# An open-label study of levopromazine (methotrimeprazine) as an add-on therapy in fibromyalgia management

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*Abbreviations:*
BDI: Beck Depression Inventory
CGI-severity: Clinical Global Impression of Severity Scale
FIQ: Fibromyalgia Impact Questionnaire
ITT: intent-to-treat
MCS: mental component summary
NSAIDs: non steroidal anti-inflammatory drugs
PCS: physical component summary
PGI-improvement: Patient Global Impression of Improvement
PSQI: Pittsburgh Sleep Quality Index
STAI: State-Trait Anxiety Inventory
SF-12: SF-12 Health Survey
SD: standard deviation

**Key words:** Fibromyalgia, methotrimeprazine, levopromazine, antipsychotic, neuroleptic, analgesic, chronic pain, sleep.

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## ABSTRACT

**Objective.** *To assess the potential efficacy and tolerability of levopromazine (methotrimeprazine) in the treatment of fibromyalgia.*

**Methods.** *Unicentre, open-label study conducted in thirty-five outpatients, aged 18 years or older, who met the ACR criteria for fibromyalgia and had not satisfactorily responded to previous fibromyalgia treatment. Levopromazine, flexibly dosed (12.5-100 mg/d), was added to the outpatients' original treatment regimens for 12 weeks. The primary outcome measure was the mean change from baseline to endpoint in the Fibromyalgia Impact Questionnaire (FIQ) total score in the intent-to-treat sample. Secondary outcomes included the Clinical Global Impression (CGI) of Severity scale, Pittsburgh Sleep Quality Index (PSQI), Beck Depression Inventory, State-Trait Anxiety Inventory, 12-Item Short Form Health Survey, and individual items of the FIQ.*

**Results.** *The mean FIQ total score did not decrease significantly at the study endpoint (63.37 SD 11.32 vs. 61.19 SD 9.32, p=0.73). Pain intensity, as evaluated by the Visual Analogue Scale, remained unchanged at study endpoint (8.5 SD 1.6 vs. 8.2 SD 1.2, p=0.49). A statistically significant reduction was observed in the PSQI score (15.65 SD 3.33 vs. 12.23 SD 3.79, p<0.001, effect size: 1.03) and the CGI-severity score (4.71 SD 0.64 vs. 4.03 SD 1.01, p<0.002, effect size: 1.06). No significant or relevant changes were seen in the remaining fibromyalgia symptoms, psychopathological scales or quality-of-life. The drug was well tolerated*

**Conclusions.** *Despite its efficacy in improving sleep quality, levopromazine does not appear to be a useful alternative treatment for fibromyalgia.*

## Introduction

Fibromyalgia is a chronic musculoskeletal condition characterized by widespread pain, fatigue, stiffness and disrupted sleep (1). It is commonly associated with other symptoms and conditions, such as depression, anxiety, cognitive disturbance, headache, irritable bowel syndrome and temporomandibular joint dysfunction (1). Fibromyalgia has a negative impact on the quality of life (2, 3) and it is associated with high rates of self-reported disability and health resource utilization (4, 5).

Fibromyalgia therapy includes both pharmacological and non-pharmacological treatments (6, 7). Among pharmacological treatments, some drugs, including the antiepileptic pregabalin, which was recently approved by the FDA for treatment of this condition, serotonin and norepinephrine reuptake inhibitors, antidepressants such as duloxetine and milnacipran, and an older antidepressant, amitryptiline, have been shown to be effective in the treatment of fibromyalgia (8). However, pharmacological treatment options are limited and are associated with only modest benefits (9, 10). Therefore, there is still a need for new therapeutic alternatives are needed for treatment of this condition. Published data suggest that both conventional (11) and atypical antipsychotics may have analgesic properties (12, 13). Although an improvement in pain and other outcomes was reported in a retrospective study of patients with fibromyalgia receiving olanzapine (14), we found that these potential benefits were obscured by its poor tolerability, especially its weight gain liability, in an open-label prospective study (15). We have also observed that ziprasidone exhibited poor tolerability and limited efficacy in the treatment of this condition in another open-label study (16). In contrast, an improvement in pain, sleep quality and mood was observed in a partially reported case series of 7 women diagnosed with fibromyalgia and treated with low-doses of quetia-

