A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF MOCLOBEMIDE AND AMITRIPTYLINE IN THE TREATMENT OF FIBROMYALGIA IN FEMALES WITHOUT PSYCHIATRIC DISORDER

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SUMMARY

Objective. To study the usefulness of moclobemide and amitriptyline in the treatment of fibromyalgia (FM) in females without psychiatric disorder.

Methods. In the present four centre, 12 week study, 130 female FM patients not suffering from psychiatric disorders were randomized to receive amitriptyline (AMI; 25–37.5 mg), moclobemide (MOCLO; 450–600 mg) or identical placebo.

Results. Seventy-four, 54 and 49 per cent of patients on AMI, MOCLO and placebo, respectively, were judged as responders. The patients on AMI also managed best regarding the respective improvements during the trial in general health, pain, sleep quality and quantity, and fatigue on visual analogue scales (VAS), the areas of the Nottingham Health Profile (NHP), as well as in the three Sheehan's functional disability scales. In the within-group comparisons, MOCLO also improved pain assessed both on VAS and on the NHP pain dimension, but the improvement was invalidated by the poor success of the drug with regard to sleep. The tolerabilities of all three drugs were comparable.

Conclusion. The study indicates that MOCLO may not be helpful in FM patients free from clinically meaningful psychiatric problems.

KEY WORDS: Fibromyalgia, Amitriptyline, Moclobemide, Drug trial.

FIBROMYALGIA (FM) is a chronic pain syndrome characterized by musculoskeletal pain, non-restorative sleep and fatigue, psychosomatic, psychiatric, neurological and a variety of protein symptoms. Further, the symptoms are aggravated by external and/or internal stress [1, 2]. Although the pathogenesis of FM is poorly understood and the symptoms appear to arise from diverse causes, the cornerstone of clinical diagnosis is the presence of multiple palpable tender points [3], which also appear to reflect the general distress of an individual [4, 5].

In epidemiological surveys, the respective prevalences of FM in the North American general population and in females aged 20–49 yr in Southern Norway have been reported to be 2% [6] and 10.5% [7]. Most of the patients are females and the prevalence increases with aging [6], since recoveries are exceptional [8, 9].

Despite increasing research efforts, considerable debate remains concerning the role of peripheral and central factors in the aetiopathogenesis of FM. Although muscular pain is an integral feature of the FM syndrome, controlled studies have failed to support a convincing role for muscle in the pathophysiology of the condition [10]. On behalf of central factors, significantly lower regional cerebral blood flow in thalamus and caudate nuclei [11], neurohormonal disturbances including low levels of insulin-like growth factor 1 (somatomedin C) [12, 13], hypothalamic–pituitary–adrenal axis hypofunction [14, 15], decreased plasma neuropeptide Y [15] and increased prolactin levels [16] have been reported in patients suffering from FM in comparison to healthy controls or patients with other musculoskeletal disorders. The observation that plasma levels, as well as the transport ratio of plasma tryptophan, are decreased in comparison to healthy subjects [17] is consistent with the hypothesis that FM also belongs to the syndromes with a serotonin deficit in the brain. Further, in comparison to healthy subjects, in addition to those of serotonin, decreased levels of metabolites of noradrenaline and dopamine [18] have been reported in cerebrospinal fluid of FM patients, suggesting that a seminal defect in FM occurs at a neuroregulatory level.

Randomized, controlled clinical trials have demonstrated that low doses of tricyclic and tetracyclic antidepressants, especially amitriptyline (AMI), are more effective than placebo in the treatment of FM [19–23]. On the other hand, other antidepressive agents, such as the selective serotonin reuptake inhibitors fluoxetine [24] and citalopram [25], in doses effective in the treatment of depression, impose only an effect comparable to placebo on FM. Goldenberg and co-workers [26], however, recently reported that AMI and fluoxetine may have an additive beneficial effect on fibromyalgic symptoms.

Moclobemide (MOCLO) is the first of a new class of reversible inhibitors of monoamine oxidase (MAO) A, the enzyme responsible for the breakdown of neurotransmitters in the sympathetic activity and the postsynaptic membrane. MOCLO inhibits the deamination of serotonin, noradrenaline and dopamine, but does not affect monoamine uptake or release [27]. It is an effective antidepressant [28–30] with a mild non-sedating adverse-effect profile [31].

