

Fibromyalgia: Disease Synopsis, Medication Cost Effectiveness and Economic Burden

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Abstract Fibromyalgia (FM) primarily affects women, and it is increasingly recognized by health care providers as more patients seek assistance for their chronic pain conditions. FM patients suffer from reduced quality of life, daily functioning and productivity. A single FM patient can cost society tens of thousands of dollars each year, with the overall expense increasing alongside disease severity. Indirect costs account for the majority of total expenditures and involve losses in productivity, reduced work hours, absenteeism, disability, unemployment, early retirement, informal care and other out-of-pocket costs. Health care utilization increases in concert with the severity of illness. Moreover, FM patients often have several comorbid illnesses (e.g. depression, anxiety and sleep disturbances), resulting in extreme escalation of overall health care expenditures. Medications with the best efficacy in the treatment of FM include the tricyclic antidepressants amitriptyline and nortriptyline, cyclobenzaprine (a skeletal muscle relaxant), tramadol, duloxetine, milnacipran, pregabalin and gabapentin. Corticosteroids, nonsteroidal anti-inflammatory drugs, benzodiazepines and opioid analgesics, with the exception of tramadol, are not considered efficacious. Medication selection should be individualized and influenced by the severity of illness and the presence of comorbidities and functional disabilities.

Key Points for Decision Makers

Chronic pain conditions such as FM are the most common cause of work-related disability leave. Work hours are frequently reduced by 50–75 %, and it is not uncommon for FM patients to become disabled and/or unemployed. The proportion of women with FM who are able to preserve their jobs has been reported to be between 34 and 77 %. Additionally, unemployment rates from 51 % to as high as 80.6 % have also been documented in the literature.

There is agreement among researchers that FM is associated with a significant cost burden. Over a 9-year period, hospital charges in the USA for FM patients amounted to approximately \$1 billion. In France, lost productivity accounted for the majority (88.5 %) of the costs, and the average cost per fibromyalgia patient escalated as the severity of illness increased (severe €10,087, moderate €6,633, mild €5,473), equating to a substantial patient and societal burden.

Amitriptyline, pregabalin and duloxetine have been reported to be cost effective medications for the treatment of FM.

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1 Introduction

Fibromyalgia (FM) is the most common cause of widespread musculoskeletal pain, affecting 2 % or more than 6 million patients in the USA and 4.7 % of Europeans [1–4].

It occurs primarily in women, affects 2–6 % of the world's population and is characterized by chronic widespread musculoskeletal pain, fatigue, headache, non-refreshing sleep, cognitive dysfunction, anxiety and mood disturbance [1–4]. FM sufferers frequently report limitations in physical functioning and activities of daily living (ADLs), resulting in decreased work productivity and health-related quality-of-life (HRQOL) [5–7]. The mental health-related symptoms, primarily depression and anxiety, have been found to be directly associated with FM pain [8–10]. Interestingly, these types of psychological symptoms have not been well documented in other neuropathic pain states [8, 9]. Moreover, reductions in pain severity have been shown to significantly improve FM-related fatigue and function, sleep disturbance and overall sleep problems, as well as patient HRQOL as measured in the eight domains (i.e. general health, physical functioning, emotional role, social functioning, mental health, bodily pain, vitality) of the Short Form-36 (SF-36) quality-of-life (QOL) instrument [10].

FM is increasingly recognized by health care providers (HCPs) as more patients seek assistance for their chronic pain conditions. This escalation in office visits has enhanced recognition of FM as a common medical condition, as well as its potential to increase use of health care resources [11–13]. A negative impact on work productivity has also been reported, creating significant patient and societal burdens [5, 6, 14, 15].

Additionally, the majority of FM patients have three or more comorbid conditions, with sleep disturbance being reported as the most common, followed by depression, anxiety, headache/migraine and chronic fatigue [12]. They are nearly four times as likely to receive pain-related medications, including antiepileptics, benzodiazepines, opioids, antidepressants and muscle relaxants, when compared with non-FM sufferers [12]. Approximately 85–90 % of FM patients are taking at least one prescription medication, with the majority taking two or more medications for their illness [11]. The most commonly prescribed medications for FM sufferers are antidepressants, followed by opioids and nonsteroidal anti-inflammatory drugs (NSAIDs). Frequently prescribed medication combinations include antidepressants/opioids, antiepileptics/antidepressants and hypnotics/opioids [11, 12].