pine (25 to 200 mg daily) (17). In a 12-week open-label study in patients with fibromyalgia, we found that quetiapine significantly improved overall efficacy measures and quality of life (18). However, in this latter study quetiapine did not ameliorate pain which, in contrast, improved after the addition of pregabalin to the quetiapine regimen (19). While we think that the promising results with quetiapine should be further tested in randomized controlled trials, we are aware that the acquisition costs of atypical antipsychotics (*e.g.* olanzapine, ziprasidone, quetiapine, etc.) are much higher than those of conventional antipsychotics (*e.g.* haloperidol, fluphenazine, etc.).

Levopromazine (also called 'methotrimeprazine'), a phenothiazine derivative, is a conventional antipsychotic that exhibits antipsychotic, tranquilizing, anxiolytic, sedative and analgesic properties (20). In some countries levopromazine is indicated for the treatment of psychosis, conditions associated with anxiety, the treatment of pain (due to cancer, zona, trigeminal neuralgia, etc.), and for the management of insomnia (20). Importantly, the acquisition cost of levopromazine is much lower than that of atypical antipsychotics or other new pharmacological options for the treatment of fibromyalgia (*i.e.* pregabalin, duloxetine). These characteristics make levopromazine a good drug candidate for initial testing for the treatment of this condition.

The objective of this study was to evaluate the potential efficacy and tolerability of levopromazine for the treatment of fibromyalgia syndrome.

## Methods

*Patients*

Male and female patients, aged 18 years and over, who met the American College of Rheumatology criteria for the diagnosis of fibromyalgia and who had not satisfactorily responded to their previous fibromyalgia treatment (*i.e.* they had a score of >4 on the pain severity item of the Fibromyalgia Impact Questionnaire) were included in the study. Patients were excluded if they had a blood dyscrasia, hepatic disease, known hypersensitivity to phenothiazines, or if they were receiving or requiring concomitant treatment with another antipsychotic.

*Study design and treatment*

This unicentre, open-label study was conducted between September 2005 and February 2007 in our chronic pain clinic. After fulfilment of eligibility criteria was ensured, patients received open treatment with levopromazine and were followed for 12 weeks. Levopromazine was added to patients' original drug regimens at an initial dose of 12.5 mg/day. This dose was subsequently adjusted according to the therapeutic response and tolerability.

The study was reviewed and approved by the Ethics Committee of the University of Granada (Spain) and conducted in accordance with the principles of the Helsinki Declaration. All patients provided written informed consent before study entry.

*Efficacy and tolerability evaluations*

A manual tender point diagnostic assessment and medical history were taken at the baseline visit. In addition, the Spanish validated versions of the following questionnaires/scales were also administered at baseline: the Fibromyalgia Impact Questionnaire (FIQ) (21-23), a Clinical Global Impression of Severity scale (CGI-severity) (24), the Beck Depression Inventory (BDI) (25, 26), the State-Trait Anxiety Inventory (STAI) (27, 28), the Pittsburgh Sleep Quality Index (PSQI) (29, 30), and the SF-12 Health Survey (31, 32). A more detailed description of the assessment tools can be found elsewhere (18).

Patients' follow-up visits were scheduled for weeks 4, 8 and 12. At week 2, a telephone contact was made to ascertain whether there were any tolerability issues. Patients were evaluated every four weeks using the FIQ and a Patient Global Impression of Improvement scale (PGI-improvement). Additionally, the CGI-severity scale, BDI, STAI, PSQI and SF-12 were administered at the study endpoint. Treatment-emergent adverse reactions were recorded at each study visit by an open question.

