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Original article

Effects of mirtazapine on quality of life of Thai patients with fibromyalgia syndrome: a double-blind, randomized, placebo-controlled trial

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Background: Fibromyalgia syndrome (FMS) is a physical and mood disorder that affects quality of life (QoL). Mirtazapine, which improves monoaminergic neurotransmission, may benefit patients with FMS.
Objectives: To compare the QoL between Thai patients with FMS and healthy Thais, and investigate the effects of mirtazapine in a pilot study.
Methods: We compared the QoL between 76 Thai patients with FMS and 80 healthy Thai volunteers (HVs). A double-blind, randomized, placebo-controlled trial using 40 patients with FMS was conducted using a block design with parallel assignment. QoL data were obtained at week 0 (baseline), and repeatedly for 13 weeks after receiving placebo or mirtazapine 15 or 30 mg/day.
Results: The mean baseline of SF-36 QoL was significantly lower in all domains in patients with FMS than in HVs (bodily pain 33 vs 87, general health 36 vs 84, mental health 63 vs 82, physical functioning 59 vs 96, role limitation because of emotional problems 41 vs 92, role limitation because of physical problems 30 vs 96, social functioning 53 vs 93, and vitality 48 vs 75 (scale 0–100, $P < 0.01$ all domains). Mirtazapine (15 and 30 mg/day) significantly reduced pain scores and improved all domains except social functioning, while placebo produced no change from baseline. Eight patients withdrew because of adverse events including somnolence and weight gain; no benefit, or lack of compliance.
Conclusions: The QoL of patients with FMS is lower than for healthy Thais. Mirtazapine is effective for reducing pain and improving QoL in patients with FMS.
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Keywords: Fibromyalgia, mirtazapine, noradrenergic and specific serotonergic antidepressant, pain, quality of life

Fibromyalgia syndrome (FMS) is a condition characterized by widespread pain and other symptoms such as fatigue, sleep disturbance, anxiety, depression, morning stiffness, paresthesia, and cognitive impairment [1]. FMS has negative effects on the quality of life (QoL) of affected individuals [2, 3]. The combination of physical and mental disorder symptoms could affect different aspects of daily activity in these patients such as work, relationships with their family, and leisure activities [4]. Patients with FMS were found to have a debilitative pain condition in common with patients referred rheumatoid arthritis (RA) [5].

The etiopathology of FMS involves abnormalities of levels of biogenic amines and other neurotransmitters such as substance P, genetic predisposition, and neuroendocrine dysfunction [6]. To date, 3 medications, an anticonvulsant (pregabalin) and 2 serotonin and norepinephrine reuptake inhibitors (SNRIs), namely duloxetine and milnacipran, have been approved by the U.S. Food and Drug Administration

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(US FDA) for patients with FMS [7]. SNRIs increase the availability of norepinephrine (NE) and serotonin (5-HT) at synaptic cleft of neurons, resulting in a better function of NE and 5-HT neurotransmission in the descending inhibitory pain control pathways, thereby reducing pain [8]. However, for most patients, the current treatments remain inadequate to reliably resolve persistent symptoms, improve functional limitations and QoL [9].

Mirtazapine is a noradrenergic and specific serotonergic antidepressant (NaSSA) characterized by antagonism of central α_2-adrenergic autoreceptors and α_2-adrenergic heteroreceptors. Antagonism of α_2-adrenergic autoreceptors enhances NE release, while blockade of α_2-adrenergic heteroreceptors on serotonergic neurons increases 5-HT release. NE decreases the activity of nociceptive neurons in the dorsal horn of the spinal cord by an action through the postsynaptic α_2 receptor to hyperpolarize neurons. Moreover, mirtazapine antagonizes both 5-HT_2 and 5-HT_3 receptors that might prevent the development of sexual dysfunction, and reduce nausea and vomiting side effects. An increase in 5-HT release together with the 5-HT_2- and 5-HT_3-receptor blockade, results in overall higher 5-HT_{1A} receptor-mediated neurotransmission, which adequately inhibits nociceptive transmission at the spinal cord [10-12]. Mirtazapine was found to have antihistaminic (H_1 receptor antagonist) effects, which provide additive benefit for insomnia [11]. Therefore, the pharmacological profile of mirtazapine appears beneficial for the treatment of FMS patients, especially the patients with concomitant pain, depression, and sleep disturbances.

To our knowledge there were no data regarding the QoL in Thai patients with FMS compared with healthy Thais, therefore, the present study aimed to investigate the effect of disease burden and the clinical effect of mirtazapine on pain and QoL in Thai patients with FMS.

Materials and methods

The study design and protocol were reviewed and approved by the ethics committee of Siriraj Institutional Review Board (SiIRB), Bangkok, Thailand. Thai patients with FMS and healthy volunteers (HVs) were included as participants in a study registered at ClinicalTrials.gov; Identifier: NCT00919295. The patients with FMS and HVs were enrolled in the study starting on June 11, 2009.

