

# Quality of Life in Patients with Fibromyalgia

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**Abstract:** *Objectives:* The aim of this review is to provide practicing clinicians with detailed information on the quality of life (QoL) of patients with fibromyalgia, and the medical and non-medical management effects on quality of life in fibromyalgia.

*Methods:* A systematic English language search of the medical literature from January 1980 to January 2013 using PubMed was conducted using the search terms “fibromyalgia” AND “quality of life.” The literature search revealed 1,086 publications; 259 were clinical trials on human patients, 230 were reviews and 20 were case reports. Three authors reached a consensus on selecting the studies based on specific inclusion and exclusion criteria. A total of 95 research studies were included in this review.

*Results:* Overall quality of life is severely impaired in patients with fibromyalgia. Comorbidities have a further negative impact on QoL. Substantial pain reductions resulting in improvement of QoL were observed with medications and non-medication interventions such as exercise, acupuncture, cognitive behavioral therapy, neurofeedback and multidisciplinary approach.

*Conclusion:* Fibromyalgia and its comorbidities including pain have a considerable negative impact on the quality of life of fibromyalgia patients. Substantial or moderate pain reduction seems to improve quality of life. A multidisciplinary approach appears to be most beneficial in management of this multifaceted illness, but more studies are needed to develop specific interventions necessary to alleviate pain and sufferings in these patients.

**Keywords:** Fibromyalgia, quality of life, pain, pain management, multidisciplinary approach.

## INTRODUCTION

Fibromyalgia (FM) is a condition marked primarily by chronic, widespread pain, tenderness of joints/muscles, fatigue, sleep difficulties, depression, anxiety, cognitive dysfunction, physical dysfunction, emotional dysfunction and poor quality of life (QoL) [1-3]. The prevalence of FM in United States is about 2% and it is estimated to affect over 5 million each year [1]. Females (3.4%) are generally more affected than males (0.5%) [4, 5]. FM usually develops during the early adolescent, rises in the middle age and peaks (at about 7.4%) between 70 to 79 years of age [4, 5]. The American College of Rheumatology (ACR) in 1990 published classification criteria for making the diagnosis of FM, which requires three months of chronic widespread pain affecting both sides of the upper and lower body, as well as the axial skeleton, and the presence of at least 11 of 18 tender points. The most updated criteria published by ACR in 2010 highlighted specific criteria using two clinician-rated measures: Wide Spread Pain Index (WPI) and the Symptom Severity (SS) scale. WPI (score range = 0-19) represents the number areas in which the patient

has had pain over the last week, and the SS scale (score range 0-12) is the sum of the severity of 3 symptoms: fatigue, unrefreshing sleep, and cognitive symptoms, plus the severity of somatic symptoms in general [1]. To diagnose FM, the patient has to meet the following three criteria: 1) WPI  $\geq 7$  and SS  $\geq 5$  or WPI 3–6 and SS  $\geq 9$ ; 2) Symptoms have been present at a similar level for at least 3 months; and 3) The patient does not have a disorder that would otherwise explain the pain [1].

FM is detrimental to an individual's QoL especially health-related QoL (HRQoL) [6], mainly in terms of vitality, mental health, and general health [7]. The concept of QoL has become increasingly important in studying this multifaceted medically disabling condition. The World Health Organization (WHO) defines QoL as the individuals' perception of their position in life in the context of the culture and value and also in relation to their goals, expectations, standards and concerns [8]. Most QoL measures include patient's reported perceptions of physical, psychological, and social domains. The most commonly used measures are the 36-item Short Form Health Survey (SF-36), Visual Analogue Scale (VAS), and Fibromyalgia Impact Questionnaire for QoL, pain and FM impact respectively [9]. As QoL research has been exponentially growing, the need arises for an in-depth

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review that synthesizes the available data on QoL in FM. This review aims at examining the QoL of patients with FM, its comorbidities and treatment effects, in order to answer the following questions:

1. What is the impact of fibromyalgia on QoL?
2. What are the effects of FM comorbidities on QoL?
3. What is the Impact of treatment on QoL in FM?

## METHODS

### Study Selection Criteria and Methodology

A systematic English language search of the medical literature from January 1980 to January 2013 using Medline/PubMed was conducted using the search terms “fibromyalgia” AND “quality of life.” The reference search revealed 1,086 publications; 259 were clinical trials on human patients, 230 were reviews and 20 were case reports. Three authors reviewed the abstracts identified in the search and reached consensus on the selected articles using the criteria described below. Inclusion criteria are: (1) publication in English or with available English translation, (2) peer-reviewed journal, (3) studies of any design focusing on FM, including meta-analyses and systematic reviews, (4) studies including instrument-measured QoL, and (5) QoL studies on FM treatments. Exclusion criteria are: therapy for chronic pain other than FM, and studies that did not include QoL measures.

### Data Extraction and Yield

The selection process yielded ninety-five studies that met the full criteria described above, including those specifically addressing HRQoL. Data was extracted and checked for accuracy, and the identified articles were then reviewed. Each selected study or article was analyzed by the type of study/objectives, number of subjects, measures, and outcomes.

## RESULTS

### 1. What is the Impact of Fibromyalgia on Quality of Life?

Reviewed studies show that patients with FM scored significantly lower on QoL measures [10-15], as highlighted in Table 1.

Patients with FM scored significantly lower on all-eight health status domains compared with people in the general population or patients with other specific conditions such as RA, osteoarthritis (OA) and

systemic lupus erythromatosis (SLE) [10]. Symptom domains that have the greatest impact on QoL are: pain, sleep disturbances, fatigue, depression, anxiety and cognitive impairment [11]. Overall, 25% of the FM patients will have a moderate improvement in the pain symptom overtime despite worsening of the illness [12]. Psychological factors seem to function as a pronounced disabling role in FM patients, with psychological distress being higher than those with other pain conditions such as complex regional pain syndrome (CRPS) or chronic low back pain (CLBP) [13, 14]. Male patients with FM experience worse QoL than depressed male patients, as depression is influential on mental health only, but FM impacts both physical and mental health [15].

### 2. What are the Effects of Fibromyalgia Comorbidities on Quality of Life?

The relationship between FM and psychiatric disorders is bidirectional, e.g., chronic pain could lead to depressive and anxiety symptoms. It is not uncommon for depression and anxiety to present hand-in-hand with pain, resulting in a low health-related QoL [16-35], as shown in Table 2.