*Statistical analysis*

The primary efficacy measure was the mean change from baseline to endpoint in the FIQ total score. All other efficacy outcome measures were secondary and consisted in the changes from baseline to endpoint in the scores of the CGI-severity, PSQI, BDI, STAI (anxiety-trait and anxiety-state scores), SF-12 (PCS and MCS scores) and individual items of the FIQ. In addition, the proportion of patients responding to treatment was calculated. Response was defined as the number of patients who were at least 'much improved' according to the PGI-improvement scale (*i.e.* a score of 1 or 2).

Demographic and baseline clinical characteristics were described using the mean and standard deviation for continuous measures (*e.g.* age, scales' scores), and the frequency and percentage for categorical variables (*e.g.* sex, comorbidity).

The intention-to-treat (ITT) sample included those patients who were prescribed levopromazine and had at least one post-baseline efficacy evaluation. Analysis of the ITT sample was performed with the last observation carried forward approach (LOCF), except for those scales that specified another method for dealing with missing data (STAI and SF-12). All effectiveness analyses were based on the ITT sample. Changes over time in the FIQ total score and subscores were analyzed using one-way repeated measures ANOVA. The significances of within group changes from baseline to endpoint in the total scores or subscores of the remaining efficacy scales were calculated with the Student's *t*-test or a non-parametric test when appropriate. They were considered significant if the *p*-value was less than 0.05. In order to interpret the clinical relevance of changes in those efficacy scales, the effect sizes were also calculated. Effect sizes were calculated as the mean change score (before and after treatment) divided by the standard deviation of the same measure before treatment (33). For interpreting the relative magnitude of change, we considered an effect size of 0.20 as small, one of 0.50 as moderate and one of 0.80 or greater as large.

**Table I**. Demographics and clinical characteristics.

| Characteristic | n=35 |
|---|---|
| Age, years, Mean (SD) | 46.0 (8.0) |
| Sex, Females, n. (%) | 31 (88.6) |
| Years since diagnosis, Mean (SD) | 2.2 (1.9) |
| Comorbid conditions, n. (%) | |
| Temporomandibular dysfunction | 34 (97.1) |
| Depressive disorder | 29 (82.9) |
| Tension-type headache | 21 (60.0) |
| Migraine | 25 (71.4) |
| Irritable bowel syndrome | 19 (54.3) |
| Chronic fatigue syndrome | 14 (40.0) |
| Current fibromyalgia medications*, n. (%) | |
| NSAIDs/acetaminophen | 29 (82.9) |
| Opioids | 13 (37.1) |
| Antidepressants | 19 (54.3) |
| Anxiolytics/hypnotics | 28 (80.0) |

NSAIDs: non steroidal anti-inflammatory drugs; SD: standard deviation.
*Patients might be receiving more than one medication for the symptoms of fibromyalgia.

## Results

*Patients' disposition, demographics and clinical characteristics*

Thirty-five patients were included in the study and constitute the tolerability sample. Thirty-one patients received post-baseline efficacy evaluations and were included in the ITT sample. Eleven patients (31.4%) withdrew from the study. The reasons for withdrawal were adverse reactions (n=6, 17.1%), lost to follow-up (n=3, 8.5%), consent withdrawal (n=1, 2.9%) and other reasons (n=1, 2.9%).

Mean age was 47.2 (SD: 7.9) years and most patients (88.6%) were female. Our sample had high rates of comorbidity and use of fibromyalgia medications at study entry (Table I). The patients were moderately to severely ill, with a mean FIQ total score of 63 points (score range 0-80) and a mean score of the severity of fibromyalgia core symptoms (ie, pain, fatigue and stiffness) of around 8 or higher, as evaluated by the corresponding 10 cm visual analogue scales of the FIQ (Table II). Baseline health-related quality of life was also deeply impaired in this sample of patients with fibromyalgia (Table III), according to their low scores on the physical and mental component summary of SF-12 (25.4 SD 4.6 and 33.4 SD 12.4, respectively) and compared with the average Spanish adult norm (50 SD 10 for each component) (34).