The primary objective of the study was to determine
whether MOCLO will produce a significantly higher number of responders than placebo in FM patients free from major psychiatric disorders. Secondly, we wanted to see the adverse event profile of MOCLO in comparison to placebo and AMI in these patients. Since the effect of MOCLO has never been studied before in the treatment of patients with FM, AMI and placebo were chosen as comparator arms. Our results may also be of interest for the pathogenetic understanding of FM.

**Patients and Methods**

**Patients**

The patients were recruited from our out-patient clinics or were invited to participate by a letter from the register of FM patients. All the patients who accepted the invitation were screened. Only female patients aged 18–65 yr and fulfilling the ACR 1990 criteria [3] for FM at screening and baseline visits were enrolled. Further, to be included, the patients had to score at baseline a minimum of 4 (moderate) on at least three of the four self-administered visual analogue scales (VAS) (from 0 = not at all to 10 = very much). The items were: (1) patient’s global assessment of general health (GH) (‘How much has FM disabled your life during the recent week?’); (2) pain (‘How much pain have you had due to FM during the recent week?’); (3) sleep quality and quantity (‘How much have sleeping problems disturbed your life during the recent week?’); (4) fatigue (‘How tired have you been during the recent week?’).

People were excluded if they suffered from severe cardiovascular, pulmonary, hepatic, haematological or renal disease, glaucoma, were pregnant or lactating, or were not willing to discontinue all medication acting on the central nervous system, non-steroidal anti-inflammatory drugs and analgesics (other than paracetamol). The tests for thyroid function, serum calcium and creatine kinase also had to lie within reference values.

To exclude the patients with major depression, psychosis, obsessive–compulsive disorder or probable psychoactive drug use disorder, including excessive alcohol consumption, at present or during the preceding 6 months, a clinical structured interview (Scid-Ro) [32] was conducted by a psychiatrist before inclusion.

**Procedure and medication**

The 12 week, double-blinded, parallel group, three-arm study was conducted in four centres. The randomization was organized centrally with sequentially numbered envelopes consisting of blocks of six. Each MOCLO and AMI capsule contained 150 and 12.5 mg of active drug, respectively. The placebo capsules were identical to the active drugs.

At the screening visit, each patient received placebo capsules and paracetamol escape medication. After the 2 week, single-blinded, placebo run-in period (at baseline), the eligible patients were assigned in a relation of 1:1:1 to one of the following three regimens: (1) one MOCLO capsule in the morning (before 10 a.m.) and afternoon (before 2 p.m.), and one AMI placebo capsule 2 h before bedtime; (2) one MOCLO placebo capsule in the morning and afternoon, and one AMI capsule 2 h before bedtime; (3) one placebo capsule in the morning, afternoon and 2 h before bedtime.

The study treatment was recommended to be taken after meals. Only paracetamol tablets (500 mg) supplied by the sponsor (up to 4 g/day) were allowed as escape medication from the screening visit onward. The patients registered their drug consumption in a diary. Check-up visits with assessments were performed at baseline, and at 2, 6 and 12 weeks. If the patient tolerated the treatment, the dose was increased at the 2 week check-up to the target dose (450 mg MOCLO and 25 mg AMI). Further, if the response was still unsatisfactory at the 6 week visit, the MOCLO and AMI doses could be increased to 600 and 37.5 mg, respectively, with a concomitant increase in the number of placebo capsules.

The patients were provided with the study drugs at each check-up visit, when they also returned unused medication and empty containers for counting.

**Assessments**

At each check-up, the physician recorded his/her clinical impression of the change (CIC) of FM (on a seven-point scale: 3 = very much improved, 0 = no change, −3 = very much worse). The patients assessed 1, 2 or 3 were judged as responders.

The patients recorded their GH, sleep quality and quantity, pain, and fatigue on self-administered 10 cm VAS. Patients’ self-administered Sheehan’s functional scales (0 = not at all; 10 = very much) (1) in work (‘How much has your working capacity decreased due to your problems at present?’), (2) in social life and free time activities (‘How much have your social life and free time activities decreased due to your problems at present?’) and (3) in the duties of family life (‘How much do your family life and duties at home suffer from your problems at present?’) were recorded at each visit. In addition, adverse events, concurrent illnesses and drug consumption were also recorded. Further, at the baseline and 12 week visits, or if the patient discontinued in the trial, the number of ACR 1990 FM tender points (out of 18) [3], the quality of life in six dimensions by the patient self-administered Nottingham Health Profile (NHP) [33] questionnaire and the attending physician’s clinical impression of the severity of FM (CIS) (from 1 = normal to 7 = one among the most severely ill patients) were recorded.

