Treatment of Fibromyalgia

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Management of the Fibromyalgia Syndrome

Diagnosing fibromyalgia is one thing; treating it is a completely different issue. Until now there has not been one adequate therapy or strategy, and therefore it is better to speak of managing of the fibromyalgia syndrome. The number of studies involving evaluation of treatment regimens are by far outnumbered by the articles considering other aspects of the syndrome. Buckelew (1) summarized the rehabilitation approach of the fibromyalgia syndrome. She made a strong plea for long-term effective intervention programs which would require a multidisciplinary rehabilitation team approach. Felson in 1989 (2) put forward important suggestions regarding treatment regimens and evaluation of these regimens. Clinical trials, randomized, controlled or uncontrolled, try to give an answer to the question whether a certain treatment is effective and secondly if this treatment is well tolerated. Future clinical trials in fibromyalgia should also answer the question why do treatments work. An example to underline this is "are the patients who improve in amitriptyline trials those whose sleep study improve?" Maybe these investigations can reveal why these therapies work and how this relates to the pathogenesis of this syndrome. Another strong recommendation is that widely used criteria for clinical improvement are needed. In treatment trials subgroups of patients can be identified which improve and therapies can be compared. Furthermore the long term efficacy and tolerability of therapies should be studied. In 1991 Simms, together with Felson and Goldenberg (3), reported on the development of preliminary criteria for response to treatment in fibromyalgia. They analyzed the outcome measures of an earlier published study (randomized controlled trial of amitriptyline and naproxen) using stepwise logistic regression analysis. They stated that clinically important improvement was until then not uniformly defined. They identified clinical assessment variables that predicted whether patients received either effective treatment or placebo. These variables were physician global assessment, patient sleep assessment and tender point score. A limitation of their study, pointed out by the authors, is that they did not include psychological outcome measures and functional assessments.

Goldenberg (4) provided an overview of treatment approaches in fibromyalgia. He formulated important methodological issues that should be met in clinical trials concerning the fibromyalgia syndrome. The study design should be with a random assignment, with comparable intervention and control groups, with an adequate number of patients, including drop-outs, patients should meet the ACR criteria, and patient and observer should be blinded. Furthermore there should be standardized measures of disease activity, like symptoms such as pain, sleep and mood, a psychological evaluation, tender point scores and an evaluation of function.

In this chapter several treatment-regimens and therapies described in the literature, will be discussed. Unfortunately not all study-designs fulfil the criteria mentioned
Chapter 13

above. Different therapies aim at different outcomes and use different outcome variables. To bring some order in the review of these articles, the studies are divided in those that are targeted on 1) pain relief, 2) on improvement of sleep and fatiguability and 3) those that are aimed to bring about a change in behavior and/or mood symptoms.

An overlap in these three treatment targets is present in many studies.

Studies targeted on pain relief

Drugtrials

Pain is the major symptom in fibromyalgia. Morning stiffness is also often mentioned by fibromyalgia patients. Logically one tried the efficacy of the anti-inflammatory drugs, often useful in the classical rheumatic diseases. Non-steroidal anti-inflammatory drugs (NSAID) are commonly used, and have been anecdotally described to be beneficial in the fibromyalgia syndrome.

As we now know fibromyalgia is not an inflammatory condition, but NSAID's might work through their analgesic effects (5). These effects are thought to be mediated through peripheral mechanisms, including a diminution in the sensitivity of peripheral nerve receptors due to decreased peripheral prostaglandin synthesis. Yunus' study (5) was well designed, and he described the results of a short term (6 weeks) double blind, placebo controlled trial of ibuprofen in fibromyalgia syndrome. Study variables were a tender point examination and self-assessed symptoms regarding pain, fatigue, sleep, depression, anxiety and stress. No significant differences were found between the ibuprofen and placebo group, and tender points significantly improved over time in both groups. Improvement in fibromyalgia features might have occurred as a result of physician or study interactions. Yunus concluded that his results showed that NSAID have no beneficial effects in fibromyalgia, and that the pain in fibromyalgia is probably central in origin. Although the study length was short, it is not very likely that a positive effect would be reached after a longer study duration.

A double blind comparison of ibuprofen, placebo and ibuprofen with meptazinol was performed by Le Gallez et al. (6) in patients with soft tissue rheumatism. Musculoskeletal rheumatism was defined as a periarticular condition or non-specific seronegative musculoskeletal condition requiring treatment with a non-steroidal anti-inflammatory agent. Meptazinol is a centrally-acting analgesic with opiate antagonistic properties, and experimentally it has been shown that the co-administration of ibuprofen with meptazinol potentiated and prolonged the analgesic effect of meptazinol in both inflamed and non-inflamed animal models. Study design was a randomized, double blind three-way crossover study of placebo, ibuprofen and ibuprofen plus meptazinol. Study length was again short, 7 weeks. Outcome variables
were pain parameters using visual analogue or verbal rating scales. Patients' overall impression and final preference showed both active treatments to be better than placebo and demonstrated a slight preference for the combination. Although in this study no mention is made of fibromyalgia, it probably is the same group of patients we know as fibromyalgia patients. These results are contradictory with those of Yunus (see above).

Russell et al. in 1991 (7) studied the effect of ibuprofen as well, in combination with alprazolam in patients with fibromyalgia. It was a randomized, double-blind, double-dummy, placebo-controlled pilot study. Alprazolam is a triazolobenzodiazepine and is used in the treatment of anxiety and/or depression with anxiety. Outcome measures were tender point examination, patient and physician assessment using Visual Analog Scales (VAS) scores, and Health Assessment Questionnaire (HAQ) was used as a measured of functional status. Furthermore a few psychometric test were used. The authors found no significant relationship between clinical measures of physical discomfort and psychological measures. This observation should be evidence against the notion that the pain in fibromyalgia has a psychological etiology. Clinical improvement in patient rating of disease severity and in the severity of tenderness upon palpation was most apparent in the subgroup of patients who were receiving both ibuprofen and alprazolam. Study length was short, 8 weeks, and the placebo effect was substantial. Analyses of variance did not reveal a significant difference in the mean change in outcome variables between the double-placebo and the other treatment groups. These results also indicate that the effect of NSAID's in fibromyalgia is very limited.