The objectives of this overview are to briefly summarize how FM is managed, including what medications are the most cost effective, and to provide insight into FM's impact on the health care system, workplace and, most importantly, the individual patients themselves. Therefore, the information presented herein is not the product of a 'meta-analysis' research methodology and should not be considered as such.

2 Diagnostics and Treatment

The 1990 American College of Rheumatology (ACR) criteria for FM requiring an individual to possess both a history of chronic widespread pain and ≥ 11 of 18 possible tender points on physical examination were updated in 2010 to a simple clinical case definition [16]. Measurement of tender points is no longer required and has been replaced with a symptom severity (SS) scale and an appraisal of the number of painful body regions, using the widespread pain index (WPI). The SS scale includes a 4-component scale measuring cognition, non-refreshing sleep, fatigue and other somatic symptoms. The diagnostic definition of FM, using the updated case format, is WPI ≥ 7 and SS scale score of ≥ 5 ; or WPI 3–6 and SS scale score of ≥ 9 .

The 2010 ACR criteria now recognize the importance of quantitative measurement of widespread pain (the WPI), incorporate crucial FM symptoms into the diagnostic benchmarks and provide severity scales to measure the magnitude of widespread pain and symptom severity [16]. As a result, the 2010 benchmarks correctly classified 88.1 % of FM cases, representing a significant increase (~ 13 %) in identification of FM diagnosis as compared with the 1990 ACR criteria [16]. Of important note is that the 2010 ACR criteria were derived from a specialty patient care environment and did not involve primary care patients. Additionally, patients with other rheumatic conditions (e.g. rheumatoid arthritis and systemic lupus erythematosus) were excluded. The 2010 ACR criteria are noticeably more patient specific, however, and offer enhanced quantitative evaluation. Therefore, these new clinically based measurements should easily assist primary care providers in identifying FM patients.

Given the fact that FM encompasses widespread pain and tenderness, fatigue, sleep disturbance, cognitive problems, anxiety and mood disturbance, no single treatment is currently adequate to target all symptoms [16, 17]. FM patients require multidisciplinary management using a comprehensive multifaceted treatment plan that integrates ongoing patient education, pharmacotherapy, cognitive behavioural therapy (CBT), lifestyle changes (e.g. stress reduction, sleep hygiene), exercise and physical therapy [18]. Complementary and alternative medicine (e.g. dietary supplements, massage therapy, acupuncture, yoga, tai-chi, meditation) may be helpful in FM patients; however, research documenting their effectiveness remains ongoing.

Medication selection is individualized and influenced by the severity of illness and the presence of comorbidities and functional disabilities. In order to optimize therapy, frequent patient monitoring is required, with treatments exclusively tailored to each patient's response. Medications with the best efficacy in the treatment of FM include the tricyclic antidepressants (TCAs) amitriptyline and

nortriptyline, cyclobenzaprine (a skeletal muscle relaxant), tramadol, duloxetine, milnacipran, pregabalin and gabapentin [2, 18–20]. Duloxetine, pregabalin and milnacipran are US Food and Drug Administration (FDA) approved for FM. TCAs, duloxetine and milnacipran are considered first-line agents [21]. While selective serotonin reuptake inhibitors (SSRIs), including fluoxetine, sertraline, paroxetine, citalopram and escitalopram, may be helpful in treating depression and/or anxiety symptoms, they have been cited as ineffective in treating chronic pain states such as FM and neuropathic pain [2, 18–22].

Corticosteroids, nonsteroidal anti-inflammatory drugs (NSAIDs), benzodiazepines and opioid analgesics, with the exception of tramadol, are not considered efficacious in FM [2, 18–20]. Tramadol prescribed with or without acetaminophen is useful, however, in significantly reducing pain intensity and improving patient functioning [22]. It is important to note that tramadol should not be prescribed in patients with seizure disorders, because of its ability to lower the seizure threshold [20].