FM aggregates 20-80% of the time with depressive disorders, and 13-63.8% of the time with anxiety disorders [16]. This suggests there must be a close link between FM and psychiatric, psychological, and behavioral factors [17, 18]. The prevalence of FM association with depression is still a subject of controversy among scholars. A study reported that approximately 30% of patients with FM met Diagnostic and Statistical Manual of Mental disorders, fourth edition (DSM-IV) criteria for depression with a 3 to 6-fold increased rate of mood disturbances [3]. Depression is associated with FM among women but not among men. Among females, depression severity is significantly correlated to FM severity [19]. Another psychiatric comorbidity problem to take into account is post-traumatic stress disorder (PTSD). There is increased prevalence of PTSD in FM patients who have major depressive disorder (MDD) [22]. However, FM and lifetime PTSD are not associated if individuals do not have lifetime MDD [22]. Lifetime PTSD was more prevalent in cases of diffuses pain, supporting the notion that pain and PTSD are bi-directional with one exacerbating the development of the other [22]. In a sample of combat-related PTSD patients, 49% met the criteria of FM according to the American College Rheumatology.

**Table 1: The Impact of Fibromyalgia on Quality of Life**

Reference	Measure	N	Summary of Findings
Ovalyolu <i>et al.</i> [4]	SF-36	530 patients (264 with RA, 149 with FS, and 117 with AS), 315 control	AS, FS, and RA have a negative impact on HRQoL.
Cacace <i>et al.</i> [5]	Fibromyalgia impact questionnaire (FIQ), Visual Analogue Scale (VAS)	53 female patients, 40 healthy female	Mean FIQ scores were 66.39 +/- 14.94 in FM patients and 13.15 +/- 5.37 in control subjects and the difference was statistically significant. This shows the association of fibromyalgia with a poor QOL.
Verbunt <i>et al.</i> [6]	FIQ, Symptom Checklist (SCL 90), SF-36	54 patients with FM (47 female), 22 patients with CRPS and 35 patients with CLBP	Patient's mental health explained better disability in FMS. Compared to patients with Complex Regional Pain Syndrome (CRPS) or Chronic Low Back Pain (CLBP), psychological distress was higher in FMS ( $p < 0.01$ ).
Arnold <i>et al.</i> [7]	Focus group with FMS patients	48 female	The negative impact of FMS on the patients is high especially on social, occupational functioning, and QOL.
Hoffman <i>et al.</i> [8]	SF-36, SF-12	n/a	FMS mental health summary scores fell 2 SD below the general population mean and physical health summary scores fell to 1 SD below the general population mean.
Yoshikawa <i>et al.</i> [11]	SF-36, BDI, the State-Trait Anxiety Inventory questionnaire	70 men	FMS negatively impacted on both physical and mental health in men with worse QOL than men with depression.
Dell'Osso <i>et al.</i> [12]	SCID-I/P, FIQ, MOS SF-36, HRQoL, TALS-SR	n/a	presence of a relationship between the lifetime exposure to potentially traumatic events, in particular loss events, and lifetime post-traumatic stress symptoms and the severity of illness and HRQoL in patients with FM
Schaefer <i>et al.</i> [13]	EQ-5D, FIQ, MAF, MOS-SS, HADS	203 patients with FM, 95% females	FM imposes a substantial humanistic burden, especially for productivity.
Walitt <i>et al.</i> [14]	SF-36	1555 patients with FM	25% had at least moderate improvement of pain over time
McDonald <i>et al.</i> [15]	US National Health and Wellness Survey	439 workers with FM, 4920 with back pain, 2670 with arthritis, 30868 control	Musculoskeletal pain conditions were highly prevalent and associated with a significant burden.
Salaffi <i>et al.</i> [16]	SF-36	2,652	QOL mental component is worse in FMS patients than RA patients and the general population.
Silverman <i>et al.</i> [11]	Analysis of variance (ANOVA), Mantel-Haenszel chi-square analysis	129	Self-reported FM severity was significantly associated with higher levels of current pain and sleep interference and the presence of comorbidity. Pain, functional disability, and fatigue severity were ranked as the top three criteria by highest proportion of physicians when evaluating FM severity
Choy <i>al.</i> [12]	Phone interview	800 patients, 1622 physicians	Most patients rated their chronic widespread pain as moderated to strong severe and symptoms were fairly to very disruptive and had a moderate to strong impact on their lives. Patients seek help from physicians not because of their symptoms per se, but because they have a poor QOL that is due to FM symptoms.

**Abbreviations:** AS=Ankylosing Spondylitis, AIMS II=Arthritis Impact Measurement Scale II, ANOVA=Analysis of Variance, BDI=Beck Depression Index, CLBP=Chronic Low Back Pain, CRPS=Chronic Regional Pain Syndrome, CWP=Chronic Widespread Pain, EQ-5D=EuroQol 5D, FIQ=Fibromyalgia Impact Questionnaire, FM=Fibromyalgia, FMS/FS=Fibromyalgia Syndrome, HADS= Hospital Anxiety and Depression Scale, HRQoL=Health-Related Quality of Life, MAF=Multidimensional Assessment of Fatigue, MOS SF-36=Medical Outcomes Study Short Form-36 Health Survey, MOS-SS=Medical Outcomes Study Sleep Scale, OE=Osteoarthritis, QOL=Quality of Life, RA=Rheumatoid Arthritis, SCID-I/P=Structured Clinical Interview for DSM-IV, SCL90=Symptom Checklist, SD=Standard Deviation, SF-12=12-item Short Form Health Survey, SF-36=36-item Short Form Health Survey, SLE=Systemic Lupus Erythematosus, TALS-SR=Trauma and Loss Spectrum Self-Report, and VAS=Visual Analogue Scale.