Participants

The QoL study in patients with FMS compared with HVs

We recruited 76 Thai patients with FMS at the Department of Rehabilitation, and Pain Management Clinic, Department of Anesthesiology, Siriraj Hospital, Mahidol University, Bangkok, Thailand into this study. The inclusion criteria were patients of Thai ethnicity who were 18 years of age or older with a diagnosis of FMS as defined by the American College of Rheumatology (ACR) 1990 diagnostic criteria [13], had at least moderate pain (pain visual analog scale (PVAS) $\geq$40 mm) [14], and did not respond to previous medications. Exclusion criteria included substance abuse within the past year, serious suicide risk, pregnancy or breastfeeding, comorbid inflammatory rheumatic diseases, used of medications or herbal agents with central nervous system (CNS) activity, regular used of analgesics with the exception of acetaminophen up to 2 g/d, or other medications that might affect the biochemical tests.

We included 80 HVs of similar age and ethnicity as the control group in the study. HVs were those with no signs or symptoms of FMS and no history of medication use for at least 2 wk before starting the study. The baseline SF-36 QoL was completed by all HVs and patients with FMS.

The efficacy of mirtazapine in patients with FMS

We enrolled 40 patients with FMS into a prospective, randomized, double-blind, placebo-controlled clinical trial designed to assess the efficacy of mirtazapine. The patients were allocated using a block size of 3 in a ratio of 1:1:1 with parallel assignment to 1 of 3 groups as follows: placebo, mirtazapine 15 mg/day, or mirtazapine 30 mg/d using a pharmacy-controlled randomization process with sequentially numbered identical containers that were administered serially by sequence generation with a random number table and the patients then monitored for 13 weeks (visit 1 at baseline (0 wk), 2 at 1 wk, 3 at 3 wk, 4 at 5 wk, 5 at 9 wk, and 6 at 13 wk). The mirtazapine tablets and pharmacologically inactive placebo identical dummy tablets were packed by Inpac Pharma (Bangkok, Thailand). The tablets in identical foil packaging were prepackaged in identical containers with consecutively numbering for each patient with FMS according to the randomization schedule. Each patient with FMS was assigned a number in the sequence by the randomization process and received

the tablets in the corresponding container. Each placebo tablet contained excipients lactose 274 mg, corn starch 34 mg, povidone K90 3 mg, sodium starch glycolate 5 mg, magnesium stearate 4 mg. The pharmacist played a vital role in the management and of the medications, and the physician and counseling psychologist were blinded assessors. The investigational drug was started at a lower dose of 7.5 mg and adjusted up to the randomized dose over 1 or 2 wk, and then maintained with the target dose for 13 wk.

Pain and QoL monitoring

All patients with FMS completed the SF-36 QoL questionnaire on 4 different occasions, including visit 1 (baseline), visit 4 (35 ± 2 d), visit 5 (63 ± 7 d) and visit 6 (81 ± 7 d). Pain severity was assessed by using the score in the bodily pain (BP) domain.

Quality of life measurement

A validated Thai version of the SF-36 QoL questionnaire [15]; a multipurpose, short-form health survey consisting of 36 items specifically designed to calculate scores of 8 dimensions as follows: bodily pain (BP), general health (GH), mental health (MH), physical functioning (PH), role limitation because of emotional health problems (RE), role limitation because of physical health problems (RP), social functioning (SF), and vitality (VT). Scores range from 0 to 100. The higher scores indicate a better health-related QoL.

Pain severity measurement

Pain severity was assessed using the BP domain of the SF-36 QoL questionnaire at visits 1, 4, 5, and 6. The BP value was calculated from 2 questions. The first question was "how much bodily pain have you had during the past 4 weeks?" (question No. 7 of SF-36). The range of answers were as follows: 1 = none, 2 = very mild, 3 = mild, 4 = moderate, 5 = severe, and 6 = very severe. The second question was "how much did the pain affect your normal work (including both full-time job and housework)?" (question No. 8 of SF-36). The range of answers are as follows: 1 = not at all, 2 = a little bit, 3 = moderately, 4 = quite a bit, and 5 = extremely. The scales of answers to question Nos. 7 and 8 were converted to provide a true indication of the answers to these questions as follows. The total score of all domains of SF-36 QoL questionnaire ranges between 0 and 100 with a lower score indicating a lower perceived health and the higher score indicating more pain. Precoded and recoded (converted) values for question No. 7 and 8 are shown in **Table 1**.

Table 1. Precoded and recoded values for question Nos. 7 and 8 of the SF-36 QoL questionnaire

Precoded and recoded values for question No. 7		
Response choices	**Precoded value**	**Recoded value**
None	1	6
Very mild	2	5.4
Mild	3	4.2
Moderate	4	3.1
Severe	5	2.2
Very severe	6	1

Precoded and recoded values for question No. 8			
	Precoded value of question No. 8	**Precoded value question No. 7**	**Recoded value**
Not at all	1	1	6
Not at all	1	2 through 6	5
A little bit	2	1 through 6	4
Moderately	3	1 through 6	3
Quite a bit	4	1 through 6	2
Extremely	5	1 through 6	1

Statistical analysis

All statistical analyses were performed with SPSS for Windows (version 16.0; SPSS Inc, Chicago, IL, USA). For all of the planned analyses, $P < 0.05$ was considered significant.