3 Medication Cost Effectiveness

Cost effectiveness studies of FM pharmacotherapy are beginning to appear in the literature. Lloyd and colleagues examined the cost effectiveness of pregabalin in severe FM compared with placebo, duloxetine, milnacipran, gabapentin, tramadol and amitriptyline [23]. A decision-analytic model comparing pregabalin (doses of 150 mg and 225 mg twice daily) with placebo and other FM medications was developed in patients with severe FM (Fibromyalgia Impact Questionnaire [FIQ] score ≥ 59 , pain score ≥ 6.5). Response rates were defined as $\geq 30\%$ improvement from the baseline pain score, plus a Patient Global Impression of Change (PGIC) rating of ‘much improved’ or ‘very much improved’. The cost-effectiveness endpoints of this study were resource utilization and the costs per responder at 12 weeks and 1 year. The model determined that pregabalin was a cost-effective choice in treating severe FM (Table 1). Both dosages of pregabalin were significantly better than placebo, which was found to be less effective and more expensive. At the 1-year endpoint, pregabalin was cost saving and more effective than placebo, duloxetine, tramadol, milnacipran and gabapentin. Amitriptyline, however, was the preferred and ‘most’ cost-effective medication in the group, with an incremental cost per responder day of US\$6.

A study conducted in the UK constructed a similar decision-analytic model comparing pregabalin 300 mg or 450 mg daily with placebo, duloxetine, gabapentin, tramadol and amitriptyline [24]. The definitions used to define severe FM and response rates were the same as those used

Table 1 Societal costs (in 2009 US\$) and responder days for placebo and medications used to treat fibromyalgia in the USA [23]

Treatment	Societal costs	Responder days
Amitriptyline	\$36,464	129.76
Pregabalin 225 mg	\$36,418	121.78
Pregabalin 150 mg	\$37,565	119.16
Tramadol	\$37,041	109.96
Duloxetine 120 mg	\$38,476	92.51
Duloxetine 60 mg	\$38,001	90.27
Gabapentin	\$37,788	90.03
Milnacipran 100 mg	\$38,380	72.09
Milnacipran 200 mg	\$38,197	66.38
Placebo	\$38,358	59.58

in the previously mentioned study. The primary effectiveness endpoint, however, was quality-adjusted life-years (QALYs). The cost (in 2008 values) per QALY gained (CQG) for pregabalin 450 mg versus duloxetine 60 mg and 120 mg was £19,224 (US\$33,834) and £14,096 (US\$7,209), respectively, with £35,737 (US\$59,601) for gabapentin and £98,072 (US\$172,607) for tramadol. Additionally, the model found that both pregabalin 300 mg and 450 mg dosages were cost effective when compared with placebo or duloxetine. Amitriptyline once again dominated in cost effectiveness over placebo and all other medications.

Cost-effectiveness research completed in the USA also used a Markov model to evaluate the economic and clinical advantages of duloxetine in managing FM symptoms over a 2-year period [25]. Clinical treatment guidelines for tricyclic antidepressants (TCAs), serotonin-norepinephrine reuptake inhibitors (SNRIs), anti-convulsants and opioids were utilized to construct a base-case treatment sequence. QALYs and additional symptom-control months (SCMs) were the main outcome measures. The results of the study were that for every 1,000 patients, first-line duloxetine, when compared with the sequence without duloxetine, resulted in an additional 665 SCMs and 12.3 QALYs, at a cost of US\$582,911 (in 2009 values), equivalent to incremental cost-effectiveness ratios (ICERs) of US\$877 per SCM and US\$47,560 per QALY. The use of duloxetine, compared with no duloxetine, as a second-line medication in FM resulted in an additional 460 SCMs and 8.7 QALYs at a cost of US\$143,752, equivalent to ICERs of US\$312 per SMC and US\$16,565 per QALY. The authors concluded that prescribing duloxetine as part of the standard FM treatment sequence lengthened the time during which patients had their pain under control and was cost effective when compared with commonly adopted treatment response thresholds.