There are a number of important medical comorbidities to note, which can impact negatively on functioning and QoL. One of these important comorbidities in FM is sleep disturbance. In a study, 99% of participant had poor sleep quality that

significantly affected QoL [24]. A high prevalence of sleep disturbances in FM patients exacerbates the FM symptoms and these problems can be associated with depression [25]. Gastrointestinal (GI) problems are not uncommonly associated with FM. The most common

**Table 2: Fibromyalgia with Comorbidity Effects on the Quality of Life**

References	Measure	N	Summary of Findings
Gormsen <i>et al.</i> [19]	Clinician-rated Hamilton depression scale, self-rated major depression inventory, clinician-rated, Hamilton anxiety scale, self-rated anxiety inventory, SF-36.	84	7.1% FM patients met diagnostic criteria for major depression. Associations between pain and psychiatric symptoms were only found in the FM group although the intensity of pain was similar.
Lange <i>et al.</i> [21]	Various	n/a	Lower QOL is seen in FM patients with depressive symptoms in addition to loss of physical functioning, sleep and sexual dysfunction.
Aguglia <i>et al.</i> [22]	HAM-D, VAS, Paykel's List of Recent Life Events	30	Depressive symptoms are associated with greater impairments in FM such as higher pain perception, and worse QOL. 83.3% had clinically significant depressive symptoms (HAM-D score > 7).
Vishne <i>et al.</i> [20]	Sheehan Disability Scale (SDS), SF-36, Hamilton Depression Rating Scale (HDRS), Clinical Global Impression-Severity (CGI-S)	84	Depressed FM patients suffered from poorer QOL. More women with FM are experiencing depressive symptoms than men and their depressive symptom severity was significantly related to severity of FM.
Goldenberg [1]	Various	n/a	There is an overlap between FM, irritable bowel syndrome, and depression with commonly shared epidemiologic, clinical and biologic factors.
Roy-Byrne <i>et al.</i> [23]	Lifetime prevalence	571	In patients with FM, the prevalence of lifetime PTSD was 20% and lifetime MDD was 42%. Patients who had both tender points and diffuse pain had a higher prevalence of PTSD (OR=3.04, 95%, CI 2.0-5.8) compared with those who had neither.
Amital <i>et al.</i> [24]	Prevalence	124 males with PTSD	49% of PTSD patients met criteria for FM. In male patients, PTSD is associated with FM. FM had a negative impact on QOL in male patients with PTSD.
Fietta <i>et al.</i> [18]	Various	n/a	Depending on the study, FM patients had a 20-80% prevalence of depressive disorders and 13-64% prevalence of anxiety disorders with QOL being significantly affected.
Theadom <i>et al.</i> [26]	Positive and Negative Affect Schedule, the Pittsburgh Sleep Quality Index, the COPE, and the SF-36	83 FM and 83 healthy controls	Poor sleep quality was reported by 99% of FM patients, an important factor in health related QOL in FM.
Bigatti <i>et al.</i> [27]	Center for Epidemiologic Studies Depression Scale, the McGill Pain Questionnaire, the Pittsburg Sleep Quality Index, and the FIQ.	600	Sleep problems are highly prevalent in FM, leading to impairments in QOL.
Moldofsky H [28]	Various	n/a	Sleep-wake problems in FM are related to pain, fatigue, and impaired quality of life.
Pamuk <i>et al.</i> [30]	VAS, Anxiety-Depression Scale	310	GI symptoms such as belching, reflux, bloating, sour taste, and vomiting are more severe in FM compared to RA and controls ( $p < 0.01$ ). Dyspepsia and constipation related QOL disturbances are more prominent in FM ( $p < 0.01$ ).
Mathieu [28]	Various	n/a	Poor QOL, increased mood disorders and healthcare seeking, are seen in FM, chronic fatigue syndrome and irritable bowel syndrome (IBS).
lfergane <i>et al.</i> [39]	Various	20 male, 72 females	Lower QOL scores and higher mental distress patients are seen in FM comorbid with migraine. In migraine patients, FM was present in 22% of females and none in males.
Amital <i>et al.</i> [25]	FIQ, SF-36, VAS, the Premenstrual severity scale.	56	Lower QOL and increased tenderness in addition to increased psychiatric comorbidity has been shown in PMDD.
Kalichman [34]	Various	n/a	Sexual dysfunction in FM such as decreased sexual desire, arousal, orgasm, and increased painful intercourse were associated with decreased QOL.
Orellana <i>et al.</i> [35]	Various	n/a	Sexual dysfunction in FM may be related to depression and poor QOL.

(Table 2). Continued.

References	Measure	N	Summary of Findings
Couto <i>et al.</i> [31]	QOL Questionnaire	311	QOL is decreased in hemodialysis patients with FM. In addition these patients experience higher depression and anxiety.
Eyigor <i>et al.</i> [32]	FIQ, Brief Fatigue Inventory (BFI), SF-36, Quality of Life-C30	122	QOL is negatively affected among oncology patients with FM.
Buskila <i>et al.</i> [36]	Various	n/a	There is a significant overlap between FM and other immunological disorders such as SLE, RA, and Psoriasis with FM detected in 65%, 57%, and 24% of patients of the above disorders respectively, linked to poor QOL.
Kuriya <i>et al.</i> [38]	SF-36	146	Decline in physical component of QOL in SLE is associated with the presence of FM.
Wolfe <i>et al.</i> [40]	SLE Activity Questionnaire (SLAQ), SLE Symptom Scale (SLESS).	23,321 Patients with RA	22% of SLE and in 17% of RA patients had FM, affecting QOL.
Ranzolin <i>et al.</i> [39]	HAQ, SF-36, DAS28 score.	270	SF-36 scores of patients with RA are worse in patients with FM.
Buskila [37]	Various	n/a	Hepatitis C virus (HCV) is immunologically associated with numerous hematologic, renal, dermatologic, rheumatic, and autoimmune disorders such as FM.

**Abbreviations:** ACR=American College of Rheumatology, BFI=Brief Fatigue Inventory, CGI-S=Clinical Global Impression-Severity, CI=Confidence Interval, DAS28=Disease Activity Score in 28 joints, FIQ=Fibromyalgia Impact Questionnaire, FM=Fibromyalgia, FSFI=Female Sexual Function Index, HAM-D=Hamilton Rating Scale for Depression, HAQ=Health Assessment Questionnaire, NP=neuropathic pain, PMDD: Post Menstrual Dysphoric Disorder, PTSD=post-traumatic stress disorder, QOL=Quality of Life, RA=Rheumatoid Arthritis, SF-36=36-item short Form health Survey, SLE=Systemic Lupus Erythematosis, VAS=Visual Analogue Scale.