Ibuprofen was studied in combination with cyclobenzaprine in fibromyalgia (8) in an open randomized study. Cyclobenzaprine is a muscle relaxant. The authors thought there might be a synergistic effect between the two drugs in fibromyalgia patients, therefor they compared ibuprofen with cyclobenzaprine and cyclobenzaprine alone. Outcome-scores were number of tender points, muscle tightness, sleep difficulty, pain intensity and duration of morning stiffness. In both treatment groups the outcome scores had improved to the same extent and no significant differences were observed. Morning stiffness however was significantly more reduced in the patients taking the combination medication. Study length was very short, 10 days. As we know from other studies the placebo-effect could be significant, and therefore the results of this study should be reevaluated in a controlled study.

Goldenberg et al. (9) performed a randomized, double-blind, placebo-controlled trial of amitriptyline and naproxen in patients with fibromyalgia. At the time of the study both naproxen and amitriptyline were described to be effective in fibromyalgia, but these reports were mainly anecdotal and uncontrolled. In this (short, 6 weeks) study of Goldenberg amitriptyline was associated with significant improvement in all outcome parameters, including patient and physician global assessments, patient pain, sleep difficulties, fatigue on awakening, and tender point score. Patients on naproxen
showed no significant effect on any outcome parameter. Patients taking the combined naproxen-amitriptyline regimen experienced minor, but not significant, improvement in pain when compared with patients who took amitriptyline alone. Amitriptyline could have a positive effect on pain by a central analgesic effect by blocking the removal of serotonin from synaptic clefts, or by the effect of amitriptyline on endogenous opioids, like endorphins or enkephalins.

In retrospect the outcomes of the different studies mentioned above question the relevance of NSAID's in fibromyalgia. But why are these medications prescribed so often by the physicians of these patients? Is it that the doctor has to do something to satisfy the patient, and is a possible positive effect only based on the placebo-effect of the (NSAID) medication?

In the last studies mentioned above NSAID's are compared with drugs acting on the central nervous system, like the tricyclic agents.

Bennett et al. (10) studied the efficacy of cyclobenzaprine, as compared with placebo in a double-blind, controlled trial of fibromyalgia patients. Cyclobenzaprine is a tricyclic agent with a chemical structure similar to that of amitriptyline, but its antidepressant effects are said to be minimal. It is used as a muscle relaxant for acute musculoskeletal disorders. Its muscle relaxant properties emanate from its ability to modulate muscle tension at a supraspinal level by reducing motoneurone efferent activity. What the authors expected to change with the therapy does not become quite clear. Patients taking cyclobenzaprine experienced a significant decrease in the severity of pain and a significant increase in the quality of sleep. There was a trend toward improvement in the symptoms of fatigue, but morning stiffness was not alleviated. These improvements in symptoms were associated with a significant reduction in the total number of tender points and in muscle tightness. Study length was 3 months. A critical note can be made on the blinded state of this study; over 50% of the cyclobenzaprine group experienced a dry mouth and/or drowsiness. So it is very well possible that these patient knew they were taking the active drug and not the placebo. The physicians also had this knowledge, because they recorded the adverse reactions.

Cyclobenzaprine was also studied by Quimby et al. (11) in a randomized, double blind, placebo controlled trial. Regarding the literature the authors postulate three hypotheses about the nature of fibromyalgia, which could explain the mode of action of these tricyclics drugs. Tricyclics may relieve fibromyalgia symptoms by prolonging non-Rapid Eye Movement (nREM) sleep (sleep disorder hypothesis), the central nervous system (CNS) pain regulation abnormality hypothesis indicates that it is the effect of tricyclics on serotonin metabolism which is important, the third (peripheral) hypothesis, the muscle spasm and local hypoxia hypothesis, suggests that cyclobenzaprine could alleviate fibromyalgia symptoms by breaking the pain-spasm-pain cycle and allowing muscles to function more normally. Cyclobenzaprine has been found to
Chapter 13

Act in the brain stem as a muscle relaxant reducing tonic motor activity. Outcome measures included daily pain diaries and patient ratings, improvement in musculoskeletal stiffness and aching, muscle pain, fatigue, poor sleep and overall improvement. Physicians also rated overall improvement. Study length was 6 weeks. The outcome measures indicated that cyclobenzaprine is effective in alleviating the symptoms of fibromyalgia in a subgroup of patients. However most patients with fibromyalgia in this study had a more accurate awareness of drug effects on their own bodies than had been expected, rendering the double blind procedure ineffective, as was recognized by the authors. In both studies (10,11) the improvement could be explained by a placebo-effect.

In 1991 a study was published by Jaeschke et al. (12), in which the results of 23 N-of-1 randomized controlled trials were reviewed concerning the clinical usefulness of amitriptyline in fibromyalgia. In this study 23 double blind, randomized, multiple crossover trials of amitriptyline were conducted in fibromyalgia patients. The participating patients had shown an improvement in an open trial of amitriptyline. The authors state that the use of amitriptyline, which has serotonergic and anticholinergic properties, is based on the hypothesis that the low pain threshold and distorted sleep pattern found in fibromyalgia may be related to the low brain serotonin. Because not all patients with fibromyalgia benefit from the use of amitriptyline, the authors tried to find a way to determine its benefit for a particular patient, for which they used the N-of-1 randomized controlled trials. After several trials it became clear to the authors that the drug benefit, if present, was evident after a short period of treatment (2 weeks). Outcome variables were tender point count and a symptom questionnaire score. The doses that were used differed, and analyzing the doses of amitriptyline used in the trials which confirmed the efficacy of the treatment, it became evident that amitriptyline can be effective in doses that might have been considered homeopathic (5 mg).

Carette and co-authors (13) reported on a 9-week double-blind trial comparing amitriptyline with placebo. The choice of amitriptyline was explained because of the serotonergic and anticholinergic activities and because in low doses it has predominantly hypnotic properties, causing REM suppression and prolongation of stage 3 and 4 nREM sleep. The patients who received amitriptyline improved significantly in their morning stiffness and pain analog scores, whereas no changes were noted in these parameters in the placebo group. Total myalgic score did not improve significantly in either group. When compared with the placebo group, the amitriptyline group improved significantly with respect to sleep pattern and patient and physician global assessments. Side-effects, however, were mentioned in 70% of the amitriptyline group.