All baseline data are presented as mean and standard deviation (SD). An unpaired *t* test (for normally distributed data) or Mann–Whitney *U* test (for nonnormally distributed or ordinal scale data) was used to compare demographic data, clinical characteristics, and the QoL between HVs and patients with FMS. For nominal measurement of demographic data, a Chi-square (χ^2) test was used to compare HVs and patients with FMS. To compare overall differences in demographic variables and the baseline clinical variables between the three treatment groups, analysis of variance (ANOVA; for normally distributed data) or a Kruskal–Wallis test (for nonnormally distributed or ordinal scale data) and pairwise comparisons were used. The efficacy was assessed based on an intent-to-treat statistical model. Data collected from patients with FMS who achieved at least 80% compliance were included in the assessment.

Results

The QoL in patients with FMS compared to HVs

A diagram of participant flow is shown in **Figure 1**. Baseline characteristics of HVs and patients with FMS are presented in **Table 2**. We recruited 76 outpatients with FMS into the study. These 76 patients with FMS (45.2 (SD 10.5) years) were age-matched with the 80 HVs (43.9 (8.5) years). Baseline age and sex characteristics were similar between HVs and patients with FMS; however, BMI of HVs was significantly higher than that of patients with FMS. As indicated in **Table 3**, all SF-36 QoL domains were significantly lower in patients with FMS than HVs (P <0.001). The mean (SD) bodily pain score of patients with FMS was significantly lower than that of HVs (33 (15.9) vs 87 (14.7), P <0.001). Rank order scores (mean (SD)) from the highest to lowest score of SF-36 QoL in HVs were as follows: physical functioning 96 (8.2), role limitation because of physical problems 96 (19.4), social functioning 93 (14.8), role limitation because of emotional problems 92 (24.9), bodily pain 87 (14.7), general health 84 (16.0), mental health 82 (14.5), and vitality 75 (17.6). We found bodily pain 30 (37.0) and the role limitation because of physical problems 30 (37.0) in patients with FMS were poor domains for these patients. Further, QoL scores for all domains of patients with FMS were lower than those of HVs. The lowest score in the HVs was the vitality domain 75 (17.6); nevertheless, this score was still higher than the highest score for patients with FMS, which was the mental health domain 63 (17.1).