At the study endpoint, the mean (SD) dose of levopromazine was 31.9 (22.3) mg/day.

*Efficacy*

The mean FIQ total score decreased by only 2 points, from a baseline of 63.4 to 61.2 at study endpoint (Table II), a change that was neither statistically significant nor clinically relevant. With the exception of 'feeling tired upon awakening', which showed a significant improvement at the endpoint with a moderate effect size, there were not any significant changes in any of the FIQ subscores (Table II). Similarly, measures of depression, anxiety and quality of life remained almost unchanged at the study endpoint (Table III). In contrast, there was a modest but significant and clinically relevant improvement in the severity of the disease, as evaluated by CGI-severity (Table III). Four (12.9%) patients were reported to be 'much improved' and 14 (45%) were 'slightly improved' according to the PGI scale.

From all symptomatologic domains, the only significant improvement was observed in sleep quality, as evaluated by the PSQI total score (Table IV). Analysis of the individual components of the PSQI (Table IV) revealed that levopromazine significantly improved sleep duration, subjective sleep efficiency and sleep quality. However, no improvement was found in sleep latency or in the use of hypnotic medication.

*Tolerability*

The most frequent adverse reactions (ie, those reported by at least 10% of the patients), as elicited by the open question were dry mouth (n=9, 25.7%), somnolence (n=6, 17.1%) and nightmares (n=4, 11.4%).

Overall, the mean (SD) weight (kg) increased slightly, but significantly, from 70.6 (13.5) at baseline to 71.9 (13.6) at week 12 ($t$=3.47, $p$=0.002).

## Discussion

Our study suggests that levopromazine, when added to a pre-existing treatment regimen, does not provide a clinically relevant benefit to patients with fibromyalgia who had not satisfactor-

**Table II**. Changes over time in the FIQ total score and subscores (ITT analysis).

| Measure (range) | Baseline | Week 4* | Week 8* | Week 12* | $F$ | $p$-value* |
|---|---|---|---|---|---|---|
| FIQ Total (0-80) | 63.4 (11.3) | 62.0 (10.0) [0.12] | 62.1 (9.1) [0.11] | 61.2 (9.3) [0.19] | 0.43 | 0.73 |
| FIQ subscores (0-10) | | | | | | |
| Physical impairment | 6.6 (1.6) | 6.7 (1.6) [-0.02] | 6.9 (1.5) [-0.15] | 7.0 (1.4) [-0.22] | 1.92 | 0.13 |
| Days felt good | 8.2 (2.7) | 8. (1.8) [-0.06] | 8.1 (2.1) [0.06] | 7.3 (3.0) [0.34] | 2.23 | 0.08 |
| Work missed | 6.3 (3.7) | 6.3 (3.3) [-0.01] | 5.5 (3.1) [0.21] | 6.0 (3.2) [0.08] | 0.92 | 0.43 |
| Work impairment | 8.3 (1.9) | 8.5 (1.1) [-0.10] | 8.4 (1.1) [-0.09] | 8.3 (1.6) [-0.03] | 0.13 | 0.94 |
| Pain | 8.5 (1.7) | 8.1 (1.3) [0.23] | 8.0 (1.2) [0.23] | 8.2 (1.2) [0.15] | 0.82 | 0.49 |
| Fatigue | 8.7 (1.6) | 8.7 (1.5)[0.00] | 8.7 (1.1) [-0.06] | 8.8 (0.9) [-0.12] | 0.20 | 0.90 |
| Tired upon awakening | 8.8 (1.6) | 7.9 (1.9) [**0.55**] | 7.8 (2.3) [**0.65**] | 7.8 (2.0) [**0.62**] | 2.85 | **0.04** |
| Stiffness | 7.9 (2.3) | 8.3 (1.7) [-0.17] | 7.7 (1.9) [0.09] | 7.6 (2.1) [0.15] | 1.37 | 0.26 |
| Anxiety | 7.6 (2.2) | 7.2 (2.5) [0.17] | 7.5 (2.1) [0.04] | 7.2 (2.3) [0.17] | 0.35 | 0.79 |
| Depression | 6.9 (3.0) | 6.5 (3.2) [0.14] | 7.2 (2.4) [-0.11] | 7.1 (2.4) [-0.07] | 0.85 | 0.47 |