A cost-effectiveness analysis using a Markov model from a Mexican Public Health System perspective evaluated the expenditures and effectiveness for amitriptyline (50 mg/day), fluoxetine (80 mg/day), duloxetine (120 mg/day), gabapentin (900 mg/day), pregabalin (450 mg/day), tramadol with acetaminophen (150 mg and 1,300 mg/day), and amitriptyline/fluoxetine (50 mg and 80 mg/day) for the treatment of FM [26]. The authors used 2006 data from the Mexican Institute of Social Security databases, expressed in 2010 Mexican Pesos (MXN\$), to retrieve direct medical costs for FM treatment. The visual analogue scale was used to assess pain relief. Improvements in functionality were assessed with the FIQ. Outcome and response measures determined that pregabalin achieved in the best pain control at 44.8 %, followed by gabapentin (38.1 %) and duloxetine (34.2 %). Not surprisingly, amitriptyline resulted in the lowest treatment expenditure at MXN\$9,047 (US\$696), followed by fluoxetine (MXN\$10,184 or US\$783) and amitriptyline/fluoxetine (MXN\$10,866 or US\$836). The probability of moving to a lower state of pain (from severe to moderate or from moderate to mild) or effective pain control was defined in the model as a decrease in pain by 50 %, as measured by the visual analogue scale, and an improvement in FIQ by 30 % when compared with baseline. When comparing pregabalin with amitriptyline, the additional cost per patient to achieve better pain control and improved functionality was between MXN\$50,000 (based on willingness to pay) and MXN\$75,000 (based on overall improvement) annually. Utilizing a hypothetical level of willingness to pay of MXN\$50,000 (US\$3,846) for one additional patient for adequate pain control and MXN\$75,000 (US\$5,769) for overall improvement, pregabalin was found to be a cost-effective alternative in 60 and 80 % of cases, respectively. The authors reported that using a conversion rate of MXN\$13 to US\$1, these expenditures (levels of MXN\$50,000 and MXN\$75,000) are well below the GDP per capita in the country (~MXN\$126,737 or US\$9,749). Therefore, on the basis of these parameters, the researchers found that the alternative medications (tramadol/acetaminophen, duloxetine, gabapentin, amitriptyline and fluoxetine) would be highly cost effective as well, as was also suggested by the World Health Organization [26]. On the basis of the research conducted in the UK [24] and the USA [25], the researchers concluded that these results from the Mexican Public Health System model would be consistent with recommending duloxetine as a second-line option for FM patients [26].

Cappelleri and colleagues [27] utilized data from three randomized clinical trials involving FM patients with mild, moderate or severe disease to examine the economic benefits of pregabalin 300 mg ($N = 551$) and 450 mg ($N = 552$), both doses being given twice daily, versus

placebo ($N = 558$). They found that treatment with pregabalin 450 mg resulted in significantly less indirect expenditures ($p < 0.0001$) and total expenditures ($p < 0.005$) than placebo. Appropriate pharmacotherapy did result in a shift towards reduced FM severity and cost of care in the population that was studied [27].

4 Absenteeism and Productivity

Chronic pain conditions are the most common cause of work-related disability leave [5, 6, 28]. They account for the largest indirect expenditures for society and significant patient economic, social, educational and vocational burdens [28]. The resultant illness-related loss of functioning and disability lead to large productivity deficits and poor HRQOL [5, 6, 9]. FM patients are often required to change to different work positions and tasks as the severity of their illness increases [5, 28]. Work hours are frequently reduced by 50–75 %, and it is not uncommon for FM patients to become disabled and/or unemployed [5, 28–30]. The range of women with FM who are able to preserve their jobs has been reported to be between 34 and 77 % [30, 31]. Additionally, unemployment rates from 51 % to as high as 80.6 % have also been documented in the literature [32, 33].

Those employees who do not lose their jobs continue to have significant struggles in their work–life functioning with FM. From an internet survey of 2,596 US FM patients, Bennett and colleagues discovered that those who remained at work thought their productivity were highly compromised, with frequent absenteeism and reduced work hours as a result of FMS-related symptoms [34]. Disability claims in this population amounted to about 20 %, with 6 % reporting the use of workman's compensation benefits. Detriments to personal life included difficulties with recreational activities (97 %) and heavy household duties (93 %), and troubles in lifting or carrying weights of 25 pounds or more (93 %). Consistent with other research, work hours were typically reduced by 50–70 % in the study participants [34].

FM patient employees are also considered to be at high risk of incidental loss of productivity, with rates between 1.9 to 3 times those in healthy controls [15, 35–37]. They are absent from work for an average number of 30 working days (15 %) per year [15, 36]. A study involving 8,513 FM employees in the USA, 8,418 employees with osteoarthritis (OA) without FM and 7,260 employee controls found that the work loss in FM patients was nearly three times that in the control cohort (29.8 versus 10.5 days, $p < 0.0001$) and significantly higher than that in OA patients without FM (29.8 versus 25.7 days, $p < 0.0001$) [15].