Because of the possible diurnal rhythm of symptoms, the visits were scheduled to take place at the same time of day. In self-administered scales, the values in the mornings were recorded.

**End points**

The proportion of responders as assessed by the physician was used as the primary efficacy end point. Responders were the patients scoring 3 (very much improved), 2 (much improved) or 1 (minimally improved) on the CIC scale at the treatment end point.
Likewise, the mean improvements of the patients on the CIC scale in each treatment arm were calculated. As the secondary end points, the study protocol determined the changes (1) on the 10 cm VAS: (i) GH, (ii) pain, (iii) sleep quality and quantity, (iv) fatigue and (v) on the three Sheehan’s disability scales; (2) on the six areas of the NHP scales; (3) in the number of ACR 1990 FM tender points; and (4) in CIS.

In addition to spontaneous reporting, the patients were asked about side-effects/adverse events at each visit. The physician’s clinical global impression (CGI) of tolerability (from 1 = very poor to 4 = very good) was used as the measure of the overall tolerability of the test drug.

**Statistical analysis**

A sample size of 38 patients per active treatment group and placebo group was calculated to be required to obtain a 5% significance level and 80% power. When anticipating a drop-out rate of 15%, 44 patients were calculated to be randomized in each treatment arm to ensure an adequate group size.

The baseline demographic measurements were compared using ANOVA. All variables considered interval scaled were tested for homoscedasticity considering the two treatment groups. If heteroscedastic, a two-sample t-test with unequal variances was applied and P values were adjusted using Bonferroni correction. The distribution of the variables was tested using D’Agostino’s test. If the variable did not have a normal distribution, Mann–Whitney’s U-test was applied.

The null hypothesis in testing was that the three treatments had an equivalent response rate. Testing was started with overall comparison where all treatment groups were included. With interval-scaled variables, analysis of variance with equal replications and with the factors study drug group and treatment effect (RANOVA) was used. With ordinal-scaled variables, the Kruskall–Wallis one-way analysis of variance was applied. In the case of statistical significance in any factor, or in their interaction, pairwise analyses were carried out. With an ordinal-scaled variable, the Mann–Whitney U-test was applied.

For discrete data, an extended \( \chi^2 \) test for three independent samples was used in overall analysis.

The treatment responses (proportions) were compared using Fisher’s exact test.

All tests were two-sided and the intention-to-treat principle was applied. Difference was deemed to be statistically significant if the two-sided \( P \) value was <0.05.

**Ethics**

The trial was conducted according to the principles of the declaration of Helsinki and the Good Clinical Trial Practice [34]. All patients gave their written informed consent and the study was accepted by the local ethics committees before the start.

**RESULTS**

**Withdrawal from the study**

A total of 184 patients were screened to participate in the trial and 130 patients were included in the study (Fig. 1). Two of them were withdrawn due to entry violation, but since all patients received study medication, they are also included in the analyses. Ninety-two patients completed the study according to the protocol. The rates and reasons for withdrawals are shown in Fig. 1. Although the overall discontinuation rate was lowest in the AMI group, the differences in overall rates or reasons for withdrawals between the treatment groups were statistically not significant.

**Patient demographics and clinical characteristics at baseline**

Patient demographics did not differ between the treatment groups (Table I). Neither did the psychiatric profiles nor the general health of the patients in the three treatment arms differ statistically significantly at screening or baseline visits (data not shown). Fourteen, 16 and 16 patients in the MOCLO, AMI and placebo groups, respectively, had earlier been treated with antidepressants.

No statistically significant differences between the study treatment groups existed either in the number of tender points, CIS, the dimensions of NHP or the

**Table I**

Demographic data of the patients at screening and their within-group distribution according to disease duration; mean [s.d.]

<table>
<thead>
<tr>
<th></th>
<th>MOCLO</th>
<th>AMI</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>47.6  [8.7]</td>
<td>49.7  [8.2]</td>
<td>48.9  [8.9]</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.6  [4.1]</td>
<td>27.8  [4.3]</td>
<td>27.8  [5.4]</td>
</tr>
<tr>
<td>Symptomatic period (yr)</td>
<td>8.6  [4.0]</td>
<td>8.2  [3.9]</td>
<td>7.9  [4.1]</td>
</tr>
<tr>
<td>0–5 yr (n)</td>
<td>12</td>
<td>12</td>
<td>15</td>
</tr>
<tr>
<td>5.1–10 yr (n)</td>
<td>8</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>&gt;10 yr (n)</td>
<td>23</td>
<td>19</td>
<td>20</td>
</tr>
</tbody>
</table>

MOCLO, moclobemide; AMI, amitriptyline; BMI, body mass index.

