mean (standard deviation).
[a]FM severity categorised as moderate or severe based on FIQ total score (moderate, 39–<59; severe, 59–100).
C$: Canadian dollars; €: Euros; FIQ: Fibromyalgia Impact Questionnaire; FM: fibromyalgia; US$: United States dollars.

by the US Bureau of Labor Statistics for 2014 (37). Of those who were working, overall work impairment was caused primarily by reduced productivity while working, but days missed because of FM were also a factor. Work productivity and activity impairment worsened as FM severity increased. Work and activity have been previously assessed in FM patients. In FM subjects participating in the 2008 US National Health and Wellness survey (11), an annual cross-sectional study, scores for work productivity and the degree of activity impairment were comparable to those in the current study. Scores for overall work impairment and activity impairment reported in the total population in the current analysis are greater than in patients with other neuropathic pain conditions, including spinal cord injury (38), painful diabetic peripheral neuropathy (39), post-trauma or post-surgical neuropathic pain (40), idiopathic painful peripheral neuropathy with small fiber involvement (41), and neuropathic pain of mixed aetiology (42).

The number of visits to healthcare professionals in the 3 months preceding randomisation in those patients who reported at least one visit was similar to the average number of visits reported in an observational study in the United States that utilised a similar questionnaire (43). In the current analysis, more visits were reported in patients with severe FM than in those with moderate FM, but the specialties visited were similar. The lack of hospitalisations and few ER visits in the current analysis was perhaps due to the chronic rather than the acute nature of FM and the eligibility requirements of the study.

Physical treatments were used more often in patients with moderate FM than in those with severe FM, perhaps reflecting the more frequent visits to massage therapists, chiropractors, and acupuncturists. In the preceding 3 months, 50.4 hours, or 6.3 work days (assuming 8 hours per working day), of unpaid help was provided for ADL, the equivalent of 5.0 working weeks per year (assuming 40 hours per working week). Patients with severe FM received more unpaid help than patients with moderate FM. The time spent providing unpaid help represents a considerable burden on FM caregivers. A previous study reported that FM caregivers provided almost 10 working weeks of unpaid help per year (7).

Out-of-pocket expenditure was considerable. Expenditure varied by geographic location, perhaps reflecting differences in healthcare provision, service availability, and cost among locations, although the small sample size of patients from outside of the United States may prevent definitive conclusions being drawn. In addition, there was no consistency on expenditure when analysed by FM severity, with the exception of greater expenditure for both prescription and non-prescription medicines in those with severe FM. Three-month out-of-pocket expenses in FM patients have been reported previously. A cross-sectional survey revealed mean total out-of-pocket expenses ranging from US$390–731, with ex-

penditure significantly increasing with increasing FM severity (13). These values are higher than reported here but included direct medical costs, such as diagnostic tests, physician office visits, hospitalisations, and ER visits, the costs of which were not covered in the current study.

This study had several limitations. Participants had to meet the entry criteria for the original clinical trial, including having moderate to severe pain and a lack of severe depression, so these findings may not be generalisable to the wider population. Detailed information on depression diagnosis, course of the condition, and current patient status relating to depression was unavailable, but the study was designed to assess the burden of FM not depression. Background antidepressant medication was limited to a single SSRI or SNRI, and a stable dose for at least the 2 months prior to randomisation was required. Most patients had moderate or severe FM and only 2 patients were categorised as having mild FM; therefore the burden of FM in this subset of patients was not determined. This was a post hoc study and the analysis by FM severity was not part of the original analysis plan. Only out-of-pocket expenses were reported; therefore the full overall cost of FM in these patients was not determined. Lastly, the patients in this study had FM and comorbid depression, but the study did not take into account the burden associated with depression. The overall symptom burden, impairment of work and activity, and use of healthcare resources in these patients may be greater than reported here.

In summary, patients with FM taking antidepressant medication for comorbid depression who were enrolled in a clinical trial had a large symptom burden that negatively impacted on work productivity and other activities, and increased healthcare resource use and burden on caregivers. The burden of FM worsened as FM severity increased. Since a relatively large proportion of FM patients take antidepressant medication for comorbid depression (1, 19), the burden of FM in these patients outside of a controlled clinical environment may be examined in future studies.

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