Improvements in pain responsiveness (at local tender points and generalized sensitivity to pain at non-tender points) and assessment of well being in patients with fibromyalgia was reported by Scudds et al. (14) after treatment with amitriptyline in a
randomized, placebo controlled, double blind crossover study. This study lasted for 10 weeks. The authors tried to replicate the results of Carette et al. (13). No statement is made on number of patients that experienced side effects of the drug.

In 1994 Carette (15) and coworkers compared amitriptyline, cyclobenzaprine and placebo in a randomized, double blind, placebo-controlled clinical trial. Next to the comparison of the relative efficacy and tolerability of the different drugs and placebo they tried to identify predictors of response to cyclobenzaprine and amitriptyline. The results showed a short term efficacy (after 1 month) of amitriptyline and of cyclobenzaprine in a small percentage of the patients. Evaluation after 6 months (long term efficacy) showed no significant differences in the three groups. The placebo response after 6 months was higher than expected. The authors were not able to determine predictors of response to cyclobenzaprine or amitriptyline. Using dolorimetry scores as an outcome measure showed no significant changes in myalgic scores over baseline values at any of the monthly other assessments. At this point they question the usefulness of these scores as an outcome measure in trials of patients with fibromyalgia. They also suggest that the tricyclic agents might be slightly more effective in improving sleep than in reducing pain.

Vaeroy et al. (16) performed a placebo controlled, double blind trial with carisoprodol, paracetamol and caffeine (Somadril comp®). Active treatment gave statistically significant improvement after treatment for pain, for sleep quality and for the general feeling of sickness. However, also in the placebo group improvement was found for the pain and sleep quality. A methodological error in this study is the wide use of other drugs in the placebo group, which makes it impossible to compare these two groups. Another critical remark is the choice of a combination of three different drugs, where the efficacy of either one alone is as yet not established. Carisoprodol is chemically related to mephenesin and meprobamate, and it is not only a muscle relaxant but also an analgesic. Furthermore it is said that carisoprodol has a depressant action on the reticular formation, but does not produce behavioral changes, in contrast to the effects of barbiturates and other hypnotics. It is suggested that the analgesic action of carisoprodol affects the central nervous centres concerned with pain perception. The consumption of paracetamol is relatively high among patients with fibromyalgia, but the efficacy of paracetamol containing drugs in these patients still remains an open question. Caffeine is believed to potentiate the effects of prostaglandin synthesis inhibitors and also to inhibit histamine release from mastcells. Based on the hypothesis that fibromyalgia might have both a peripheral and a central pain component, and on the fact that sleep disturbances may be involved in the pathogenesis of the syndrome, they designed this study as a parallel double-blind trial testing the combination of drugs mentioned earlier, versus placebo. However, because of this insufficient study design, no conclusions can be drawn.

An anecdotal report on lithium carbonate augmentation therapy in fibromyalgia is written by Tyber (17). The author stated that lithium may augment the antidepressant
effect of tricyclic antidepressants (TCA) in treating depressions in psychiatry, and that the combination of amitriptyline and lithium has been effective in treating the painful shoulder hand syndrome, so the clinical features common to fibromyalgia suggest that lithium is a useful adjunct therapy to TCA therapy for fibromyalgia. This theory should be tested in a randomized, placebo-controlled, double blind study.

Clark et al. (18) presented the results of a double blind crossover trial of prednisone versus placebo in the treatment of fibromyalgia. Their choice for a corticosteroid drug is explained by the possibility that fibromyalgia may represent the prodromal phase of one of the classical connective tissue diseases like RA or SLE. Each patient was randomly assigned to either prednisone 15 mg/day or placebo for 14 days of therapy and then therapy was switched for a further 14 days. Study length was 4 weeks. The assessments made included analogue scores for pain, sleep disturbance, morning stiffness and fatiguability, and dolorimetry readings of pain tolerance over 14 representative tender points. Overall there was no improvement while taking prednisone, in fact most measured variables showed a trend towards deterioration with this therapy.

A number of studies are performed with S-adenosylmethionine (SAM) (19-23). One of the first of these studies was by Tavoni (19). This was a report on a double blind, placebo-controlled, crossover study in 25 fibromyalgia patients with intramuscular administration of SAM. Seventeen patients completed the study; 6 withdrew for unexplained reasons and 2 developed an abscess at the site of the intramuscular injection. The choice for SAM is explained by the known anti-depressant properties of this drug. SAM is a methyl donor in many important methylation reactions in the brain. Study length was 8 weeks. Outcome variables were number of painful areas and tender points, assessment of depressive state (Hamilton Depression Rating Scale). The authors do not take clearly take a stand at what they wanted to achieve with SAM treatment. Their results showed that the number of tender points and tender areas decreased and that the score of the Hamilton Depression Rating Scale improved with SAM treatment, where these variables did not significantly change after placebo treatment. Furthermore the authors describe a good correlation between number of tender points and depressive state (assessed with Hamilton Depression Rating Scale). These results are promising, but only a small number of patients participated in this study and study length was relatively short.