GI comorbidity is irritable bowel syndrome (IBS) [3], and it is associated with low QoL [27]. FM is common in patients with autoimmune disease [29, 30]. Its coexistence negatively affects the QoL of FM patients [29-31]. It is related to worst scores on the disease activity score in 28 joints (DAS28) in RA patients [31]. Up to 65% of SLE meets the criteria of FM. This overlap is also seen in patients with Hepatitis C, arthritis, vasculitis, arthralgia, and myalgia [28-32]. FM is common among females with migraine headache. Patients suffering from migraine associated with FM had lower QoL scores, and higher levels of mental distress [33]. Headaches are usually considered part of FM and not merely a comorbid disease. Sexual dysfunction is very common in female patients with FM, especially with the coexistence of MDD and this negatively affects the QoL of patients [34, 35].

### 3. What is the Impact of Treatment on QoL of FM Patients?

As the presentation of FM differs from patient to patient, the treatment approach should be individualized based on the symptoms, the symptoms severity, and the potentially existing comorbidities or functional impairments. The goal of treatment should be to address and alleviate chronic, widespread pain, which will consequently result in improvement in the QoL [36-100], as shown in Table 3.

#### a. Medication Effects on QoL in FM

##### Pregabalin

Pregabalin (Lyrica®), an anticonvulsant drug, is the first agent that was approved in 2007 by the USFDA for the treatment of FM. This agent is safe and efficacious in reducing pain and other symptoms of FM such as disturbed sleep and fatigue. It also improves daily function and HRQoL in some patients [39-44]. A multicenter, double-blind, 8-week randomized clinical trial on 150mg, 300mg and 450mg daily of pregabalin for the treatment of pain, disturbance of sleep, fatigue, and quality of life in 529 patients with FM compared with placebo showed that Pregabalin at 450 mg/day was effective in reducing symptoms of pain, sleep disturbances, and fatigue in FM patients compared with placebo [45]. Another multicenter, randomized, double-blind, placebo-controlled trial assigned 748 FM patients to receive either placebo or pregabalin 300, 450, or 600 mg/day for 13 weeks. This study demonstrated that pregabalin was safe and effective in improving pain, sleep, and quality of life in FM patients compared to control [46]. The regular daily dose is 300mg to 450mg daily. Adverse effects reported are dizziness, increased sleep, weight gain, dry mouth, blurred vision, extremities edema, constipation, euphoric mood, and difficulty with attention. These adverse effects appeared to be dose dependent [45, 46].

Table 3: Effects of Treatment of Fibromyalgia on the Quality of Life

Reference	Design	Measure	N	Summary of Findings
<b>(A) Reduction of Pain effects on QOL and other outcomes in Fibromyalgia:</b>				
Moore <i>et al.</i> [44]	Randomized clinical Trials (RCTs)	QALY	2,575	Reduction of pain intensity predicts improved quality of life and other positive outcomes in FM. Patients who are not experiencing pain reductions are less likely to experience improved QOL and would need to be tried on alternative interventions.
<b>(B) Medication-Only effects on Pain and QOL of Fibromyalgia:</b>				
<b>I) General Medications Studies</b>				
Goebel A [41]	Review of RCTs	Various	n/a	Intravenous Immunoglobulin (IVIg) is effective to reduce pain in complex regional pain (low-dose). Open label trials showed evidence in other pain syndromes such as FM. However, dosing and specific effects on QOL, remain to be studied further.
Häuser <i>et al.</i> [42]	Meta-analysis of randomized placebo-controlled clinical trials	Various	1,427	Antidepressant medications are associated with improvement in pain, depression, fatigue, sleep disturbances, and HRQOL in patients with FM.  Strong association exists for antidepressants with improved HRQOL (SMD, -0.31; 95% CI, -0.42 to -0.20).
Lee <i>et al.</i> [43]	Review of randomized, placebo-controlled studies.	Various	n/a	Both SSRIs (fluoxetine and paroxetine) and SNRIs (duloxetine and milnacipran) improve pain, functioning, and quality of life.
Wu <i>et al.</i> [45]	Review	Various	/a	QOL of FM patients generally show improvement with pharmacologic agents.
<b>II) Specific Medications Studies</b>				
<b>1. Pregabalin (PGB)</b>				
Ablin <i>et al.</i> [46]	Review	Various	n/a	Pregabalin is the first specific medication approved for FM. Initial evidence shows that it improves pain and QOL. This may signal new development of other medications specific to FM.
Häuser <i>et al.</i> [47]	Meta-analysis of RCTs	Various	8,733	Pregabalin and gabapentin reduced pain, enhanced sleep, fatigue and anxiety, and improved HRQOL.
Häuser <i>et al.</i> [48]	Analysis of randomized controlled trials	Various	7,739	Comparing Pregabalin to other FM meds, PGB is superior to Milnacipran in reducing pain and sleep problems, inferior to Duloxetine in reducing depressed mood. PGB is superior to DLX in reduction of fatigue, has less side effects such as headache, and diarrhea.
Owen [49]	Review	Various	n/a	Pregabalin reduced pain and associated FM symptoms in addition to improving QOL.
Straube <i>et al.</i> [50]	Meta-analysis of 5 randomized clinical trials	SF-36	3,808	Pregabalin has a positive impact on the QOL in FM on most of the SF-36 domains.
Grazyna [51]	Review	Various	n/a	Pregabalin is a Convenient medication that is well-tolerated, and showed effectiveness in FM.
<b>2. Duloxetine</b>				
Ucelyer <i>et al.</i> [52]	Randomized, placebo-controlled trials	FIQ, The Brief Pain Inventory (BPI), The Clinical Global Impression of Severity scale (CGIS), Quality of Life Depression Scale total score, SF-36	354	Dosed at 60 mg/day and 120 mg/day, duloxetine was equally effective in pain management and improvement in QOL (trial duration: 12 weeks).

(Table 3). Continued.