Results are expressed as mean (standard deviation) [effect size]>
*Bold figures indicate significant changes ($p$<0.05) and/or at least moderate effect sizes (≥0.50).
FIQ: fibromyalgia impact questionnaire; ITT: intent-to-treat.

**Table III**. Summary of other secondary outcomes (ITT analysis).

| Outcome measure | Baseline mean (SD) | Endpoint mean (SD) | *t* | *p*-value* | Effect size* |
|---|---|---|---|---|---|
| CGI-severity | 4.7 (0.6) | 4.0 (1.0) | 3.50 | **0.002** | **1.06** |
| BDI total score | 27.8 (9.7) | 28.8 (10.8) | 0.97 | 0.34 | -0.09 |
| BDI Somatic factor | 12.5 (3.7) | 12.4 (4.3) | 0.20 | 0.84 | 0.02 |
| BDI Cognitive factor | 15.2 (7.0) | 16.2 (7.3) | 0.14 | 0.18 | -0.13 |
| STAI-State | 38.9 (11.0) | 39.7 (10.7) | 0.43 | 0.67 | -0.08 |
| STAI-Trait | 40.3 (9.9) | 42.1 (10.2) | 1.22 | 0.23 | -0.19 |
| SF-12 PCS | 25.4 (4.6) | 26.3 (5.2) | 0.81 | 0.43 | -0.18 |
| SF-12 MCS | 33.4 (12.4) | 32.3 (11.8) | 0.38 | 0.71 | -0.09 |

*Bold figures indicate significant changes ($p<0.05$) and/or at least moderate effect sizes (≥0.50).
BDI: Beck Depression Inventory; CGI: Clinical Global Impression; ITT: intent-to-treat; MCS: mental component summary; PCS: physical component summary; SD: standard deviation; STAI: State-Trait Anxiety Inventory.

**Table IV**. Change at endpoint in the Pittsburgh Sleep Quality Index scores (ITT analysis).

| PSQI score | Baseline mean (SD) | Endpoint mean (SD) | *t* | *p*-value* | Effect size* |
|---|---|---|---|---|---|
| TOTAL score | 15.7 (3.3) | 12.2 (3.8) | 4.45 | <0.001 | 1.03 |
| Subjective sleep quality | 2.4 (0.6) | 1.6 (0.8) | 5.94 | <0.001 | 1.43 |
| Sleep latency | 2.3 (0.8) | 2.3 (0.9) | 0.00 | 1.00 | 0.00 |
| Sleep duration | 2.1 (1.1) | 1.4 (1.1) | 4.16 | <0.001 | 0.68 |
| Sleep efficiency | 2.0 (1.3) | 1.3 (1.3) | 4.04 | <0.001 | 0.56 |
| Sleep disturbances | 2.5 (0.6) | 2.2 (0.7) | 3.43 | 0.002 | 0.61 |
| Sleep medications | 2.3 (1.2) | 1.9 (1.4) | 1.46 | 0.15 | 0.27 |
| Daytime dysfunction | 2.3 (0.9) | 2.1 (1.1) | 2.32 | 0.03 | 0.29 |

*Bold figures indicate significant changes ($p<0.05$) and/or at least moderate effect sizes (≥0.50).
ITT: intent-to-treat; PSQI: Pittsburgh Sleep Quality Index.

ily responded to previous treatment. Levopromazine did not improved any of the core symptoms of fibromylagia (ie, pain, fatigue or stiffness), excepting sleep, and did not provide any improvement in the associated symptoms of anxiety and depression.