Oral SAM as treatment in 44 fibromyalgia patients was studied in a double blind clinical evaluation by Jacobsen et al. (20). Five patients dropped out because of side-effects (4 during active treatment, 1 during placebo treatment). According to the authors this drug has, next to anti-depressant effects, also anti-inflammatory and analgesic effects. Study length was 6 weeks, which is very short. Improvements were seen for clinical disease activity (VAS for subjective quantification of pain at rest, pain at movement, quality of sleep and overall well-being), pain experienced during the last week, fatigue, morning stiffness and mood evaluated by Face Scale. The
tender point score, isokinetic muscle strength, mood evaluated by Beck Depression Inventory and side effects did not differ between the treated and control group. These results are different from those of Tavoni et al., where a significant improvement was seen in the depressive state. These studies did not use the same assessments of depression, and therefore a reliable comparison cannot be made. SAM was also studied by Di Benedetto (21). He compared SAM with transcutaneous electrical nerve stimulation (TENS). Both groups consisted of 15 patients. It was a 6-week controlled trial. No mention is made of drop-outs in this study. In the TENS-group there were five sessions a week in which four tender points were treated. Clinical evaluations included manual and instrumental assessment of tender points, assessment of anxiety and depression using psychological rating scales (Hamilton and Zung), evaluation of subjective parameters using visual analogue scales of pain, sleep, fatigue and well-being, and laboratory tests. In conclusion SAM significantly decreased the total number of tender points, unlike TENS, had a significant beneficial effect on the subjective symptoms of pain and fatigue and significantly reduced the scores on the psychological rating scales (anxiety and depression). In the TENS group there was only at the end of the treatment significantly reduced scores on an used anxiety scale (Hamilton Anxiety Scale). The authors ascribe this effect of TENS to the placebo-effect (increased attention given to the patients). This study was not performed in blinded manner, which is very difficult to do in TENS-treatment regimens. SAM was subject of further study by another Italian group (22). They studied the effect of an intramuscular injection of SAM in Sjögren's syndrome and fibromyalgia. Study population consisted of 10 patients with Sjögren's syndrome, 10 patients with fibromyalgia and 10 patients with both syndromes (no dropouts). Clinical and psychologic evaluations took place at baseline and after 4 weeks. The group with only the fibromyalgia symptoms had the best results. After treatment they had a lower number of tender points and painful areas, and decreased scores on the depression scales used. In the group with both of the syndromes, the number of tender points and number of painful areas were reduced as well. In the Sjögren group there was no improvement in symptoms. The number of patients in each group was small and this study was not placebo-controlled; the improvements could be based on the placebo-effect. The investigator was not blinded to the diagnosis of the patients. Again another study was published from Italy (23). They treated a group of 47 fibromyalgia patients with SAM for 6 weeks (intramuscular and orally) and found significantly decreased tenderness at painful sites and significantly improved general well being compared with the baseline, and reduction of scores on several psychological inventories (scales). In their patient group no adverse side effects were reported. Furthermore they noted that SAM is known as an antidepressive agent, with no anticholinergic activity. This in contrast with tricyclics drugs, where anticholinergic side effects are often a limitation in usefulness. This study was performed without a control group and had no blinded design. Therefore the findings of this particular study
are not very reliable and conclusions can not be drawn. In a study Bengtsson (24) showed that a complete sympathetic blockade by a stellate ganglion blockade with a local anaesthetic markedly reduced the number of tender points and also produced a marked decrease in resting pain. An intravenous regional sympathetic blockade with guanethidine reduced the number of tender points in the neck, shoulder and arm, but had no effect on resting pain. The authors hypothesized that the sympathetic blockade brings about an improvement in microcirculation followed by reduction in pain and tender points, which would imply that sympathetic activity may play a role in the pathogenesis of fibromyalgia. The authors tried to perform this study in a controlled and a double-blind fashion, which is very difficult to achieve with this kind of treatment, and that could not be accomplished. Only 8 patients had the real blockade (stellate ganglion and regional sympathetic), which is a small number. Because pain and tender points are widespread existent in most patients with fibromyalgia this treatment modality can not be used in daily practice. A year later Bengtsson et al. (25) published on epidural opioid blockade, at rest and during exercise in 9 fibromyalgia patients. The authors hypothesized that the pain is nociceptive and due to muscular changes. Although this study was not primarily conducted to examine treatment of fibromyalgia, they found that resting pain and tender points diminished significantly after the opioid injection. A local anaesthetic epidural blockade (with lignocaine) abolished pain at rest and tender points. These findings were, according to the authors, evidence for the peripheral (nociceptive) or spinal origin of the pain in fibromyalgia. No pain relief would have pointed to more central, supraspinal causes. This, again, was an uncontrolled and unblinded study. In 1994 a study on the effect of an antidiencephalon immune serum on pain and sleep in patients with fibromyalgia was published (26). This study comprised a double-blind, randomized, therapeutical trial of 36 female ambulatory fibromyalgia patients, and lasted 8 weeks. Patients received either the immune serum, or amitriptyline or a placebo. Three assessments were made, at the start of the treatment, at 4 weeks and at the end, at 8 weeks. Study variables were clinical parameters, like a tender point count, subjective pain scores and associated symptoms (sleep disturbance, fatigue, finger swelling etc), and sleep EEG polygraphic data. Also mood ratings and VAS scores on sleep quality, morning restfulness and fatigue were obtained. The immune serum is said to belong to the group of heterologous polyspecific polyclonal antibodies and these are shown to improve some psychosomatic disorders. They are supposed to act as functional immunomodulators at the level of the organ or tissue. Drop-out ratio in this study was over 35%, and a large placebo response was seen. This meant that in the three groups just 6 or 7 patients were left for further analysis. For future studies they suggest to include also a non-treated group with minimal health care contacts to eliminate the placebo response as best as possible. A global subjective improvement was seen in the immune serum group, and also most prominent changes in stage-4 sleep and fatigue scores. No improvement in pain scores was observed in this group.
The placebo response in this study was substantial. Next we will describe two studies that used homeopathic treatment. Fisher et al. (27) stated that the homeopathic medicine Rhus toxicodendron 6c (a 10-14 dilution of poison oak leaves in ethanol) was effective for a selected subgroup of patients with fibromyalgia. The authors do not tell how to select possible positive responders. The trial was double blind, placebo controlled, and of crossover design and included 30 patients. Study length was 2 months. Assessments comprised the number of tender points, VAS of pain and sleep, and overall assessment. Comparison was made between values at the end of active and placebo treatment periods. The authors described that the patients did better in all variables when they took active treatment rather than placebo. No side-effects are reported and we have to assume that the patients could not tell if they got active treatment or placebo.

Jacobs et al. (28) performed a double blind, placebo-controlled modified cross over examination with injections with rheumajecta and vasolastine in 30 patients with fibromyalgia. Rheumajecta and vasolastine are complementary, homeopathic substances which are used occasionally in the Netherlands in all kinds of rheumatic conditions, but its usefulness has not been established. The effect of rheumajecta and vasolastine was compared with that of a placebo over two periods of three months. Assessments made included tender point examination, use of analgetics and NSAID's, subscales "pain" and "health" of a Dutch, validated version of the Arthritis Impact Measurement Scale (AIMS), and furthermore an extended version of the (translated) Campbell Questionnaire, number of drop-outs in relation to lack of result between the placebo and homeopathic treatment, and patient assessment. The authors did not find significant differences in effectiveness between rheumajecta and vasolastine and the placebo treatment. There were no serious side effects seen in the patients who used the rheumajecta and the vasolastine. This means there is no rationale for the use of these substances in fibromyalgia; the choice for a placebo is cheaper and just as effective.