Reference	Design	Measure	N	Summary of Findings
Arnold <i>et al.</i> [53]	Pooled analysis of 4 placebo-controlled, randomized, double-blind trials	The Brief Pain Inventory (BPI), CGI-S, Patient Global Impression-Improvement scale (PGI-I), 17-item Hamilton Depression Rating Scale (HDRS-17), FIQ, SF-36	797 on duloxetine and 535 on placebo	12 weeks of duloxetine 60-120 mg/d, improved FM symptoms such as pain ( $P < .001$ ) compared with placebo. Duloxetine was superior to placebo on all measures especially QOL measures: SF-36 mental ( $P < .001$ ) and physical ( $P = .026$ ) components.
Häuser <i>et al.</i> [55]	Comparative study of 17 RCTs	Various	7,739	DLX and PGB are superior to MLN in pain and sleep problems reduction. DLX is superior to PGB and MLN in improving depressed mood although less effective in fatigue reduction.
<b>3. Milnacipran</b>				
Harris <i>et al.</i> [17]	Review of Double-blind, placebo-controlled trials	Various	125	Milnacipran was shown to produce significant improvements in pain, physical function, fatigue and overall QOL compared to placebo.
Lawson [56]	Review article	Fibromyalgia Impact Questionnaire (FIQ) and Patient Global Impression (PGI).	n/a	Milnacipran improved pain and measures of QOL in FM.
Kranzler <i>et al.</i> [57]	Review of 2 pivotal clinical trials	The Outcome Measures in Clinical Rheumatology Trials (OMERACT)	2084	Milnacipran improved pain, and health-related QOL, in addition to physical and mental functioning, fatigue, cognitive impairment.
Hauser <i>et al.</i> [58]	Meta-analysis	Various	6152	Amitriptyline cannot be regarded as the gold standard of FMS therapy with antidepressants because of the methodological limitations of its trials
<b>4. Tramadol/Acetaminophen</b>				
Bennett <i>et al.</i> [59]	Multicenter, double-blind, randomized, placebo-controlled study	FIQ	315	Tramadol/acetaminophen was effective for FM symptoms.
Schug [60]	Review	Various	n/a	Tramadol/acetaminophen is a well-tolerated and effective combination in pain syndromes including FM. Reduction of pain intensity and improvement of function and QOL have been demonstrated.
<b>5. Nabilone</b>				
Skrabek <i>et al.</i> [61]	Randomized, double-blind, placebo-controlled trial	VAC, FIQ	40	Nabilone titrated up to 1mg BID improved pain and QOL in patients with FM compared to placebo in 4-week trial.
Ware <i>et al.</i> [62]	Randomized, double-blind, active-control, equivalency crossover trial	FIQ, Sleep indicators	32	Nabilone did not show effects on pain or QOL, however it was effective in improving sleep in FM patients.

(Table 3). Continued.

Reference	Design	Measure	N	Summary of Findings
Staud <i>et al.</i> [63]	Review	VAC, FIQ	n/a	Significant improvement in pain and QOL were demonstrated on 4 weeks of nabilone. Washout resulted in loss of benefits and return to pre-trial pain and QOL scores.
<b>6. Sodium Oxybate</b>				
Russell <i>et al.</i> [64]	Randomized placebo-controlled trial	Patient's pain rating on a visual analog scale (PVAS), FIQ, and the Patient Global Impression of Change (PGI-C). Secondary measures included QOL.	188, 78% (147) completed the trial	Sodium Oxybate significantly improved the symptoms of FM, Pain index and Vitality index domains of the SF-36 but not the overall physical or mental SF-36 components.
<b>7. Oral Bovine Colostrum Immunoglobulin</b>				
Waaga-Gasser <i>et al.</i> [66]	Pilot study	VAS	4 patients	3 of the 4 patients experienced pain relief and improvement in QOL when they received oral immunoglobulin produced from bovine colostrum (BCC). This study was originally designed to test BCC effects on apoptosis in mononuclear cells.
<b>8. Lidocaine</b>				
Schafrański <i>et al.</i> [65]	Open Label	FIQ, VAS, and Health Assessment Questionnaire	23	Intravenous lidocaine reduced pain and improved QOL in FM patients. FIQ score significantly improved after the 5 <sup>th</sup> infusion (73.52 +/- 16.56 vs 63.29 +/- 21.21, p=0.02), an effect maintained after 30 days. Similar results were seen regarding VAS (8.19 +/-1.76 vs 6.84 +/- 2.44, p=0.01).
<b>9. Methotrexate</b>				
Buskila [37]	Review	Various	n/a	Methotrexate is effective in treating immunologically-linked disorders such as FM and Hepatitis C Virus (HCV) infection.
<b>(C) Exercise</b>				
Stephens <i>et al.</i> [67]	Randomized controlled pilot trial	FIQ, Childhood Health Assessment Questionnaire (C-HAQ), Quality of My Life (QOML) scale, Pediatric Quality of Life Inventory (PedsQL)	30 children	FM symptoms, QOL, physical function, and pain significantly improved in both exercise groups, especially the aerobic group.
Sanudo <i>et al.</i> [68]	Randomized controlled trial	FIQ, SF-36	42 females	Results confirm that a long-term combination of aerobic exercise, strengthening and flexibility improves psychological health status and health-related quality of life in patients with fibromyalgia
Wong <i>et al.</i> [78]	Randomized controlled trial	FIQ, and SF-36.	66	Tai Chi improved FM symptoms and improved QOL compared to the control group. SF-36 physical-component between-group difference, 7.1 points (P = 0.001), and the SF mental component between-group difference, 6.1 points (P = 0.03).
Tomas-Carus <i>et al.</i> [70]	Randomized controlled trial	SF-36	30 women	Improved QOL was achieved through a long-lasting exercise therapy in warm water.
Häuser <i>et al.</i> [71]	Meta-analysis of 35 RCTs	Various	2,494	Land-and water-based aerobic exercise (AE) significantly reduced pain and HRQOL maintained at follow-ups. AE reduced pain (-0.31 [-0.46, -0.17]; <0.001), and limitations of HRQOL (-0.40[-0.60, -0.20]; <0.001) after treatment.



(Table 3). Continued.

