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Management of Fibromyalgia
What are the Best Treatment Choices?

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Abstract

Fibromyalgia still represents an enigma to modern medicine and the aetiopathogenesis is far from explored. The management of patients with fibromyalgia is thus mostly based on empirical research, and only a few controlled

studies have been performed. Basic drug therapy rests on the administration of amitriptyline and conventional analgesics. Such therapy should be initiated only after careful patient information and delineation of therapeutic goals are provided. Any drug therapy should be administered in combination with physical treatment and cognitive behavioural therapy. Because of the appearing contours of pathogenic mechanisms, hopefully a number of new drugs will be available to the patients with this complex pain syndrome in the near future.

1. Background

During the last few decades there has been much focus on an apparently new and increasing cause of disability: a condition of generalised pain accompanied by excessive fatigue and exhaustion. The most common symptoms are poor sleep, not feeling refreshed in the morning, headache, anxiety, depression, irritable bowel symptoms, paresthesias, and a feeling of swelling, most often located to hands and fingers.[1,2] Modulating factors such as pain aggravation after physical activity and in relation to stress and changes in weather are often reported. This condition has been coined fibromyalgia.

The American College of Rheumatology (ACR) 1990 classification criteria[3] for fibromyalgia are based on two cut-off values, for pain extent and for number of tender-points (TP). Thus, to fulfil the ACR-90 criteria an individual has to present with chronic widespread pain and at least 11 out of 18 positive TP. The presence of associated symptoms is not required, and the distinction between primary (which excludes individuals with concomitant diseases) and secondary fibromyalgia is no longer made. These criteria have established a basis for comparing patients from various studies.

The occurrence of fibromyalgia is extremely common and ranges from 2.0 to 10.5% (only women) in the general population.[4-8] It should be noted, however, that although the prevalence is high, there exist both milder and more serious variants of the syndrome, which show great variations regarding outcome.[9-15] There is so far only one study addressing the incidence of fibromyalgia. During a 5.5-year observation time an incidence of 0.58% yearly was reported among initially pain-free women.[16]

Several studies have been undertaken to study outcome and prognosis.[13,17-26] So far, the majority of studies of adults have concluded that complete and sustained disease remission in fibromyalgia is rather rare.[9,13,17,19-21] However, other authors have reported a considerable number of individuals who no longer fulfilled the ACR-criteria for fibromyalgia at follow-up.[18,23-26] Thus, fibromyalgia, as defined by the criteria, does not seem to reflect a discrete disease entity exhibiting stable and persistent clinical manifestations. It should also be noted that according to the studies of Buskila and Mikkelson,[24,25] children seem to have a better outcome than adults.

The aetiology of fibromyalgia is still unknown, while the pathogenesis is hopefully soon to be disclosed. A few clinical observations suggest a familial aggregation of fibromyalgia,[27,28] and sibship analyses have shown significant genetic linkage of fibromyalgia to the *HLA* region.[29] Genetic analyses have also disclosed some allelic abnormalities in serotonin precursor genes.[30]

Different hypotheses have involved theories about major affective disorder mechanisms,[31] various peripheral mechanisms involving muscle deconditioning, microtrauma,[32,33] disturbed energy metabolism,[34] and microcirculation in microfibres that may confer sensitisation of nociceptive neurones in the muscle[35,36] and disorder of pain modulations.[37-39] In 1992, Yunus[40] suggested that the pain in fibromyalgia was due to an interaction of central and peripheral physiological mechanisms. This view has later been supported among others by Henriksson and coworkers[41] and Russell.[42] Different studies have shown significantly elevated substance P levels in the cerebrospinal fluid (CSF) of patients with fibromyalgia,[43-45] and decreased blood and CSF levels of serotonin and tryp-

tophan.[46] The possible role of excitatory amino acids in enhancing synthesis of nitric oxide in the pathogenesis of pain in patients with fibromyalgia is discussed in an article by Larson and coworkers.[47] The phenomenon of central nervous system (CNS) plasticity[48] has been further investigated and may perpetuate the aberrant central mechanisms in a vicious cycle, resulting in self-sustained chronicity. Furthermore, the theory of dysfunction in the central pain-modulating system is supported by the findings of non-rapid eye-movement sleep (stage 4) abnormalities.[49,50] Finally, it is becoming increasingly clear that the deficiency of a single neurochemical substance is not the single cause of fibromyalgic symptomatology. Almost all of the hormonal feedback mechanisms controlled by the hypothalamus are altered. Elevated basal values of adrenocorticotropic hormone (ACTH), follicle-stimulating hormone (FSH) and cortisol, as well as lowered basal values of insulin-like growth factor 1 (IGF-1, somatomedin C), free liothyronine (triiodothyronine; T_3), and estrogen,[51] appear rather characteristic of fibromyalgia.