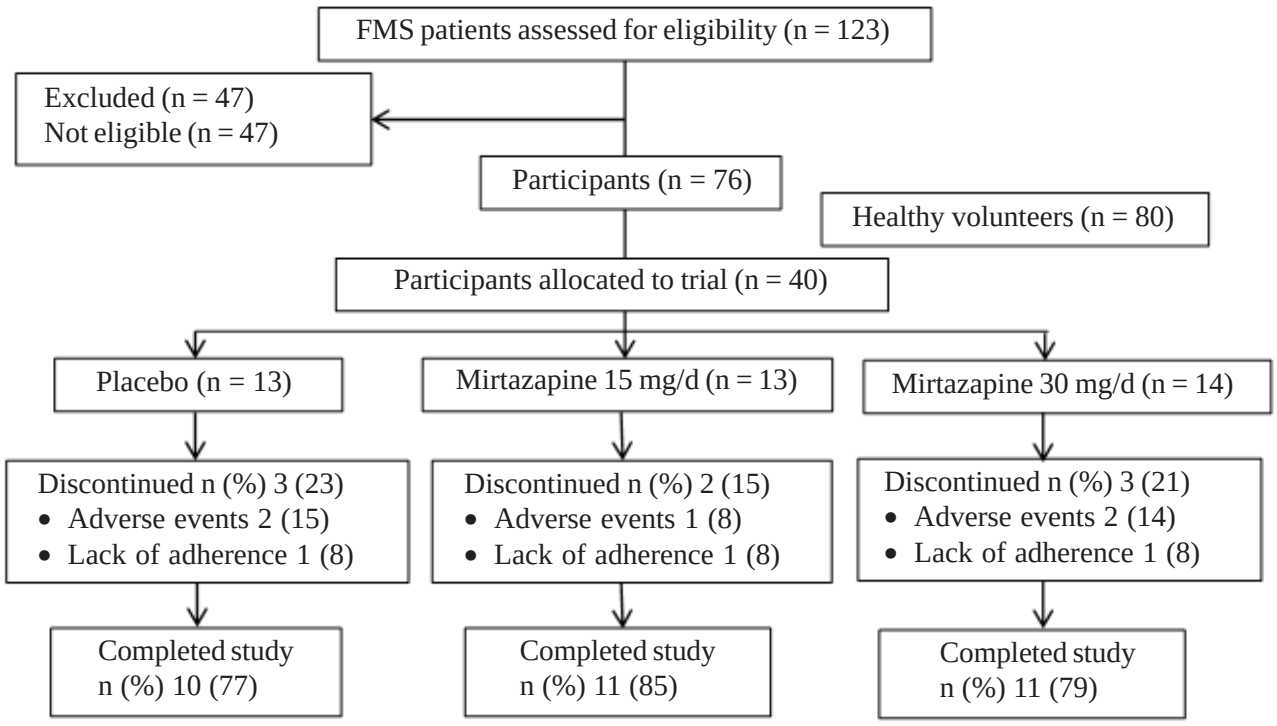

Figure 1. Flow diagram of trial of mirtazapine for patients with fibromyalgia syndrome using a randomized parallel design and placebo control.

Table 2. Baseline characteristics of Thai patients with FMS compared with Thai HVs

Characteristic	HV (n = 80)	FMS (n = 76)	*P*
	Mean (SD)	Mean (SD)	
Age (y)	43.9 (8.5)	45.2 (10.5)	NS
Female, n (%)	77 (96.3)	75 (98.7)	NS
Bodily pain (0–100)	87 (14.7)	33 (15.9)	<0.001
Body mass index (kg/m^2)	23.1 (3.1)	21.8 (3.2)	0.012
Duration of widespread pain (y)	0 (0)	3.8 (3.5)	–

Table 3. Baseline QoL of Thai patients with FMS compared with Thai HVs

Characteristic	HVs (n = 80)	FMS (n = 76)
	Mean (SD)	Mean (SD)
Bodily pain (0–100)	**87 (14.7)**	**33 (15. 9)**
How much bodily pain have you had during the past 4 weeks? (1–6)	5.5 (0.7)	2.5 (0.7)
During the past 4 weeks, how much did pain interfere with your normal work? (1–6)	5.3 (1.0)	2.8 (1.0)
General health (0–100)	**84 (16.0)**	**36 (19.7)**
In general, would you say your health is? (1–6)	3.7 (0.8)	2.0 (1.0)
How true or false is each of the following statements for you? (1–6)		
I seem to get sick a little easier than other people (definitely true, mostly true, don't know)	4.6 (0.9)	2.7 (1.4)
I am as healthy as anybody I know	4.6 (0.8)	2.5 (1.2)
I expect my health to get worse	4.5 (1.0)	3.0 (1.3)
My health is excellent	4.3 (0.9)	1.9 (1.0)
Mental health (0–100)	**82 (14.5)**	**63 (17.1)**
Have you been a very nervous person? (1–6)	5.0 (0.8)	3.8 (1.1)
Have you felt so down in the dumps that nothing could cheer you up? (1–6)	5.8 (0.6)	5.1 (1.0)
Have you felt calm and peaceful? (1–6)	4.6 (1.2)	3.2 (1.2)
Have you felt down hearted and blue? (1–6)	5.4 (0.9)	4.7 (1.1)
Have you been a happy person? (1–6)	4.7 (1.2)	3.8 (1.3)
Physical functioning (0–100)	**96 (8.2)**	**59 (21.6)**
Vigorous activities (1–3)	2.7 (0.5)	1.5 (0.6)
Moderate activities (1–3)	3.0 (0.2)	2.0 (0.7)
Lifting or carrying groceries (1–3)	2.9 (0.3)	1.9 (0.7)
Climbing several flights of stairs (1–3)	2.9 (0.4)	1.9 (0.7)
Climbing one flight of stairs (1–3)	3.0 (0.1)	2.7 (0.5)
Bending, kneeling, or stooping (1–3)	2.9 (0.4)	1.9 (0.7)
Walking more than a mile (1–3)	3.0 (0.2)	1.9 (0.8)
Walking several blocks (1–3)	3.0 (0.1)	2.3 (0.7)
Walking one block (1–3)	3.0 (0.0)	2.7 (0.6)
Bathing or dressing yourself (1–3)	3.0 (0.0)	2.9 (0.4)
Role limitation because of emotional problems (0–100)	**92 (24.9)**	**41 (37.9)**
Cut down the amount of time you spent on work or other activities (12)	1.9 (0.3)	1.3 (0.5)
Accomplished less than you would like (1–2)	1.9 (0.3)	1.4 (0.5)
Didn't do work or other activities as carefully as usual (1–2)	1.9 (0.3)	1.5 (0.5)