Schaefer and colleagues [37] reported that the most common reasons for FM-related loss in productivity in the USA were fatigue, chronic pain, inadequate or non-refreshing sleep, and comorbid illness (e.g. depression, anxiety). Furthermore, employment status differed significantly ($p < 0.001$) on the basis of FM severity, with a higher proportion of mild FM patients (71.4 %) being employed (full-time or part-time) than moderate FM (61.2 %) or severe FM cases (28.5 %) [37]. Disability, unemployment and/or early retirement were found to be directly related to disease severity, with the incidences of absenteeism for severe, moderate and mild FM being reported as 52.6, 22.4 and 9.6 %, respectively; 36.1 % of severe FM sufferers and 14.3 % of moderate FM sufferers described as fully disabled [37]. There were no reports of disability among the mild severity level in this study.

5 Impact on Quality of Life

The SF-36, FIQ and Revised Fibromyalgia Impact Questionnaire (FIQR) are frequently utilized to evaluate FM QOL. The FIQR is a 21-question instrument measuring HRQOL [9, 10]. The FIQR is closely correlated to the FIQ and shows a good association with similar domains in the SF-36. FIQR scoring characteristics are comparable to those of the original FIQ. Therefore, it is possible to assess previous FIQ scores with future FIQR results. The FIQR has wide-ranging psychometric properties, discriminates between FM patients and patients with rheumatoid arthritis, systemic lupus erythematosus or major depressive disorder, takes just over a minute to complete, is very simple to score and can be administered via an online survey [9, 10]. A copy of the FIQR is available online at <http://www.fmmgmt.com/pdf/Quiz/FIQR.pdf>.

When compared with the general population or individuals with other pain states such as OA, gout, epicondylitis, herniated disk, whiplash, systemic lupus erythematosus or rheumatoid arthritis, FM sufferers have significantly lower scores on all eight domains of the SF-36, indicating reduced quality of life, and demonstrating a very consistent pattern of disease-related impairment (high scores) on the FIQ and FIQR [10, 38–43]. Thus, the magnitude of the overall health-status burden of FM is at least as large as that of a variety of widely accepted health conditions that are already considered as impairing [44]. Comorbid illness in the FM patient will obviously impair HRQOL even further. Interestingly, one study showed that male FM patients are at an even greater risk of experiencing poor health status than their female counterparts, even though FM is nine times as prevalent in females [44].

6 Health Care System Burden

Several studies have been conducted on FM's burden on the healthcare system [11–15, 44–55]. There is agreement among researchers that FM is associated with a significant cost burden. Table 2 provides a summary of annual expenditures per patient from several countries. One of the earliest studies, completed by Wolfe and colleagues [50], was a 7-year prospective follow-up involving 538 FM patients in the USA. The average cost per patient per year was US\$2,274 (in 1996 values), with hospitalization being the largest expenditure contributor, followed by medications at US\$882 and US\$731, respectively.

Two cross-sectional studies (one in the USA and the other in France and Germany) evaluated health resource utilization (HRU) in 442 FM patients (203 in the USA, 70 in France and 169 in Germany) [11]. HRU information related to physician office visits, hospitalizations, diagnostics tests and prescription medications was obtained via a chart review; patient out-of-pocket expenditures and lost productivity data were collected by patient 'self-report' questionnaires. Most of the participants were taking one prescription medication (92 % in the USA, 83 % in France and 93 % in Germany), and the majority were taking two or more medications (73 % in the USA, 70 % in France and 56 % in Germany). Interestingly, the types of medications that were prescribed varied by region, as did the severity of illness and patient satisfaction with the prescribed medications (Table 3). The authors reported that the mean adjusted annual direct costs (2009 data) per patient were significantly higher in the USA (US\$7,087) than in Germany (US\$2,417) and France (US\$481), as were the total costs (US\$18,671 in the USA, US\$10,743 in France and US\$10,132 in Germany). Indirect costs, which represented the majority of all costs, were higher in Germany (US\$10,001) and in France (US\$8,718) than in the USA (US\$6,431) [11]. The USA had the highest total cost per FM patient at US\$18,671, followed by France at US\$10,743 and, finally, Germany at US\$10,132. Medication-related expenditures were much higher in the USA (US\$3,419) than in France (US\$312) or Germany (US\$606). Because there were reduced medication-related expenditures reported in France, FM sufferers there were less satisfied with their medication regimens and reported low effectiveness, as compared with those in the USA and Germany. Possible reasons for this include the three FDA-approved medications (duloxetine, pregabalin and milnacipran) available for the treatment of FM in the USA compared with none in Europe, as well as differences in medication pricing and the use of brand versus generic medications between countries. Physician office visit expenditures were also significantly higher in the USA (US\$1,529) than in France (US\$297) and Germany