In 1995 Russell et al. (29) reported on the effects of Super Malic® on different pain scores in 24 fibromyalgia patients in a randomized, double blind, placebo controlled, crossover pilot study. This study lasted 10 weeks. Super Malic® is a proprietary tablet containing malic acid and magnesium. Malic acid is a naturally occurring, nontoxic, organic dicarboxylic acid. The choice for these two substances is explained by the role these two substances play in the processes of generating ATP. Russell suggests there is a muscle energy metabolism problem, but as we know from other studies (see chapter 2) that is questionable. However, no treatment effect was seen in this blinded, placebo controlled study. In an open label trial with higher doses and longer duration the authors did find improvements in pain scores, but this should be replicated in a blinded, placebo controlled study as well.

Non-drugtrials
It is rather stunning that there are so little controlled studies published, or perhaps even undertaken, on the effects of physiotherapy (physical therapy), one of the most used therapy-forms in fibromyalgia. Mostly this form of physiotherapy is a passive one, like massage, all kinds of warmth-applications and electrotherapy. An Austrian group of researchers (30) compared two non-medicinal treatment methods, hydrogalvanic baths on the one hand (12 patients) and progressive Jacobson relaxation training on the other hand (13 patients), with regard to the effect on various psychological pain parameters. Both therapies lasted 5 weeks. The authors wanted to assess the subjective pain experience in two different ways: from a psychophysical and a behavior-oriented point of view. Prior to the start of the therapies different pain scales regarding different aspects, accompanying symptoms, correlation with sleep and of pain behavior were filled in by the patients. At the end of the therapies this procedure was repeated. With factor analysis they found three different factors; pain behavior, consequences of pain and coping behavior. Comparing the two groups, both at the beginning and at the end of the two treatment methods, no significant differences were found. Both groups did better after the treatment. A very weak point of this (pilot) study is that they did not use a control group with no interventions, and that the positive effect could be explained by the attention the patients got during the study period (placebo-effect).

**Studies targeted on sleep symptoms**

Goldenberg et al. (9) in his randomized controlled trial of amitriptyline and naproxen in the treatment of patients with fibromyalgia, see above, found a significant improvement in the amitriptyline group in all outcome parameters, including patient and physician global assessments, patient pain, sleep difficulties, fatigue on awakening, and tender point score. Goldenberg hypothesized that the effect of amitriptyline in fibromyalgia patients could be related to the effect on the sleep disturbances, but their results showed that there were more positive effects in outcome variables than sleep alone (see above).

Wysenbeek (31) presented his results of a therapeutic trial of imipramine in 20 fibromyalgia patients. Imipramine is a tricyclic drug and it is said that these psychotropic drugs are known to facilitate nREM deep sleep pattern and thus were suggested beneficial for treatment of fibromyalgia. Of 20 patients only 2 patients responded favourably. This study was not carried out in a randomized, placebo-controlled, double-blind way. Study length varied from 1 week up to more than 3 months (1 patient). What outcome parameters were used is not clear. This study shows a lack of response of fibromyalgia patients to tricyclic therapy, e.g. imipramine. The study design, however, makes definite conclusions impossible. The effects of cyclobenzaprine on sleep physiology and symptoms in patients with
fibromyalgia were studied by Reynolds et al. (32), in a randomized, double blind placebo controlled crossover study. Study population was small, only 12 patients, and the study lasted 12 weeks. Only 9 patients completed the study. They found that patients receiving cyclobenzaprine showed a decrease in evening fatigue and an increase in total sleep time. Pain, including tender point count and dolorimetry, mood ratings, and α-nREM sleep anomaly were unchanged by cyclobenzaprine. With the exception of a decrease in evening fatigue, the authors were not able to demonstrate an effect of cyclobenzaprine on symptoms in a small number of patients with fibromyalgia. Similarly, with the exception of an increase in total sleep time, they were unable to document any specific effect of cyclobenzaprine on sleep physiology. Because of the small number of patients no definite conclusions can be drawn from this study.

Chlormezanone, an effective muscle relaxant and probably acting via reduction of the τ-efferent discharge to motor fibres of muscle spindles was studied by Pattrick et al. (33). Chlormezanone should also have some benzodiazepine-like effects on sleep physiology, but without reduction in phase IV sleep. The authors conducted a double blind placebo controlled study, which lasted for 6 weeks in 42 fibromyalgia patients. Outcome measures included sleep quality, inactivity and morning stiffness, morning alertness, tender point score, mood change and global opinion of patient and observer. In conclusion the authors could not find a beneficial therapeutic effect after use of chlormezanone. The authors suggest that the lack of results of a peripherally acting relaxant, in this case chlormezanone, supports the importance of more central abnormalities in fibromyalgia. Chlormezanone had no apparent clinical effect on sleep in the fibromyalgia patients that participated in the study.

Zopiclone, a nonbenzodiazepine hypnotic, was studied in the treatment of sleep abnormalities in 45 fibromyalgia patients by Drewes et al. (34). The study design was double blind, placebo controlled and lasted 12 weeks. Four patients dropped out of the study. Reduced δ-sleep and α-contamination in nREM 2-4 have been found in fibromyalgia patients. As δ-sleep is thought to be essential for physiological restoration it has been proposed that various symptoms in fibromyalgia could be considered part of a non-restorative sleep disorder. Zopiclone has been found to induce sleep structure comparable to normal sleep and to increase δ-sleep in some patients, contrary to traditional benzodiazepines which normally reduce δ-sleep. In this study a significant improvement of tiredness during the day and subjective sleep complaints was observed, but no effects on pain or stiffness were recorded. The sleep structure remained unchanged during treatment. There was no increase or reduction of the δ-sleep during zopiclone treatment, and there was no significant change in the intrusion in the deeper sleep stages during treatment. This seems contradictory; the sleep structure did not change but the subjective symptoms of tiredness and sleep complaints showed an improvement. This is not further explained by the authors. In another study the effect of zopiclone was evaluated as well (35). This concerned an
eight week double-blind randomized trial with zopiclone and a placebo in 49 fibromyalgia patients. Sixteen patients dropped out of the study. Parameters used were widespread tenderness and pain, visual analogue scales and pain drawings. Additional outcome measures used were a subjective global sleep score, duration and severity of morning stiffness and subjective improvement (scored by patient and examiner). In the zopiclone group there was an improvement in subjective sleep quality (like in the study of Drewes), but in the placebo group there was similar improvement. Patient-assessment in the zopiclone group was scored higher than in the placebo group. The examiner scored 50% of the patients in both groups, treatment with zopiclone and placebo, higher at 8 weeks. Widespread tenderness, visual analogue scales and pain drawings were not scored differently in the treatment and placebo group. These results show a very limited (positive) effect of zopiclone over placebo treatment.