Table 3. (Con) Baseline QoL of Thai patients with FMS compared with Thai HVs

Characteristic	HVs (n = 80)	FMS (n = 76)
	Mean (SD)	Mean (SD)
Role limitation because of physical problems (0–100)	**96 (19.4)**	**30 (37.0)**
Cut down the amount of time you spent on work or other activities (1–2)	1.9 (0.2)	1.2 (0.4)
Accomplished less than you would like (1–2)	2.0 (0.2)	1.3 (0.5)
Were limited in the kind of work or other activities (1–2)	2.0 (0.2)	1.4 (0.5)
Had difficulty performing the work or other activity (1–2)	2.0 (0.2)	1.3 (0.5)
Social functioning (0–100)	**93 (14.8)**	**53 (12.3)**
During the past 4 weeks, to what extent has your physical health or emotional problem interfered with your normal social activities with family, friends, neighbors, or groups? (1–5)	4.8 (0.5)	3.8 (1.0)
During the past 4 weeks, how much of the time has your physical health or emotional problem interfered with your social activities? (1–5)	4.6 (0.9)	3.5 (1.0)
Vitality (0–100)	**75 (17.6)**	**48 (19.1)**
Did you feel full of pep (glad, joyful, pleasant)? (1–6)	4.5 (1.2)	3.1 (1.3)
Did you have a lot of energy? (1–6)	4.5 (1.3)	2.9 (1.5)
Did you feel worn out? (1–6)	5.3 (0.8)	4.0 (1.2)
Did you feel tired? (1–6)	4.7 (1.0)	3.6 (1.1)

All dimensions were significantly different to the level of $P < 0.01$

Mirtazapine efficacy assessment in patients with FMS

We randomly allocated 40 Thai patients with FMS to study the efficacy of mirtazapine (15 mg/d or 30 mg/d) compared with placebo: 13 received placebo, 14 received mirtazapine 15 mg/d, and 13 received mirtazapine 30 mg/d. There were no significant differences in any characteristic at baseline as shown in **Table 4**. Adverse events found were somnolence, increased appetite, and weight gain. During the study period, 3 patients withdrew from the placebo group (because of adverse effect (15%) and lack of adherence (8%)), 2 patients withdrew from the mirtazapine 15 mg/d group (because of adverse effect (8%) and lack of efficacy (8%)), and 3 patients withdrew from the mirtazapine 30 mg/d group (because of adverse effect (15%) and lack of efficacy (7%) as shown in **Figure 1**.

Table 4. Between-group comparisons of mean characteristics and bodily pain of patient with FMS at baseline

Baseline characteristics	Placebo (n = 13)	Mir 15 mg (n = 13)	Mir 30 mg (n = 14)	Mir 15 + 30 mg (n = 27)
	Mean (SD) or n (%)			
Age (y)	47.4 (37.9)	42.7 (45.4)	43.9 (35.2)	43.3 (56.6)
Female, n (%)	13 (100)	13 (100)	14 (100)	27 (100)
Body mass index (kg/m^2)	22.6 (12.3)	22.0 (9.0)	22.1 (12.0)	22.0 (14.5)
Duration of widespread pain (y)	4.0 (11.5)	3.3 (8.3)	3.1 (10.1)	3.2 (13.0)
Bodily pain (0–100)	34 (55.9)	40 (52.6)	28 (32.9)	35 (15.1)

There were no significant differences in baseline characteristics between any of the groups.