Table 2 Total annual expenditures (in US\$) per patient and patient's out-of-pocket costs for fibromyalgia by countries studied

Reference	Country	Cost year	Total costs per patient (SD) ^a	Patient OOP costs (SD)	Notes	
Knight et al. [11]	USA	2009	\$18,671 (\$22,848)	\$750 (\$1,756)	2 separate, cross-sectional, observational studies; N = 442 (US 203; France 70; Germany 169)	
	France		\$10,743 (\$18,457)	\$74 (\$363)		
	Germany		\$10,132 (\$16,053)	\$297 (\$740)		
Berger et al. [12]	USA	2005	\$9,573 (\$20,135)		US health insurance claims database of 33,176 FM patient records	
Silverman et al. [13]	USA	2004	FM: \$10,911 (\$16,075) RA: \$10,716 (\$16,860)		Retrospective cohort from healthcare claims database of 14,034 FM, 7,965 RA and 331 FM + RA patient records	
	USA	1998	FM + RA: \$19,395 (\$25,440) FM: \$5,945 (\$7,776) RB: \$2,486 (NP)		US health insurance claims database of 4,699 FM patient records	
White et al. [15]	USA	2005	FM: \$10,199 (\$17,411) OA: \$10,861 (\$24,549) RB: \$5,274 (\$14,206)		US health insurance claims database of 8,513 FM, 8,418 OA and 7,260 control patient records	
	USA	1998	FM: \$5,163 (\$9,483) DP: \$8,073 (\$14,052)			
	USA	2009	FM + DP: \$11,899 (\$14,450) Mild FM: \$10,219 (\$13,502) Moderate FM: \$26,217 (\$32,866) Severe FM: \$42,456 (\$39,146)	\$1,560 (\$2,956) \$1,944 (\$3,232) \$2,925 (\$5,432)		Cross-sectional, observational study recruiting a sample of 21 mild FM, 49 moderate FM and 133 severe FM patients
	USA	1996	\$2,274 direct costs only			7-year prospective, longitudinal, multicentre study of 538 FM patients
Haviland et al. [51]	USA	1999–2007	\$1 billion in hospitalization costs over 9 years		Nationwide inpatient sample hospital database of an estimated 63,772 FM patients	
Kim et al. [52]	Korea	2009	\$1,481 (\$2,206) over 3 months		Cross-sectional, observational study recruiting 2,098 FM patients	
Winkelmann et al. [53]	France	2008	\$11,060 (\$20,815)		Cross-sectional, observational study recruiting 299 FM patients	
	Germany		\$10,158 (\$19,899)			
Perrot et al. [54]	France	2008	Total: \$11,060 (\$20,815) Mild FM: \$7,662 (\$17,993) Moderate FM: \$9,286 (\$18,897)	Total: \$144 (\$701) Mild FM: \$130 (\$384) Moderate FM: \$151 (\$599)	Cross-sectional, observational study recruiting 88 FM patients (17 with mild FM, 33 with moderate FM and 28 with severe FM)	
			Severe FM: \$14,122 (\$23,499)	Severe FM: \$103 (\$866)		
			FM: \$7,814 (NP) CLBP: \$8,533 (NP) AS: \$3,205 (\$1,793)	FM: \$2,334 (NP) CLBP: \$2,193 (NP) AS: \$715 (\$3,166)		
Boonen et al. [55]	Austria and the Netherlands	2002			Observational study recruiting 70 FM patients, 110 CLBP patients and 111 patients with AS	

Table 2 continued

Reference	Country	Cost year	Total costs per patient (SD) ^a	Patient OOP costs (SD)	Notes
Rivera et al. [56]	Spain	2010	Control: \$2,313 (\$3,807) FM: \$16,210 (\$14,475)		Prospective observational multicentre study recruiting 232 FM patients and 110 controls without FM

AS ankylosing spondylitis, *CLBP* chronic low back pain, *DP* depression, *FM* fibromyalgia, *NP* not provided, *OOP* out-of-pocket, *RA* rheumatoid arthritis, *RB* regular beneficiary, *SD* standard deviation

^a Rates of conversion to US\$ were based on the yearly average currency exchange rates, obtained from the US Internal Revenue Service website (see <http://www.irs.gov/Individuals/International-Taxpayers/Yearly-Average-Currency-Exchange-Rates>)

(US\$564). These findings were a result of differences in HRU and the cost of physician visits between countries. The researchers concluded that the significant HRU and costs found in the three countries revealed the considerable global economic burden of this disease [11].