The lack of an effect of levopromazine on pain is somewhat surprising, since this drug is considered to have primary analgesic effects (11). Levopromazine has been compared with meperidene and morphine in patients with postsurgical pain, cancer pain, and migraine in several randomized clinical trials (11). In these trials, levopromazine was as potent as meperidine and, although efficacious, was generally less potent than morphine (11). However, some authors think that these trials have important methodological flaws, including lack of a placebo control in most trials and failure to distinguish between analgesia and sedation (35). Given the flaws in these trials, they believe that the analgesic effect of levopromazine has not been well demonstrated (35). It is also important to consider that levopromazine was administered parenterally in most of the above-mentioned trials. In a randomized, placebo-controlled trial in obstetric patients with postdelivery pain, 25 mg of oral levopromazine was no more efficacious than placebo at relieving pain (36). Therefore, as was suggested previously (11), the lack of an effect of oral levopromazine on pain could be due to its low oral bioavailability.

In this study, the only benefit obtained with levopromazine was improvement in the sleep measures. However, in our view, this is an important effect, since sleep disturbance appears to be a key component of the fibromyalgia syndrome. Over 90% of the patients with fibromyalgia and chronic fatigue syndrome complain of unsatisfactory sleep, and most people with fibromyalgia have a disturbance in their sleep known as alpha EEG sleep arousal disorder that, although not specific to this condition, is considered to be a sensitive indicator of nonrestorative sleep and daytime symptoms (37). Many of the daytime symptoms in these patients, such as morning aching, fatigue and stiffness, may be related to the sleep disturbance associated with fibromyalgia (37, 38). In fact, sleep and pain appear to reciprocally exacerbate each other (39). In patients with fibromyalgia, it has been reported that an increased pain sensitivity is associated with a greater sleep disturbance (40). In addition, in patients with chronic pain, sleep problems have been associated with anxiety and depression (41) and with decrements in health-related quality of life, as measured by SF-36 (42). The importance of sleep improvement in our study is reflected in the fact that it was accompanied by an improvement in the overall subjective impression of disease severity (*i.e*. a significant and clinically relevant improvement in the CGI score). However, despite this effect of levopromazine, we think that there are better therapeutic alternatives for treating sleep disturbances in patients with fibromyalgia, such as the nonbenzodiazepine hypnotics zopiclone and zolpidem, which have been demonstrated to be efficacious in patients with fibromyalgia (43-45), and trazodone or cognitive behavioural therapy, which, in addition to being associated with significant sleep improvement in this population (46, 47), might have a positive impact on other fibromyalgia symptoms. Quetiapine, an atypical antipsychotic with sleep promoting properties (48) and preliminary promising results in patients with fibromyalgia (18), may also be a better second-line option.

Our study has several limitations. This was an uncontrolled study, but we do not think that this is a major issue since our study was negative and uncontrolled designs tend to overestimate rather than underestimate treatment effects. Second, we included a sample of severe and somewhat refractory fibromyalgia patients with high comorbidity that could bias the results against levopromazine. However, using the same inclusion criteria, we found that quetiapine improved sleep, overall symptomatology and quality of life in a sample of patients with fibromyalgia

that was quite similar to the group in the present study (18).

Overall, our study suggests that levopromazine (methotrimeprazine) is not a useful alternative for the treatment of patients with fibromyalgia. Despite its clinically significant effect on sleep measures in our study, its use as a sleep aid should be confined to selected patients who do not respond to other sedatives (eg, zolpidem, zopiclone, etc.) that are better studied and may be better tolerated.

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