Reference	Design	Measure	N	Summary of Findings
Ortega <i>et al.</i> [72]	Controlled trial	FIQ, SF-36, VAS	14 females	Exercise improved FM patients' HRQOL. The exercise program had an anti-inflammatory effect as evidenced by lowering of inflammatory markers such as CRP, and monocyte TNF-alpha.
Olivares <i>et al.</i> [73]	Randomized control trial	FIQ, 15D questionnaire	36 females	12-week course of tilting WBV therapy was associated with improvements in FIQ scores (12%) but not in the 15D questionnaire.
<b>(D) Hydrotherapy (HT)</b>				
Vitorino <i>et al.</i> [74]	Randomized clinical trial	SF-36, sleep diary	50 females	QOL improved in both groups of hydrotherapy and conventional therapy in all domains, with no difference between groups of FM.
<b>(E) Acupuncture</b>				
Targino <i>et al.</i> [85]	RCT	SF-36, VAS	58 women	Acupuncture addition to FM treatment is beneficial for pain and QOL lasting for 3 months post-treatment.
Itoh <i>et al.</i> [86]	RCT	VAS, FIQ	16	Acupuncture treatment improved pain and QOL for FM patients. After the 5th week, QOL improved in the 10-treatments group compared to 5-Non treatments group (P = 0.026).
<b>(F) Cognitive Behavioral therapy (CBT)</b>				
Casale <i>et al.</i> [89]	Review	Various	n/a	Cognitive-behavioral therapy and exercise are beneficial non-pharmacological treatments with positive impact on pain and QOL.
Furlong LV <i>et al.</i> [77]	Factor Analysis	n/a	138 women	CBT could improve symptoms and QOL in FM patients by focusing on positive affects and experiences and improving overall physical functioning.
Bernardy K <i>et al.</i> [80]	Systematic Review and Meta-analysis of Randomized Controlled Trials	Standardized mean differences (SMD)	910	CBT improved coping with pain and depressed mood, but had no significant effect on HRQOL after treatment and at follow up.
<b>(G) Neurofeedback (NFB) Intervention</b>				
Kayiran <i>et al.</i> [81]	Randomized, controlled, rater blind, clinical trial	VAS, FIQ, SF-36, Hamilton and Beck Depression and Anxiety Inventory Scales.	36	Neurofeedback (NFB) has improved pain, FM symptoms, and QOL. NFB group did significantly better than controls (p< 0.05) on each measure.
<b>(H) Multidisciplinary treatment:</b>				
Van Abbema <i>et al.</i> [83]	Prospective study	The Revised Illness Perception Questionnaire (IPQ), FIQ	87	Patients with severe symptoms and limitations need intensive multimodal programs. Clinically significant improvements were noted in the QOL of 34 patients with FMS in such programs.
Häuser <i>et al.</i> [84]	Meta-analysis of 9 RCTs	Standardized mean differences (SMDs), weighted mean differences (WMDs), confidence interval CI)	1,119	Evidence shows that multicomponent treatment reduced pain, FM symptoms, and HRQOL limitations. Long-term effects could not be established. Multicomponent treatment significantly reduced pain (SMD -0.37; 95% confidence interval [95% CI]-0.62,-0.13), and limitations to HRQOL (SMD -0.59; 95% CI -0.90, -0.27) after treatment.
Kroese <i>et al.</i> [85]	RCT	FIQ, EQ-5D	105	Part-time daycare multidisciplinary intervention for 12-weeks with aftercare meetings had a positive effect on QOL.

(Table 3). Continued.

Reference	Design	Measure	N	Summary of Findings
Scascighini <i>et al.</i> [82]	Systematic review of RCTs	Various	n/a	Multidisciplinary treatment is beneficial for FM patients. A standard of multidisciplinary programs should be internationally established to guarantee good outcome in the treatment of FM and chronic pain.
Oh <i>et al.</i> [86]	Open trial	FIQ, SF-36, and a satisfaction survey	521	FM symptoms and QOL improved for 6-12 months, following a 1.5-day interdisciplinary treatment program.
<b>(I) Current treatments</b>				
Schmidt <i>et al.</i> [87]	RCT	n/a	177 females	Primary outcome analyses did not support the efficacy of Mindfulness-based stress reduction (MBSR) in fibromyalgia, although patients in the MBSR arm appeared to benefit most.
Bernardy <i>et al.</i> [88]	Meta-analysis review	Various	239	Further studies with better treatment quality and adequate methodological quality assessing all key domains of FM are necessary to clarify the efficacy of hypnosis/guided imagery in FM.
Fiz <i>et al.</i> [89]	Journal article	VAS, FIQ, Pittsburgh Sleep Quality Index (PSQI), SF-36	28 FM cannabis users, 28 FM non-users	The use of cannabis was associated with beneficial effects on some FM symptoms. Further studies are warranted.

**Abbreviations:** BID=twice a day, BPI=Brief Pain Inventory, CBT=Cognitive Behavioral therapy, CI=Confidence Interval, DLX=Duloxetine, EQ-5D=Euro QOL-5D, FIQ=Fibromyalgia Impact Questionnaire, FM=Fibromyalgia Syndrome, HRQOL=Health Related Quality of Life, MBSR: Mindfulness-Based Stress Reduction, MLN=Milnacipran, PGB=Pregabalin, PGI=Patient Global Impression, QALY= Quality-Adjusted Life Year, QD=once a day, QOL=Quality of Life, RCTs=Randomized Controlled Trials, SMD=Standardized Mean Differences, SNRIs=Serotonin Norepinephrine Reuptake Inhibitors, SSRIs=Serotonin Receptive Reuptake Inhibitors, VIGI=Intravenous Immunoglobulin.

### Duloxetine

Duloxetine (Cymbalta®), a serotonin-norepinephrine reuptake inhibitor (SNRI) was the second agent approved in 2008 by the USFDA for the treatment of FM. This agent was approved based on the results from two 3-month clinical trials done on 874 patients with fibromyalgia [47, 48]. In both trials, duloxetine was associated with more than 30% reduction in pain compared to placebo group. Pain was measured with the Brief Pain Inventory (BPI). More than 60% of the patients in both studies had improvement of general well-being and QoL [47, 48]. These clinical trials demonstrated safety and efficacy of duloxetine for the treatment of FM patients especially women with or without major depression [47-49]. The dose of duloxetine is usually 60 mg once daily (QD) or twice daily (BID). This is safe and effective in reducing pain and improving sleep, depression, and QoL [50-52]. The most common adverse effects are nausea, dry mouth, decreased appetite, constipation, agitation, increased sleep and sweating [53, 54]. About 20% of the FM patients taking this medicine discontinued it versus 12% of the placebo patients.