An administrative claims database analysis from a large US employer compared 4,699 employees with at least one FM claim between 1996 and 1998 with a 10 % random sample of the overall beneficiary population [14]. The total annual costs for FM claimants were US\$5,945 versus US\$2,486 for the typical beneficiary (in 1998 values, $p < 0.0001$). Direct medical expenditures accounted for US\$4,393 and US\$1,939 of total annual costs for FM patients and typical beneficiaries, respectively ($p < 0.0001$). The prevalence of disability was twice as high among FM employees as it was in the overall employee cohort ($p < 0.0001$). The authors concluded that hidden disability-related costs and comorbidities can greatly increase the true burden of FM. Another study by these researchers found that the mean annual employer payments (direct plus indirect costs) per patient were US\$5,163 for FM only, US\$8,073 for depression only and US\$11,899 for FM plus depression (US\$US 1998) [46]. The incremental expenditures per FM claimant with depression (US\$9,413) were also reported as being higher than the aggregate (US\$8,264) of the incremental per-claimant costs of FM-only and depression-only claimants [46].

A US health insurance data study conducted in 2005 found that mean [standard deviation (SD)] annual expenditures for FM patients were approximately three times higher at US\$9,573 (US\$20,135) versus US\$3,291 (US\$13,643) for the randomly selected control group ($p < 0.001$); the median costs were five times higher (US\$4,247 versus US\$822) [12]. The mean age of the patients in this study was 46 years, and 75 % of the participants were women. This study confirmed that FM patients have a comparatively large number of comorbidities, as well as high levels of health care utilization and expenditures.

Research evaluating claims data (1999–2005) was conducted to examine HRU among matched FM, OA and control cohorts [15]. Employees with FM had more claims than employees with OA for mental health-related illness (e.g. depression, anxiety or sleep disturbance), chronic fatigue and most pain-related conditions (e.g. back pain, neurological pain, headache, migraine, abdominal pain or chest pain). FM patients had more hospital emergency room visits and less inpatient care, were more likely than OA patients to seek treatment from rheumatologists or non-physician specialists, and used significantly more medications, primarily antidepressants. Narcotic analgesics, however, were more commonly prescribed for OA patients. The total annual health care expenditures (direct and indirect) were US\$11,829 for FM and US\$12,303 for

Table 3 Fibromyalgia disease severity, most common medications prescribed and patient 'self-evaluation' in the USA, Germany and France [55]

	USA (%)	Germany (%)	France (%)
Disease severity			
Mild (FIQ score <39)	10	25	21
Moderate (FIQ score 39 to <59)	24	30	36
Severe (FIQ score 59 to 100)	66	45	43
Medication most commonly prescribed			
Anti-inflammatories		65	39
Antidepressants	56	34	34
Analgesics other than anti-inflammatories	51	31	60
Antiepileptics	36		
Anxiolytics			30
Patient self-evaluation			
Medications extremely to very effective	23	29	4
Patient extremely satisfied with pharmacotherapy	14	12	0
Patient somewhat satisfied with pharmacotherapy	47	39	42

FIQ Fibromyalgia Impact Questionnaire

OA, demonstrating that both FM and OA impose a significant and similar economic burden.