5-Hydroxy-L-tryptophan was studied in an open study in 50 fibromyalgia patients (36). Thirty percent reported side effects. The study lasted three months. All the clinical variables studied, i.e. number of tender points, anxiety, pain intensity, quality of sleep and fatigue showed a significant improvement compared with the baseline results. Nearly 50% of the patients had a good or fair clinical improvement in the overall evaluation of the patient condition as assessed by the patient and investigator. These results could be due to the placebo-effect, because it was an uncontrolled, non-blinded study. However in an earlier study Caruso et al. found in a double blind study that 5-hydroxy-L-tryptophan was more effective than placebo in the treatment of fibromyalgia. The choice of tryptophan was explained by the supposed insufficient concentration of circulating tryptophan in fibromyalgia, which in turn fails to provide adequate serotonin for the maintenance of slow-wave sleep.

An anecdotal remark in regard to treatment of fibromyalgia came from Geller in a case report treated with fluoxetine hydrochloride (37). The theoretical background of the possible working mechanism is that this drug is known to block re-uptake of serotonin in the brain, and therefore could influence the sleep problems and pain experience in fibromyalgia patients. It took 5 years before a double-blind placebo controlled trial of fluoxetine in fibromyalgia appeared (38). Study length was 6 weeks. Forty-two fibromyalgia patients participated in this study, but only 25 completed the trial. The goals were to improve the clinical status (assessed with tender point count, dolorimetry scores and several VAS scores) in fibromyalgia and to see if an alteration in depressive symptomatology would appear (Beck Depression Scales, AIMS Anxiety and Depression). The authors found no differences between the groups after treatment, and concluded that fluoxetine does not improve signs and symptoms in fibromyalgia. Drop-out ratio was fairly high. The study group was not very depressed at baseline, and this makes it hard to evaluate if fluoxetine could play a role in the treatment of depressed fibromyalgia patients. Fluoxetine is known to be effective in the treatment of depressive patients, in general.
Non Pharmacologic treatment programs, aimed at improvement in pain, sleep and mood

Moldofsky (39) suggested exercise in the form of cardiovascular fitness training as a possible treatment-modality in the fibromyalgia syndrome. This observation was prompted by the great difficulty he had in inducing fibrositic tender points in a marathon runner who, as it happened, was participating in his sleep studies. Tender points could not be induced in this normal subject after experimental induction of intrusions during his usual slow-wave stage IV δ-rhythm sleep. In other normal subjects, florid tender points and a nonrestorative sleep pattern developed. From this observation Moldofsky hypothesized that cardiovascular fitness training might be favourable in patients with the fibromyalgia syndrome. Because formal proof of this hypothesis was lacking McCain et al. (40,41) studied the effect of physical fitness training in the fibromyalgia syndrome. He said that exercise could lead to alterations in opioid and non-opioid as well as neural and hormonal intrinsic pain regulatory systems. Strenuous exercise leads to predictable increases in serum levels of endorphin-like immunoreactivity, ACTH, prolactin, and growth hormone. Such alterations are associated with decreased pain sensitivity, commonly known as "post-run hypalgesia". An additional mechanism why exercise may be beneficial is that exercise improves mental status. According to McCain there are several studies that confirmed this statement. Ratings of self esteem and Beck Depression Inventory scores were significantly improved after cardiovascular fitness training compared with the ratings of the placebo and no-treatment control groups. Exercise may also benefit fibromyalgia patients because of its effects on slow-wave sleep. It appears that exercise results in a delay and decrease of REM sleep, an increase in stage II sleep, and a weak decrease in slow-wave sleep latency. An important remark McCain makes after these theoretical explanations is that strenuous exercise at sustained levels not only induces physiologic changes but may also be responsible for the development of a stress response. McCain suggested stress could play an very important role in the induction or perpetuation of the fibromyalgia syndrome. How this could be studied is not further elucidated. A definition of stress is not given either. In McCain's study 42 patients with fibromyalgia were randomly assigned to enter either a cardiovascular fitness training program or a program consisting only of flexibility exercises. There was not a no-treatment group included. Patients met in supervised groups three times weekly for a 20-week observation period. Thirty-eight patients completed the study. The cardiovascular fitness group underwent gradual heart rate-elevated training using a bicycle ergometer. Patients undergoing flexibility training had no statistically significant net reduction in their peak work capacity (at 170 beats per minute). Patients in the fitness group had statistically significant improvements in total myalgic scores at five selected tender points and patient's and physician's global assessment scores. Psychologic profiles as measured by Symptom Checklist-90R improved
in both groups. The author concluded that cardiovascular fitness training in fibromyalgia patients improves subjective and objective measurements of pain, but only moderately. As noted before, a no-treatment group should have been involved as well.

Mengshoel et al. (42) reported also on the effects of 20 weeks of physical fitness training in 18 female patients with fibromyalgia. There were two training sessions a week. There was a control group as well (17 patients), who were asked not to change their level of physical activity. Patients were assigned at random to the training or control group, with age as a randomization block factor. In order to improve endurance capacity in their fibromyalgia patients Mengshoel developed a modified low impact aerobic dance program. In this study they wanted to evaluate the effects of twenty weeks of endurance training on the variables of pain, fatigue, physical fitness and pain coping. Assessments were at the start of the program and at the end of the program, after 20 weeks. In the training group the intensity was kept at a heart rate level of 120-150 beats per minute. To prevent muscular fatigue frequent changes in the activation of different muscle groups were undertaken. Aerobic fitness, dynamic endurance work of the upper extremities, static endurance work of the upper extremities and dynamic endurance work of the lower extremities were measured following standard procedures. To assess the subjective symptoms pain and fatigue visual analogue scores were used. The Vanderbilt Pain Management Inventory was used to assess pain coping. The study was completed by 11 patients in the training group and 14 in the control group. After twenty weeks of exercise all the patients in the exercise group felt that exercising had increased their feelings of general well-being. Improved dynamic endurance work performance for the upper extremity was found in the training group, not in the control group. No statistical significant changes or differences in general pain, pain coping and fatigue were seen after 20 weeks. The authors conclude that fibromyalgia patients may undergo low-intensity dynamic endurance training without experiencing exacerbation of their general pain and fatigue symptoms. If this program is of benefit for the patients seems questionable, because the results are modest. The increased feeling of well-being could be related to the attention the patients received by just being in the training program.