![Fig. 1.—Study schedule and the number of patients and exclusions, as well as the schedule and reasons for discontinuations during the trial.](image-url)
areas of Sheehan’s functional scales, or in the symptomatic VAS at baseline (Tables II and III).

Clinical improvement
Seventy-four per cent of the patients in the AMI arm responded beneficially to the therapy, while the respective figures in the MOCLO and placebo arms were 54 and 49%. The differences of AMI vs MOCLO and AMI vs placebo were statistically significant (0.044 and 0.017, respectively), while the difference between the MOCLO and placebo arms did not reach statistical significance.

The respective clinical impression of changes (CIC; mean [s.d.]) of FM at 12 weeks in the MOCLO, AMI and placebo groups was 0.58 [1.40], 1.14 [1.05] and 0.38 [1.42] (Fig. 2). A statistically significant improvement took place in all treatment groups (RANOVA), but in pairwise comparisons the difference in CIC was statistically significant in favour of AMI; between AMI and MOCLO (P = 0.046) and between AMI and placebo (P = 0.003), while the difference between MOCLO and placebo was not statistically significant. The beneficial effect of AMI was already discernible at 2 weeks (Fig. 2).

The physician’s clinical impression of the severity (CIS) of FM and the number of tender points decreased during the study in all treatment groups

<table>
<thead>
<tr>
<th>Table II</th>
<th>Visual analogue scales of patients’ symptoms and findings at baseline and at end (mean [s.d.])</th>
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<tbody>
<tr>
<td></td>
<td>Baseline</td>
</tr>
<tr>
<td></td>
<td>MOCLO</td>
</tr>
<tr>
<td>GH</td>
<td>6.2 [1.8]</td>
</tr>
<tr>
<td>Pain</td>
<td>5.7 [2.1]</td>
</tr>
<tr>
<td>Fatigue</td>
<td>5.3 [2.3]</td>
</tr>
<tr>
<td>No TP</td>
<td>15.9 [2.2]</td>
</tr>
<tr>
<td>CIS</td>
<td>3.95 [0.72]</td>
</tr>
</tbody>
</table>

MOCLO, moclobemide; AMI, amitriptyline; GH, general health; TP, tender point; CIS, physician’s Clinical Impression of Severity.

In within-group comparisons: *P < 0.05; **P < 0.01; ***P < 0.001.

<table>
<thead>
<tr>
<th>Table III</th>
<th>Changes in self-assessed dimensions in quality of life (Nottingham Health Profile) and in Sheehan’s functional disability (mean [s.d.]) during the treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>MOCLO</td>
</tr>
<tr>
<td>Nottingham Health Profile dimensions</td>
<td></td>
</tr>
<tr>
<td>Energy</td>
<td>43.5 [37.1]</td>
</tr>
<tr>
<td>Pain</td>
<td>57.8 [28.7]</td>
</tr>
<tr>
<td>Sleep</td>
<td>36.6 [29.8]</td>
</tr>
<tr>
<td>Social</td>
<td>2.6 [8.7]</td>
</tr>
<tr>
<td>Sheehan’s functional scale areas</td>
<td></td>
</tr>
<tr>
<td>Social</td>
<td>4.9 [2.0]</td>
</tr>
</tbody>
</table>

MOCLO, moclobemide; AMI, amitriptyline.
In within-group comparisons: *P < 0.05; **P < 0.01; ***P < 0.001.
Changes in symptoms, quality of life and functional disability

The changes and descriptive statistics of the symptoms on VAS, the six dimensions of NHP and the three areas of Sheehan’s disability scales at baseline and at the end of the follow-up are demonstrated in Tables II and III.

According to overall RANOVA, a statistically highly significant improvement occurred in GH perception, pain, quality and quantity of sleep, and fatigue (Table II). At the end, the sleep index of the AMI group was statistically significantly lower than that of the other treatment groups (P < 0.01). In within-group comparisons, statistically significant improvements took place in all VAS of the patients in the AMI arm, while the improvements in the GH and pain, or GH, sleep and fatigue scales of the patients on MOCLO or placebo, respectively, were statistically significant (Table II).