Research ($N = 203$) by Chandran and colleagues [49] conducted between August 2008 and February 2009 from 20 US community-based physician offices confirmed previous findings that direct and indirect costs associated with FM are higher among patients with greater severity of illness; indirect costs accounted for the majority of expenditures at all FM severity levels. There were significant ($p < 0.001$) differences in employment status across severity levels. While about 62 % of patients with mild FM were employed full time and none were disabled, only 19.5 % of those with severe FM were employed full time and 36.1 % reported being disabled. Among patients with moderate FM, 36.7 % were employed full time and 14.3 % were disabled. Sleep disturbance, especially insomnia, was the most common comorbid illness across all FM severity levels (mild 53.3 %, moderate 71.4 %, severe 69.2 %). Other comorbidities of significance as severity worsened were depressive symptoms, anxiety and major depressive disorder. Antidepressants, opioids and antiepileptics were the most commonly prescribed medications, with the number of medications prescribed increasing along with the severity of illness (mild 1.8, moderate 2.3, severe 2.8). The mean direct, indirect and total annualized expenditures by disease severity were all found to be significant. Indirect costs (mild 52.5 % of US\$10,219, moderate 78.4 % of US\$26,217, severe 78.1 % of US\$42,456) accounted for the majority of the total annual expenditures [49].

Recently published research conducted in Austria/the Netherlands, Spain, the USA, Korea and Europe affirms earlier findings on the effect of FM on HRQOL and/or that FM-related health economic expenditures impose a significant burden on the global society [51–56]. Over a 9-year period, hospital charges in the USA for FM patients

amounted to approximately US\$1 billion [51]. A European cross-sectional study of 299 FM patients conducted in France and Germany found that FM imposes a significant societal burden, with more than 75 % of these expenditures being driven by indirect costs resulting from lost productivity [53]. Consistent with other research findings, European FM sufferers with greater severity of illness had more than a 200 % difference in costs as compared with those with mild illness [53]. Perrot and colleagues [54] reported that the mean total annual costs per patient for treating FM in France was 7,900 (in 2008 euros) or US\$11,060, with direct costs of €910 (US\$1,274) and indirect costs of €6,990 (US\$9,831). Lost productivity accounted for the majority (88.5 %) of the costs, and the average cost per FM patient escalated as the severity of illness increased (severe €10,087, moderate €6,633, mild €5,473), equating to a substantial patient and societal burden [54].

7 Patient Out-of-Pocket Expenditures

As one might imagine, on the basis of the information presented, FM is very costly not only for society but to the patients as well. FM patients find themselves needing informal care, paid household assistants, specialized dietary supplements and other alternative therapies (e.g. spa treatments) [55, 57]. Research into patient out-of-pocket expenditures is very limited. Patient diaries or monthly questionnaires reveal that the mean number of hours per year for paid and unpaid household help was 107.5 and 66, respectively [55, 57]. Zijlstra et al. [57] reported that the hours per year of informal care in FM patients was 152. On the basis of these numbers, the expenditures relating solely to paid help and informal care can easily reach several thousand dollars per year for FM patients.

Patient out-of-pocket expenses in the USA for prescription and non-prescription medications, physical treatments, herbs, vitamins, other dietary supplements and professional services to assist with ADLs by severity level were recently examined [49]. The mean annualized total patient out-of-pocket expenses were significant and were found to increase by FM severity level (US\$1,560, US\$1,944 and US\$2,924 for mild, moderate and severe illness, respectively). In France, patient out-of-pocket costs (in 2008 values) for professional services to assist with ADLs amounted to US\$130 for mild illness, US\$151 for moderate illness and US\$150 for severe illness [54]. Research completed in Austria and the Netherlands reported that FM patients paid US\$2,334 (in 2002 values) annually out of pocket, which was comparable to out-of-pocket costs for chronic low back pain patients in the study with US\$2,193 in self-expenditures [55]. These out-of-pocket costs obviously produce additional hardship for FM sufferers as they attempt to cope with decreased work hours, reduced income and increased disability in their daily lives.

8 Conclusions

Fibromyalgia is a global chronic illness and affects a significant number of people. Clinical management of FM is challenging and must involve early disease detection and cost-effective pharmacotherapy, as well as input from multiple medical specialists and individualized patient regimens. The overall financial burden of FM around the globe is significant, comparable to those of other chronic conditions, and can cost society tens of thousands of dollars per patient. Those with greater severity of illness have larger overall expenditures and, when treated properly, the severity level can be reduced, thereby decreasing the total cost of care. Many FM patients are unemployed and disabled, and they experience losses in HRQOL, functioning and productivity, as well as rising out-of-pocket expenses for household help and informal care. Comorbid depression, anxiety and sleep disturbance can significantly contribute to the severity of illness and overall health care expenditures. Continued research and awareness of FM's impact on our society remain warranted.

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