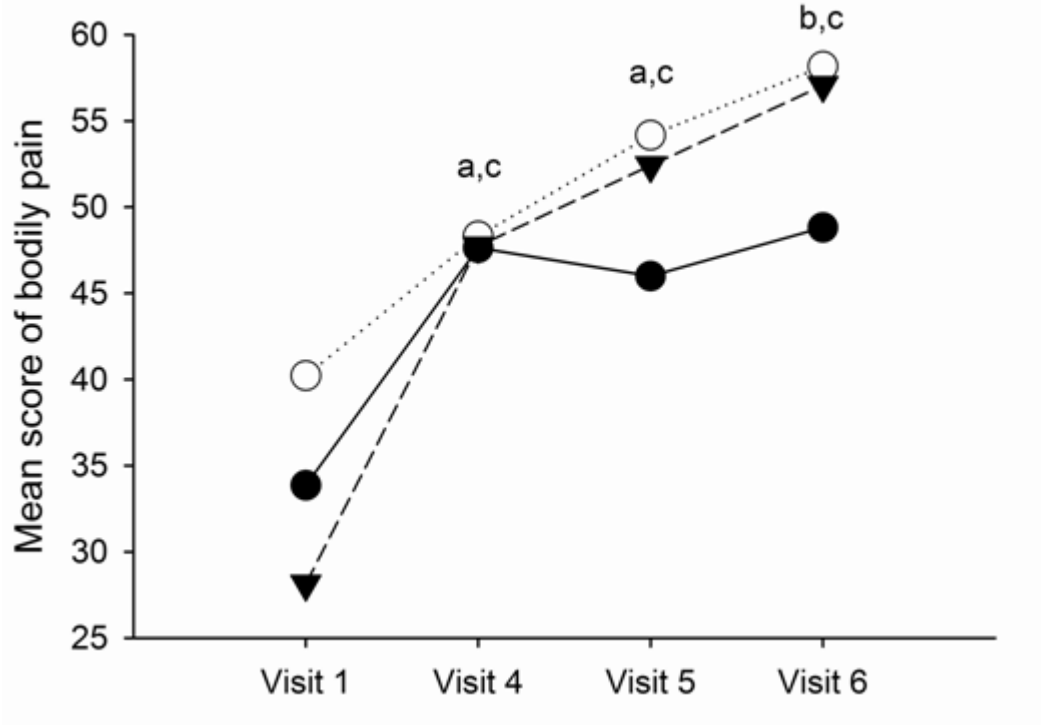

Figure 2. Mean of the score for the bodily pain domain of SF-36 QoL for patients with FMS receiving placebo (solid circles, solid line), mirtazapine 15 mg/d (solid triangles, dashed line), or 30 mg/d (open circles, dotted line) at visits 1, 4, 5, and 6.
[a]$P < 0.05$ (mean change from placebo baseline), [b]$P < 0.05$ (mean change from mirtazapine 15 mg/d baseline), [c]$P < 0.05$ (mean change from mirtazapine 30 mg/d baseline). For clarity, error bars are not shown (see Table 5).

Efficacy of mirtazapine on bodily pain

We found that the bodily pain (BP) scores between the 3 groups of patients with FMS were not different at any time. However, when we compared the mean (SEM) of BP score between the end of the study (visit 6) and baseline, we found that patients with FMS who received mirtazapine, either at 15 or 30 mg/d showed a significant reduction in BP ($P < 0.05$), while those on the group receiving placebo did not show any significant difference in scores from baseline. The data are presented in **Figure 2** and **Table 5**, which also shows scores for other QoL domains.

Efficacy of mirtazapine on QoL

Data for QoL are summarized in **Table 5**. At baseline, none of the mean scores for any domain of the SF-36 between 3 groups of patients with FMS were significantly different. There was no significant difference in the mean change from baseline (visit 1) between the 3 groups of patients with FMS at visits 4, 5, or 6. We found that patients in the mirtazapine groups had a significant improvement in almost domains of QoL except social functioning when we compared the mean change from baseline between visits 1 to 4, visit 1 to 5, or visit 1 to 6 of patients in the mirtazapine groups and placebo group. We found mirtazapine 30 mg/d had a greater effect on QoL than it did in patients receiving mirtazapine 15 mg/d or placebo. At visits 4, 5, and 6, patients receiving mirtazapine 30 mg/d showed a significant increase in physical function, role limitations because of physical problems, bodily pain, vitality, role limitation because of emotional problems, and mental health. However, general health perception only increased significantly at visit 6. Role limitation because of physical problems was significantly increased in patients receiving mirtazapine 15 mg/d at visit 5, bodily pain at visit 6, general health perception at visits 5 and 6, role limitation because of emotional problems at visit 6, and mental health at visit 5. Patients receiving placebo showed a significant increase in role limitation because of physical problems at visit 5, bodily pain at visits 5 and 6, vitality at visits 5 and 6, social functioning at visit 4, role limitation because of emotional problems at visits 4 and 5, and mental health at visits 5 and 6. At the end

of the study, patients receiving placebo showed significant increases in 2 domains of SF-36 QoL: mental health and vitality. The mental health domain scores in patients receiving mirtazapine 15 mg/d and 30 mg/d were dramatically improved to the level of HV scores (81 (14.4) and 83 (12.4) respectively vs 82 (14.5) for HVs), while the scores of mental health domain in the placebo group were lower than in HVs (72 (11.5) vs 82 (14.5) respectively).

Table 5. Mean scores for each domain of the SF-36 QoL in patients with fibromyalgia syndrome in each group at visits 1, 4, 5, and 6 compared with baseline