Beneficial changes also occurred in all dimensions of NHP with all treatments, except in mobility and in social life (Table III). The sleep and energy indices especially were improved more by AMI than by the two other treatments. In within-group comparisons, AMI improved sleep, energy, pain and emotion dimensions statistically significantly. On the other hand, only pain or sleep dimensions reached statistically significant improvements in MOCLO or placebo groups, respectively (Table III).

AMI also improved most the changes in the dimensions of Sheehan’s disability index as shown in Table III. In within-group comparisons, the improvements of all dimensions were statistically significant only in the AMI treatment group, although MOCLO also improved the areas of social life and family relationships (Table III).

Adverse events

The percentage of patients with at least one adverse event was 77, 74 and 80 in the MOCLO, AMI and placebo treatment groups, respectively. The corresponding figures of those adverse events, whose causal relation with the drug used by the attending physician was judged as possible or probable, were 58, 43 and 53%. The differences were not statistically significant. The majority of discontinuations took place during the first month of the trial (Fig. 1). The discontinuations due to adverse events did not differ statistically significantly between the treatment arms (Fig. 1).

The most typical adverse events with at least a possible causal relationship to medication were headache and difficulties in falling asleep with MOCLO, dry mouth and fatigue with AMI, and fatigue and headache with placebo-treated patients. Four adverse events were judged as serious. Three of them were pre-scheduled operations. Additionally, one woman using AMI was hospitalized for 2 days due to a vasovagal collapse. She had had similar attacks earlier, but the causal relationship was judged to be possible and the treatment was discontinued. All adverse events were reversible.

The respective mean [s.d.] CGI of tolerabilities (1 = very poor; 4 = very good) in the MOCLO, AMI and placebo groups were 2.72 [1.10], 2.90 [1.05] and 2.64 [1.07] (not significant).

Compliance with study medication and use of additional escape medication

Compliance (the difference between the capsules the patients should have taken and those returned) with the study protocol was excellent: 98, 97 and 97% in the MOCLO, AMI and placebo groups, respectively. On the other hand, the mean daily consumption of paracetamol was statistically significantly greater in the placebo group than in the two other groups (P = 0.012). The average (s.d.) number of 500 mg paracetamol tablets/patient consumed during the 84 day study period was 52.6 (62.0) in MOCLO, 40.0 (33.6) in AMI and 73.1 (53.8) in the placebo group.

DISCUSSION

To our knowledge, this is the first randomized clinical trial assessing the efficacy and tolerability of a selective and reversible MAO A inhibitor, MOCLO, in the treatment of FM.

We were unable to prove that MOCLO 450–600 mg/day is helpful in the management of FM patients. When regarding that MOCLO elevates the concentrations of serotonin, noradrenaline, dopamine and adrenaline, and decreases their metabolites in the brain [27], and that the central nervous system of FM patients appears to suffer from a deficit of these monoamines [18], the result was unexpected.

The trend in the principal outcomes of the patients on MOCLO, however, was more favourable than that of the cases treated with placebo, although the differences did not reach statistical significance.

However, when considering the individual outcomes, the patients on MOCLO improved statistically significantly with respect to pain during the treatment period. Also, the statistically significant less use of escape paracetamol by the patients on both active drug arms than by the cases in the placebo group supports the view that MOCLO is also effective in pain modulation in FM. The improvement in GH VAS of the MOCLO-treated patients most probably is also a reflection of pain reduction.

It is also of interest that the specific serotonin re-uptake inhibitors fluoxetine [24] and citalopram [25] have been proven to be failures in the treatment of FM, although Goldenberg et al. [26] obtained a positive result with fluoxetine in a cross-over study of 19 FM patients. Further, in the latter study, the combination of fluoxetine with AMI was even more beneficial than the drugs individually. The result is confusing when considering that fluoxetine has been shown to be ineffective in diabetic neuropathic pain [35], in contrast to tricyclic antidepressants [35] and even other serotonin
re-uptake inhibitors, citalopram [36] and paroxetine [37].