### Milnacipran

Milnacipran (Savella®) is a dual serotonin and norepinephrine reuptake inhibitor (SNRI) [60] that was approved in 2009 by the USFDA for the treatment of

FM. This drug was approved based on two pivotal phase III trials that included 2084 patients over a period of 6 months and 3 months respectively. 1460 patients were treated with milnacipran and 624 were on placebo. The two studies demonstrated that a greater number of FM patients who were on either 100mg or 200mg of milnacipran daily had at least 30% reduction in pain from their baseline and rated themselves as either very much improved or much improved. Most patients receiving milnacipran also had significant improvements in the physical function, mental function, fatigue, cognitive impairment and HR-QoL [17, 55-59]. Prior to the approval of milnacipran for the treatment of FM, a randomized double-blind, placebo-controlled trial was done in 2004 on 125 patients [60]. These patients received either placebo or milnacipran for 4 weeks (up to 200mg) followed by 8 weeks at a constant dose [60]. This study showed that 75% of patients receiving milnacipran reported overall improvements in the symptoms compared with 38% in the placebo group ( $p < 0.01$ ). Patients also reported moderate reduction in pain and improvement in QoL [60]. Also, a result from a phase II clinical trial showed that 125 FM patients receiving milnacipran had significant improvement in pain and also improvements in the general well-being, fatigue, QoL, and other symptoms [61]. Milnacipran was safe and generally tolerated by patients [57-61]. The most common adverse effects were mild to

moderate in severity such as nausea, vomiting, dry mouth, constipation, hot flashes, hyperhidrosis, palpitation, tachycardia, and hypertension.

Comparing the effects of the above agents is important. A meta-analysis examining the efficacy of the antidepressants amitriptyline, duloxetine, and milnacipran revealed that duloxetine was superior to milnacipran in pain reduction, sleep regulation, and QoL improvement [62].

There are a number of other drugs available that may aid in FM treatment. Such drugs are tramadol/acetaminophen combination, nabilone, sodium oxybate, methotrexate, immunoglobulins, and intravenous lidocaine. Tramadol/acetaminophen treatments greatly improve pain reduction, physical function, and QoL, and reduce disability without serious adverse effects [63, 64]. Nabilone could be used as an adjunct agent for the treatment of FM, but its value in improving QoL is questionable. Studies suggest that nabilone improves mainly the sleep pattern of FM and has no effect on pain, mood and/or QoL [65, 66]. There is also no long-term effect with the use of nabilone for the treatment of FM because after a 4-week washout period, all benefits are lost [67]. Another possible medication is sodium oxybate, which appears effective, well tolerated, and improves symptoms of fibromyalgia [68], but further study is warranted to confirm this fact. Intravenous lidocaine is effective in relieving pain and improving QoL in FM patients such that five sequential infusions produced significant improvement that was maintained for about 30 days in an open clinical trial constituting 25 FM patients [69]. Methotrexate (an anti-metabolite/ anti-folate drug) has been used to treat FM and Hepatitis C [29]. Immunoglobulins have been used to treat FM and patients had improvements in the intensity of pain and QoL. This was demonstrated in a pilot study of four patients treated with immunoglobulins [70]. Three out of the four FM patients had pain relief and QoL improvement [70]. This could point to the presence of an immunological element in pathogenesis of FM. Further trials are needed to study and establish the efficacy of these medications in the treatment of FM, especially since the very small size of the sample limits the statistical significance to that study.

### ***b. Non-Medical Treatments' Effects on QoL in FM***

#### Exercise

Exercise is one of the most common non-pharmacological treatments of FM because of its

potential to improve the QoL in FM patients. Several studies have demonstrated positive effects of exercise program in improving symptoms [71] and QoL in patients with FM [72-77]. A 3 years longitudinal study on the effects of exercise on 41 women with FM showed that there was a significant improvement in the FM Impact Questionnaire ( $P < 0.0005$ ) for the exercise training group compared to the control after 6 months of combined exercise program [75]. In a 12 weeks intervention of either aerobics or qigong, there was significant improvement in symptoms, pain, physical function, exercise performance, and QoL in both exercise groups [72]. A study showed that women with FM who were randomly assigned to an aerobic, strength, and flexibility group significantly improved in health status and functional capacity compared to control [73]. In a prospective study, Tai Chi improved FM symptoms and quality of life compared to the control group [78]. In addition, long-lasting exercise therapy in warm water produced relevant gain in muscle strength with improvement in physical and emotional problems, mental health status, and QoL [74]. There were significant reductions in pain, and improvements in the mood, physical fitness and QoL after treatment with 'land and water-based' aerobic exercise [79]. An aquatic exercise program positively improved pain, lower limb muscle strength [80], other symptoms and QoL in FM patients [80-82]. In addition a study showed that FM patients had a decreased production of tumor necrotic factor (TNF) alpha release and decreased production of C-reactive protein (CRP), giving more support to the presence of an inflammatory disorder in FM [81]. Whole Body Vibration therapy is a new physical therapy intervention that prevented loss of HRQoL in women who were once physically untrained [83]. FM patient who benefited from exercise are usually advised to continue with the exercise program in order to maintain the long time benefit.

#### Hydrotherapy

Hydrotherapy is another management considered helpful in patients with FM because of the improvement in QoL, the total sleep time, and reduction in the total naptime [84].

#### Acupuncture

Acupuncture is often used to treat FM because of the beneficial effects on relieving pain and improving QoL in patients with FM [85-87], but more studies are needed to evaluate the effectiveness of acupuncture in the management of FM.

### Cognitive Behavioral Therapy (CBT)

Cognitive behavioral therapy is among the commonly used non-medical treatment of FM. Cognitive behavioral interventions are designed to improve the QoL and reduce pain in FM patients [88]. It seems to help FM patients improve their way of thinking and their coping strategy. In a meta-analysis of the study of the efficacy of CBT in 910 patients with FM, the most important finding was that CBT reduced depressed mood (SMD -0.24, 95% CI -0.40, -0.08;  $p=0.004$ ) at post treatment. There was a significant effect on self-efficacy pain post treatment, and the operant behavioral therapy significantly reduced the number of physician visits at follow-up. These studies underscored that CBT is a promising intervention for sleep disturbances and other impairments in patients with FM [89]. CBT appeared to help FM patients cope with pain and reduce depressed mood and healthcare-seeking behavior [90]. In a single blind, randomized controlled trial of 114 adolescents, CBT was found to be a safe and effective treatment option for improving the symptoms of depression and functional disability of the adolescents with juvenile FM [91].