Quality of life domains (scales 0–100)	Placebo Mean ± SEM (n = 13)	Mirtazapine 15 mg Mean ± SEM (n = 13)	Mirtazapine 30 mg Mean ± SEM (n = 14)
Bodily pain			
Visit 1	34 ± 15.5	40 ± 14.6	28 ± 8.8
Visit 4	48 ± 11.2*	48 ± 19.1	48 ± 17.4*
Visit 5	46 ± 10.4*	54 ± 22.9	52 ± 22.1*
Visit 6	49 ± 18.4	58 ± 18.2*	57 ± 19.0*
General health			
Visit 1	38 ± 20.4	37 ± 21.2	36 ± 16.5
Visit 4	48 ± 15.5	47 ± 19.4	48 ± 20.4
Visit 5	48 ± 18.78	54 ± 21.3*	50 ± 23.2
Visit 6	47 ± 17.2	59 ± 18.2*	53 ± 23.4*
Mental health			
Visit 1	57 ± 13.8	71 ± 14.7	63 ± 16.9
Visit 4	67 ± 13.2	80 ± 12.2	78 ± 11.1*
Visit 5	74 ± 12.1*	86 ± 11.7*	85 ± 11.3**
Visit 6	72 ± 11.5*	81 ± 14.4	83 ± 12.4*
Physical functioning			
Visit 1	55 ± 4.1	71 ± 5.9	60.7 ± 3.8
Visit 4	61 ± 5.4	75 ± 6.8	72.9 ± 4.9**
Visit 5	58 ± 5.4	78 ± 5.2	72.1 ± 6.0*
Visit 6	58 ± 7.2	80 ± 5.1	76.7 ± 6.0*
Role limitation because of emotional problems			
Visit 1	28 ± 30.0	59.0 ± 38.9	33.3 ± 39.2
Visit 4	67 ± 36.5*	77.8 ± 38.5	75.0 ± 40.5*
Visit 5	73 ± 29.1*	86.1 ± 22.3	69.4 ± 46.0*
Visit 6	64 ± 40.7	88.9 ± 16.4*	75.0 ± 38.0*
Role limitation because of physical problems			
Visit 1	23 ± 29.7	44 ± 43.5	20 ± 26.3
Visit 4	46 ± 31.3	58 ± 44.4	57 ± 44.1*
Visit 5	57 ± 42.0*	67 ± 41.7*	65 ± 41.9*
Visit 6	57 ± 46.2	63 ± 37.7	65 ± 45.8*
Social functioning			
Visit 1	49 ± 14.8	53 ± 5.5	51.8 ± 9.6
Visit 4	56 ± 6.5*	50 ± 13.1	56.3 ± 6.5
Visit 5	52 ± 9.4	50 ± 9.2	47.9 ± 14.9
Visit 6	53 ± 9.8	48 ± 9.0	52.1 ± 4.9
Vitality			
Visit 1	43 ± 15.6	59 ± 21.9	49 ± 15.7
Visit 4	52 ± 10.6	65 ± 22.6	61 ± 14.0*
Visit 5	58 ± 10.8*	70 ± 23.8	65 ± 17.8*
Visit 6	59 ± 11.2*	64 ± 17.2	66 ± 17.9*

*$P < 0.05$, **$P < 0.001$; Wilcoxon signed-rank test

Discussion

FMS is characterized by chronic widespread pain throughout the body of the patients. Aside from pain, sleep and mood disturbances, headache, fatigue, body stiffness, muscle weakness, numbness, irritable bowel and urethral syndromes, and cognitive difficulties are commonly found in patients with fibromyalgia [1]. In addition, patients with FMS have a poorer overall health status compared to patients with other specific pain conditions, including myofascial pain syndrome, systemic lupus erythematosus, chronic widespread pain, rheumatoid arthritis, and primary Sjögren's syndrome [5]. The prevalence of FMS has increased since we have had a simple tool based on ACR 2010 and modified 2010 criteria for diagnosis of FMS in clinical practice. The ACR 1990 criteria are still considered to be the criterion standard for diagnosis of FMS. ACR 1990 criteria required two domains for the diagnosis of FMS as follows: (1) a history of chronic widespread pain for more than 3 months and effecting all sides of the body, and (2) pain on tender point testing (TeP) ≥11 of 18 specific sites. These criteria require TeP examination, which was found to be a limitation in primary care settings. Therefore, the new diagnosis has been developed, including the ACR 2010 criteria (preliminary diagnosis) and the modified 2010 ACR criteria (preliminary research). Both criteria evaluate the symptoms based on a severity scale and widespread pain index, while excluding TeP examination. Jones et al. [16] reported that the prevalence of fibromyalgia in the same population according to the ACR 1990, ACR 2010, and modified 2010 ACR criteria were 1.7%, 1.2%, and 5.4%, respectively. This study supported that the ACR 2010 criteria were comparable to the ACR 1990 criteria in detecting cases of FMS. The modified 2010 ACR criteria showed the greatest prevalence. However, it may be affected by a small sample size, so we justify our use of the ACR 1990 criteria.

Clinical characteristics and QoL in patients with FMS compared to HVs

It is widely found that patients with FMS are significantly impaired in all domains of QoL. In addition, patients with FMS are in poorer in health status overall compared with patients with other specific pain conditions [17, 18].

To our knowledge, there were previously no data on the QoL in Thai patients with FMS compared with healthy individuals. This is the first study that investigated the effects of disease burden and the clinical effect of mirtazapine on pain and QoL of Thai patients with FMS.

We found no significant differences in age or sex between FMS patients and HVs, while the BMI was significantly higher in HVs. Our findings suggested that the majority of Thai patients with FMS are middle-aged women. These findings are consistent with previous findings that patients with FMS were more commonly likely to be women at middle age than men [7].