The conflicting results may be explained by the patient selection. The pathogenesis and chronicity of FM, as it is diagnosed today [3], most probably relate to various causes [2]. Further, the patients may include individuals with different pain processing mechanisms, as shown by Sörensen et al. [38] in their placebo-controlled cross-over study with morphine, ketamine and lidocaine. Moreover, we know little about the distribution of serotonin, the density and distribution of different types of serotonin receptors [39], as well as the affinity of the transmitter for different types of receptors within the central nervous system, which all influence the effects of individual drugs. In fact, Hrycaj et al. [40] recently reported in a placebo-controlled study that a proportion of FM patients also respond to a specific serotonin receptor type-3 antagonist, ondansetron. Further, depressive features are common in FM and the interaction of antidepressants on a patients’ psychic profile cannot be overruled when considering the conflicting results of various drug studies. Additionally, to our knowledge, no drug trial so far has addressed the effects of the drugs on other plausible mechanisms for pain modulation, such as the elevated levels of substance P in cerebrospinal fluid [41–43], metabolism of other neurotransmitters or disturbances in hypothalamic–pituitary axis functions [11–16].

Both AMI and MOCLO were well tolerated in the doses used in the present study, as shown in the comparable physicians’ global clinical impressions in tolerability with placebo as well as in the paucity of drop-outs due to adverse reactions. The most typical adverse reactions were predictable. Although MOCLO was dosed early during the day, difficulty in falling asleep was a major adverse reaction to the drug. In accordance with the finding, MOCLO also managed poorly with respect to sleep quality and quantity. In fact, the alpha wave intrusion pattern during the non-REM deep-sleep phase has been proposed as a pathogenetic factor contributing to FM [44], although treatments with cyclobenzaprine [45] or AMI [21] did not have any effect on this pattern in formally conducted drug trials. Nevertheless, we suggest that sleeping problems contributed to the modest improvements in fatigue VAS and NHP energy dimension in the patients on MOCLO. Therefore, we suggest that the beneficial effects of MOCLO on pain were invalidated by its negative effects on sleep quality and quantity in this study.

AMI has a wide range of pharmacological actions, including inhibition of serotonin and norepinephrine re-uptake, blockade of alpha-adrenergic receptors, and antagonism of muscarine, cholinergic and histaminic receptors. Its sedative and anticholinergic actions appear almost immediately, while the effects on pain and sleep modification are variable and delayed [23]. In accordance with earlier studies [20, 21], in our study AMI had an especially beneficial effect on sleep and consequently on fatigue, which was also mirrored in an increased energy level in patients on AMI. The present study also confirmed that AMI treatment in small doses not only decreases the symptoms, but also improves the quality of life as well as perceived disability in patients suffering from FM. Further, the benefits of AMI appeared early, and remained and even increased throughout the 3 month study period. However, one should remember that the long-term benefits of tricyclic antidepressants in FM remain to be shown.

Further, AMI was shown to be superior to the selective, reversible MAO A inhibitor, MOCLO, in our patients free from major psychiatric disorders. It is of practical interest, however, that MOCLO also imposed beneficial effects on pain. Since patients suffering from clinically significant psychiatric disorders were excluded from the present study, the usefulness of MOCLO in depressive FM patients deserves to be addressed further in controlled studies.

According to the present criteria [3], the palpation of tender points is the cornerstone of clinical FM diagnosis. Although the number of tender points in the present study decreased statistically highly significantly in all treatment arms, the changes were of little clinical value. The finding is in accordance with earlier drug trial reports, which found neither any correlation between the number of tender points and myalgic score nor decreased pain [19, 21, 26]. Very recently, a group from The Netherlands also reported no correlation between the mean tender point score and self-reported pain in FM [46]. On the other hand, the tender point count both in FM [4] and in rheumatoid arthritis [47] has been reported to correlate with general distress of the patients. Therefore, the existing evidence supports the view that tender points and self-reported pain may represent different aspects of pain response in FM [46]. Further, the number of palpable tender points cannot be used as a measure of FM severity or a response criterion in clinical trials.

The present study confirmed that even the best available symptomatic drugs in FM, the small-dose tricyclic antidepressants, only modestly improve the symptoms, functional capacity and quality of life of non-depressed FM patients. MOCLO also decreased pain, but its effects were invalidated by its negative effects on sleep quality. When taken together, MOCLO may be useful in patients suffering from chronic pain, but not in FM where sleeping problems occupy a very central position. Since both peripheral and central abnormalities have been suggested to be involved in the pathogenesis of FM, the mechanisms of the beneficial effects of AMI as well as MOCLO remain to be elucidated. However, when adding that chlormethazone, a peripherally acting muscle relaxant, was proved to be ineffective in the treatment of FM [48], the findings of the majority of studies support the importance of central rather than peripheral mechanisms behind these actions.

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