Burckhardt et al. (43) tried to overcome this pitfall in a randomized controlled clinical trial of education and physical training in 99 female fibromyalgia patients. These 99 patients were assigned to three different groups, one group received a standardized 6-week selfmanagement education program, a second group got besides this education program a 6h physical training program and the third group served as a control group. The training program was designed to assist the patients to exercise independently (at home). Eighty-six completed the study. The control group however got treatment after three months. This means that follow-up of the control group was limited. The follow up of the experimental groups was 6 months. Assessments were made at pretest, at three months (6 weeks after finishing the experimental program), and after 6 months.
As outcome measures were used self-report questionnaires (Fibromyalgia Impact Questionnaire, Fibromyalgia Attitudes Index, Quality of Life Scale-Satisfaction, Self Efficacy Scale), physical fitness test, tender point count, and a myalgic score. The Beck Depression Inventory was also administered. The experimental programs had a significantly positive impact on quality of life and self-efficacy. There were however no significant differences between the two treated groups on any of the outcome variables. There were no changes in tender points scores or any of the physical fitness variables at any testing point. The authors suggest several reasons that may have influenced their outcomes. The length of time of the experimental programs was short, namely 6 weeks, especially in relation to behavioral changes. Furthermore the authors think that some participating women had no motivation to become better, or show a better symptom management, because of the financial benefits of being sick-listed. A hypothesis brought up by the authors why there was no significant difference between the two experimental groups is that the measurements of these two different group were made in other seasons, which may have had an influence on outcome. The most simple interpretation of the results is not mentioned; the treatment programs are just not effective in this study population. The positive changes measured could be due to the placebo-effect. A trial with a group of patients who are offered social contacts with other patients compared with a group with no further contact or other interventions should be set up to evaluate the role of these social contacts on feelings of well-being, pain experience and sleep problems.

A controlled trial of hypnotherapy in the treatment of fibromyalgia was published by Haanen et al. (44). Forty fibromyalgia patients were randomly divided over a hypnotherapy group and a group which physical therapy. They did not use a control group. The physical therapy consisted of massage and training in muscle relaxation. Because of established usefulness of hypnotherapy in certain diseases where psychological factors are thought to contribute to the pathogenesis (like chronic asthma, irritable bowel syndrome, peptic ulcer disease) the authors hypothesized that hypnotherapy could play a role in the management of fibromyalgia. Therapy lasted 3 month, and the last evaluation took place at 24 weeks, which makes a study length of 6 months. The exact number of drop-outs is not given. The patients in the hypnotherapy group showed a significantly better outcome with respect to their pain experience, fatigue on awakening, sleep pattern and global assessment at 12 and 24 (follow-up) weeks. There was no improvement in the total myalgic score measured by a dolorimeter. This means the subjective parameters improved, but the (relatively) objective parameter, myalgic score, did not change significantly. Feelings of somatic and psychic discomfort as measured by the Hopkins Symptom Checklist, showed a decrease in the hypnotherapy group, but they remained abnormally strong in many cases. At the baseline these feelings were already very strong. In this trial hypnotherapy was more successful than physical therapy in improving complaints in fibromyalgia patients. However the group with physical therapy could be regarded as
a control group, because all patients already had had some form of (unsuccessful) physical therapy in the past. The hypnotherapy was really new and the impact of this therapy could be based on the placebo-effect.

Cognitive behavioral treatment (CBT) in fibromyalgia patients was studied by Bradley (45) and Nielson et al. (46). Bradley (45) described CBT-procedures in general and presented experimental designs that could be used in randomized controlled clinical trials of CBT in patients with fibromyalgia. Bradley stated that several investigators have attempted to use cognitive-behavioral interventions to alleviate pain and disability among patients with rheumatic diseases, because they assume that patients perceptions and evaluations of their life events influence their emotional and behavioral reactions to those events. Fibromyalgia patients are confronted with chronic complaints that can not be fully explained or are fully understood, and can not be cured. Therefore they develop the belief that the pain, disability and other complaints are uncontrollable. These feelings lead to increased negative affect, pain and sleep disturbances, as well as reduced attempts to engage in activities of daily live and to develop effective coping behaviors. Cognitive-behavioral interventions are designed to teach patients skills necessary to control their pain and other forms of impairments and disabilities and to believe that they can successfully employ these skills.

In the study of Nielson (46) the treatment was conducted in an inpatient program and included 30 fibromyalgia patients. Number of drop-outs was 5. The program lasted 3 weeks and included medical, psychological, social work, physiotherapy, occupational therapy and nursing staff. All team members were skilled in the nature of the CBT approach. The authors defined target and nontarget variables and the hypothesis was that only target variables, specifically addressed by the CBT program, would change and that no changes would be expected in nontarget variables for which no treatment had been purposely devised. Assessments were made 5 months for study entry, i.e. start of the program, at the start of the program and at the end of the program. Target variables were pain severity, perceived interference with life, sense of control over pain, emotional distress and pain behavior and variables distilled from several used psychometric instruments. Nontarget variables were perceived support by others, response by significant others to pain, marital adjustment and activity level. There were no significant changes, not in the target and not in the nontarget items, at the 2 pretreatment assessments. Comparison of the pretest and posttest scores indicated that the target variables changed in the expected direction, and these changes were significant. The nontarget variables did not change significantly. The authors themselves made some restrictions as to the generalization of the result of their study. One thing was of course the short observation period and no follow up assessment. The program consisted, next to CBT, also of some other interventions, like cardiovascular fitness training, flexibility exercises and use of tricyclic antidepressants. This makes it hard to establish if the improvements can be accounted
The authors stressed the effect of the multidisciplinary nature of their interventions, which they thought relied heavily on cognitive-behavioral strategies. Three years later the outcomes of a longterm follow up of this same study were published (47). The followup assessment was conducted after a mean of 30 months after discharge in 22 (of 25) patients. Compared with the pretreatment psychometric variables, longterm improvement was found in three of 10 target variables (worry, observed pain behavior, control over pain), the other 7 variables changed in the direction of improvement. The posttreatment assessment, directly after the 3-week treatment period, showed a significant improvement in all 10 target variables, see above. The results of the follow-up assessment made the authors conclude that CBT could play a role in the longterm treatment of fibromyalgia syndrome. However they did not take into account any cointerventions that might have taken place in the follow-up period. To achieve a change in behavior in 3 weeks time seems unlikely, the more since this behavior would have been present for many years before.