All FMS symptoms have a serious impact on various aspects of patients' lives, including personal relationships, career, and mental health. Symptoms of FMS such as chronic widespread pain, fatigue, sleep disturbance, anxiety, depression, and morning stiffness are associated with low QoL in patients with FMS [17]. In the present study, the SF-36 Thai questionnaire was used to assess QoL in patients with FMS and HVs. We found that patients with FMS had lower QoL in all domains compared to HVs, especially the RP domain (30 vs 96 in HVs), BP domain (33 vs 87), and GH domain (36 vs 84). Previous studies conducted in Turkey and The Netherlands also showed the lowest score in RP domain in patients with FMS [17-18]. The lowest score in the RP domain, which related to somatic symptoms was directly explained by the main symptoms of FMS especially pain and fatigue.

The low levels of NE, 5-HT, and dopamine in FMS patients may be associated with pain and neuropsychiatric symptoms such as depression, anxiety, and cognitive deficits [17, 19-21].

However, the QoL scores of FMS patients in MH, RE, and SF domains, which related to the mood symptoms were not so different from Thai HVs, even though the differences were statistically significant. This might be due, at least in part, to the importance of coping mechanisms including religion, spirituality, accepting pain, and social support in Thai patients who suffer from chronic pain [22]. A few studies have suggested that appropriate coping strategies may help improve QoL in patients with FMS [23-24]. According to the results of the present study, it was evident that Thai patients with FMS suffered from low QoL in all domains. This may have an impact on poor function in workplace and life. Therefore, treatment is essential in improving the clinical symptoms of these patients.

Mirtazapine efficacy assessment

Mirtazapine is an NaSSA that increases the level

of NE and 5-HT neurotransmitters at the synaptic cleft by blocking the α2 presynaptic receptor at noradrenergic and serotonergic neurons. Increasing levels of NE and 5-HT in the descending inhibitory pain pathway by mirtazapine may lead to pain suppression at the spinal cord level and in the CNS providing benefits in terms of improving mood disorders. Moreover, mirtazapine has 5-HT_2 and 5-HT_3 receptor blocking properties that result in no or less sexual dysfunction and an antiemetic effect, respectively. In addition, an indirect increase in 5-HT levels at 5-HT_{1A} receptors also has an analgesic effect [10-12]. Moreover, mirtazapine has an antihistaminic effect (as an H_1 receptor antagonist) and thus would provide additional benefits in patients with FMS who have insomnia or loss of appetite. Therefore, based on its pharmacological profile, mirtazapine should be useful for the treatment of FMS, especially in the patients who concomitantly exhibit pain, depression, and sleep disturbances.

We found that mirtazapine 15 and 30 mg once daily before bedtime was effective in decreasing pain in Thai patients with FMS, especially in the BP domain of the SF-36 QoL. Other studies have also found that mirtazapine improved pain severity and QoL in other patients with pain, such as in patients with cancer pain, and patients with chronic pain and concomitant depression [21, 25]. The score of each domain of QoL increased after mirtazapine treatment, especially in the patients who took mirtazapine 30 mg daily. Mirtazapine 30 mg/d significantly improved all QoL domains except SF. This may be explained by the side effect (i.e. sedation) of mirtazapine, which potently blocks H_1 receptors. The RP domain score, which was the worse domain affected in our patients with FMS, was significantly improved from 20 to 65 by mirtazapine at 30 mg/d. This pharmacological effect of mirtazapine was attributed to its analgesic and antidepressant effects.

The mental health score of patients was increased to the same levels of HVs after receiving mirtazapine either at the doses of 15 and 30 mg/d. Our study confirmed that mirtazapine can improve mood in patients with FMS, presumably because of its antidepressant effects.

To date, duloxetine, milnacipran, and pregabalin have been approved from the US FDA for FMS treatment. Duloxetine and milnacipran are SNRI antidepressant drugs, which increase NE and 5-HT in the descending inhibitory pain pathway. All three drugs reduce pain and improve QoL; however, duloxetine is ineffective in reducing fatigue symptoms, milnacipran does not improve sleep disturbance, and pregabalin does not improve depressed mood [8]. The risk of headache and nausea with duloxetine and milnacipran are higher compared with pregabalin. The most common adverse effects of mirtazapine found in our study were somnolence, increased appetite, and weight gain. This is in accordance with a previous study, which found that the most common adverse effects of mirtazapine were dry mouth, somnolence, hyperphagia, increased appetite, and body weight gain [23]. Three patients with FMS withdrew from our study because of adverse effects. However, tolerance to somnolence typically occurs within 7–10 d after the treatment [25] and therefore counseling may help improve drug adherence in affected patients. The majority of adverse events in our study were mild or moderate, and no serious adverse events were reported.

Conclusions

The general goal of FMS treatment is to develop an individualized approach based on a patient's symptoms and their severity. Our results suggest that mirtazapine is effective in reducing bodily pain and improving mood symptoms with well-tolerated adverse effects. Based on mechanism of action of mirtazapine, the drug showed benefit for all domains of SF-36 QoL except SF. However, we only recruited a small number of participants, and additional studies should be performed with more participants to confirm our results.

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Conflict of interest statement

The authors declare that there is no conflict of interest in this research.

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