### Neurofeedback (Electroencephalography; EEG Biofeedback)

Neurofeedback is a strategy that enables individuals to alter their brainwaves [92]. Neurofeedback Sensory Motor Rhythm treatment is also helpful in improving pain reduction, psychological symptoms, and QoL in FM patients [93]. In a case series of three patients, neurofeedback reduced most of the FM symptoms after 10 sessions [92]. In a randomized, rater-blinded study, neurofeedback was effective in reducing pain, psychological symptoms and improving QoL associated with FM [93].

### Multidisciplinary Team Approach

Multidisciplinary team approach is advocated for the treatment of FM because of the complex nature of the illness. This approach encompasses knowledge and skills that consists of many health providers such as a physician, social therapist, physiotherapist, psychotherapist, and creative arts therapist. They develop the plan and strategy that best work for the patient in order to reduce pain and improve the patient's QoL. This approach seems to be beneficial and significantly improves the QoL of FM patients. Patients treated using the multidisciplinary approach reported improvements in daily living, symptoms and QoL [94, 95]. Therefore, an intensive multimodal program seemed most suitable for patients with severe

symptoms and limitations. Additional studies demonstrated that multi-component treatment is very effective in reducing symptoms and improving the QoL in patients with FM [96, 97].

There are other new treatments that are currently being examined that may be helpful in reducing FM symptoms severity in the near future. One of them is a combination of mindfulness meditation and yoga exercise, called 'mindfulness-based stress reduction,' which does not have empirical support for efficacy, but does have modest benefits for some patients [98]. Another is the effect of hypnosis/guided imagery which did reduce pain, but did not reduce limitations of HRQoL in the treated group compared to controls [99]. Further studies are needed to understand the effectiveness of hypnosis/guided imagery as a potential treatment for FM [88]. A recent study analyzing cannabis use of FM patients showed a significant reduction of pain and stiffness, enhanced relaxation, and increase in well being feelings [100]. SF-36 score for the mental health component was also higher for cannabis users than in non-users [100].

## **DISCUSSION**

### **The Impact of FM on QoL**

Pain, functional disability, and fatigue were ranked as the top three symptoms suffered by FM patients. Sometimes patients are unable to commit to regular social activities due to the erratic nature of pain symptoms. Leisure activities like sports and travel can be difficult in patients suffering from this illness. Patients with FM may struggle with lack of support from loved ones due to insufficient public awareness of this illness and its burden [11]. FM can impair patients' cognition as well as social and occupational functioning, leading to disrupted relationships with family and friends. The family, especially the spouse or partner, is burdened to compensate for the patient's lack of contribution in family responsibilities. Work quality and duration are also negatively impacted by the pain and impaired concentration, resulting in most patient having to quit their job, which in turns have financial repercussion. The symptoms of FM can impact negatively on a patient's education. Patients with FM sometimes have difficulty completing or pursuing higher education as they could not sit through classes and could not focus due to pain, fatigue, depression, anxiety and cognitive impairment. They often times require painkillers to manage their pain. All of the above themes are central to QoL impairments in patient with FM.

## Effects of FM Comorbidities on QoL

The presence of depressive symptoms is associated with great impairment in patients with FM. Indeed, the psychiatric comorbidity lowers pain tolerance threshold and worsens QoL in patients with FM [20]. Patients with FM and depression exhibited a poorer outcome of multi-model rehabilitation than FM patients without depression. FM patients with depressive symptoms show more sleep disturbances, lower sleep quality, sexual dysfunction, loss of physical function level, and lower QoL [19, 21]. Moreover, studies have shown that the degree and impact of PTSD are highly correlated with degree and impact of FM, especially in male patients [23]. Medical comorbidities such as sleep, GI, autoimmune disturbances, headache, and sexual dysfunction are quite prevalent in FM, all leading to poor QoL. Sleeping-waking brain disturbances are involved in the pathogenesis of FM symptoms and these negatively impacted the QoL of FM patients [26]. In patients with FM, the severity scores of dyspepsia symptoms, constipation, and dyspepsia-related QoL disturbances were higher than in patients with RA and controls. There is a positive correlation between the incidence of these comorbidities and increased health care seeking, higher levels of mood disorders, and reduction in QoL advocating a common underlying pathophysiology [27]. More research is needed to investigate autoimmune disturbances in FM, shown to negatively affect QoL, as treatment implications could include more indications for immune-suppressants.

## Impact of Treatment on QoL of FM Patients

Medication is currently the main treatment modality of FM. Medications such as antidepressants [selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs)], are proven to improve pain, depression and QoL in FM patients [36, 37]. Substantial or moderate pain reduction predicts beneficial outcomes and improved QoL, which do not occur without pain relief [37]. Reduction in pain is an effective predictor of determining if a patient should continue treatment or discontinue treatment to undertake an alternative therapy [38]. As shown in this review of treatments, substantial improvements of QoL were observed with medications and non-medication interventions such as exercise, acupuncture, cognitive behavioral therapy, neurofeedback and multidisciplinary approach, as detailed above.

## FUTURE DIRECTIONS

For future studies, it would be important to examine the relationship between FM, FM comorbidity, and treatment on the specific QoL dimensions (such as the eight SF-36 subscales: vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, and mental health activity). Prospective research and meta-analyses would need to examine this relationship in order to detect the impact on specific QoL dimensions and determine what treatments would be best to ameliorate the impact of the illness on QoL.

## CONCLUSIONS

We present a comprehensive review of FM and its effects on the quality of life, comorbidity influences, and medical and non-medical managements of FM. It is important for clinicians to diagnose and effectively manage FM in order to improve patients' QoL and decrease healthcare utilization and cost. Our study showed that FM and its comorbidities have a considerable negative impact on the QoL of patients. Studies showed that substantial or moderate pain reduction as well as the utilization of the multidisciplinary approach improve quality of life and can predict positive outcomes of other comorbidities associated with FM. Medical and non-pharmacological treatments of FM seem to have positive influence on QoL of patients. More research is needed to understand the physiopathology of FM and develop more specific and effective interventions to improve QoL beyond current interventions that traditionally focus on pain control and symptom management.

## DISCLOSURES

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