Cognitive-behavioral intervention in juvenile primary fibromyalgia syndrome was studied by Walco et al. (48) in a pilot study. They treated (just) seven girls (8-18 years old) with fibromyalgia using cognitive-behavioral techniques aimed at reducing pain and facilitating sleep, as well as strategies aimed at increasing mastery over the pain and improving mood. In the treatment techniques muscle relaxation and guided imagery were used. Before treatment the average pain intensity was measured with a VAS. The intervention consisted of 4 to 9 sessions, dependent of the result. In which time span this was executed is not mentioned. The girls who completed the treatment (5 girls) reported that the pain was absent or negligible at the end of the program. Based on an interview it was concluded that the girls returned to premorbid levels of functioning. A contact by telephone was made after several months and from these interviews the authors concluded that the results were still very good. Of course these results can not lead to any definite conclusions; a randomized, controlled and blinded study should be performed.

Deluze et al. (49) published the results of a controlled trial of electroacupuncture in 70 fibromyalgia patients. It was a randomized study with blinded patients and evaluating physician. The duration of the study was three weeks. Fifty-five patients completed the study. Acupuncture is said to raise pain threshold in for instance painful nerve stimulation. Mode of action in acupuncture may be a neurohormonal mechanism, by activating some endogenous pain control mechanisms. Patients were randomized to electroacupuncture or a sham procedure. Outcome measures used in this study were pain threshold, number of analgesic tablets used, regional pain score, pain recorded on visual analogue scale, sleep quality, morning stiffness, and patient's and evaluating physician's appreciation. Seven of these eight outcome measures showed a significant improvement in the treatment group and none were improved in the sham treatment group. The authors state that with the sham treatment they used...
the patients could not distinguish this from a real electroacupuncture treatment. Study duration was very short and long-term efficacy of this treatment form should be established.

EMG-biofeedback training in 15 patients with fibromyalgia was studied by Ferraccioli et al. (50). Because several psychosomatic syndromes have been successfully treated with biofeedback the authors saw reason to undertake this particular study. First a number of patients entered an open study and after that a controlled trial was conducted (with other patients). Fifteen sessions were given, twice weekly. Treatment period was 8 weeks. The electrodes were placed on the forehead. The intention was to learn the patients to relax, using auditory feedback of ongoing muscular tension. The authors found in more than half of the participating patients a longstanding clinical benefit. Clinical assessments were, among others, number of tender points, morning stiffness and VAS scores. A follow up of twelve months was conducted, with assessments every 3 months. Patients continued the relaxation training at home. The authors can not explain the possible working mechanisms of EMG-biofeedback training in fibromyalgia. A decrease of plasma ACTH and ß-endorphins may occur during EMG-biofeedback training, and this may bring about an antistress effect. In the controlled trial a sham EMG-biofeedback training was difficult to carry out. What these patients did at home, following the 15 sessions, is not clear. In the controlled study only 12 patients participated, which is a very small number (6 in each group).

A pilot study on the effects of a multidisciplinary program, consisting of cognitive and exercise aspects, showed after ten weeks a reduction in general pain intensity and all (16 female) patients had made adjustments to their everyday life (51). The purpose of the program was to learn fibromyalgia patients how to solve their problems related to activities of daily life, and thereby reduce stress. Assessments were made by using a questionnaire related to the adjustments of daily life they carried out after the 10 week program. These adjustment are divided (by the authors?) in practising relaxation techniques, dietary changes, changes in goal setting and coping with activities, increased physical activity level and ergonomical improvements. It remains vague if the assessments were just based on subjective reports or on objective data. No control group was included and this makes it difficult to draw definite conclusions on the efficacy of this program. Furthermore at six months follow-up the score values had returned to baseline values, with the exception for the sensory pain score. The rationale behind the possible benefit of dietary changes in fibromyalgia is not explained.

Concluding remarks

There is no golden standard in the treatment approach of fibromyalgia patients. Treatment strategies aimed only at one of the symptoms of the fibromyalgia syndrome
seem not to be appropriate. The fibromyalgia syndrome has to be considered as a chronic pain syndrome, with many implications for social and emotional functioning, and therefore these aspects have to be taken into account as well. To achieve this a multidisciplinary approach is necessary. The choice for relevant outcome variables is a very difficult one and many different variables are used. This makes it even harder to compare the different studies. Many trials were not able to show that the occurrence of a positive change after an intervention was not merely due to a placebo-effect. To keep up a blinded design was also difficult in most studies. Another problem encountered in evaluating therapy trials is that if the difference in outcome between two groups is statistically significant, is it clinically significant as well? And, if the difference is not statistically significant, was the trial big enough to show a clinically important difference if it had occurred? With a small number of patients a type II error is large and the power of the study (sensitivity) very low. Follow-up assessments and study length were mostly short and number of patients were small. Longterm follow up studies to establish the longterm effects of treatment protocols are very needed.

Therapy trials with NSAID's showed no convincing positive results. No studies are known on the effect of paracetamol in fibromyalgia, but it is frequently prescribed. The same is true for physical therapy. No controlled studies are published on the effect of physiotherapy in fibromyalgia. Whether endless passive modalities of physical therapy (including massage) have to be continued, despite lack of improvement, remain very doubtful. Continuing the therapy could make the patient dependent of the therapist (therapy), without having any actual profit of the therapy. There seems to be a modest place for tricyclic drugs (amitriptyline) in alleviating symptoms in a subgroup of fibromyalgia patients, especially related to sleep complaints. At this time there is no substantial proof that fitness programs alleviate the symptoms of the fibromyalgia patients.
Chapter 13

References

Chapter 13


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