The present findings of dysfunctions in such a variety of different fields do mirror the heterogeneity of fibromyalgia, and probably indicate that fibromyalgia has a complex aetiopathogenesis. Thus, because of the lack of a known clear-cut aetiopathogenesis, most therapeutic options have so far had an empirical basis. In the last decade numerous studies with different new, possibly pain-modulating substances, have been undertaken on the basis of neurophysiological research. Several of these studies show promising results, and hopefully this field of research will be expanded and lead to the availability of efficacious new drugs for the management of fibromyalgia.

2. General Therapeutic Considerations

Before considering any therapeutic options, a definite diagnosis should be established. Moreover, as fibromyalgia very often co-exists with other diseases that generate similar symptoms,[52-55] such conditions must be ruled out and, if possible, treated.

Fibromyalgia is a chronic condition, often with an insidious onset. As the condition becomes chronic and more severe, a number of secondary problems occur. The accumulation of pain and fatigue over years influences work capacity and exerts considerable impact on the daily life of the patient.[13] Failure to continue working often leads to economic problems, and the diminished capacity to participate in daily life compromises social activities, possibly leading to family problems, feelings of hopelessness and isolation. Clearly, any therapeutic programme in patients with fibromyalgia should include a broad multi-disciplinary approach.

As there is no known cure for fibromyalgia, therapy should be aimed at reducing pain and easing the management of the whole situation for the patient and her family. At present, the available tools for treatment have been of a mainly nonpharmaceutical nature, as only a few drugs have been shown effective in some patients.

Before initiating therapy, however, the expectations of the patient should be clarified. Careful patient education ought to include information regarding the chronic disease course, and the lack of a causal cure. Information of the lack of an association between fibromyalgia and other serious diseases, including rheumatoid arthritis, should also be stressed. Previous use of therapy should be delineated and knowledge of any secondary problems obtained. Finally, the goal of treatment should be clarified and agreed upon. The choices of further strategies depend on what has been tried earlier, the availability of local treatment possibilities, and the overall situation of the patient.

3. Non-Pharmaceutical Treatment

Physical treatment, biofeedback and coping strategies including cognitive therapy are the most important approaches. Transcutaneous electrical nerve stimulation (TENS) and acupuncture are often applied, but because of the lack of controlled studies, the possible effects are not well documented.

3.1 Physical Treatment

Physical treatment in fibromyalgia is aimed at altering clinical features such as pain, fatigue, deconditioning, muscle weakness and sleep disturbances. During the last decade, approximately 10 to 15 studies have been undertaken to evaluate the efficacy of physical training aimed at minimising the symptoms. Bennett and coworkers[56] as well as Clark and coworkers[57] have reported that the majority of patients with fibromyalgia are physically unfit, and also suggested that deconditioning might result in concomitant symptoms such as tachycardia, dizziness, fatigue and anxiety. McCain and coworkers[58] showed that patients who performed a supervised cardiovascular fitness training not only improved in cardiovascular fitness, but also showed improvement in measures of pain compared with a similar group receiving flexibility exercises. In support of these findings, Wigers and coworkers[59] found that individuals who took part in an aerobic exercise group experienced reduced pain distribution and improved perceived energy. Moreover, Martin, Nichols, Verstappen and coworkers[60-62] all found some benefits in the exercising groups with respect to pain reduction, TP score, and increased physical and social activities. In contrast, Mengshoel and coworkers[63] were unable to demonstrate any differences between the exercise group and a control group. The studies of Grange and coworkers[23] and Wigers[64] concluded that maintenance of adequate physical activity is associated with a positive long term outcome in fibromyalgia.

However, there are shortcomings in most of the above mentioned studies. Short duration of intervention, variation between the studies of components of the actual physical activity applied, small numbers of patients, control groups also receiving effective intervention, absence of long-term follow-up, high dropout rates and different outcome parameters all make it difficult to compare the value of the different factors evaluated. In spite of these limitations, however, it may be concluded that patients with fibromyalgia should be encouraged to perform regular physical activity and that a significant number of such patients experience improvement.

3.2 Transcutaneous Electric Nerve Stimulation and Acupuncture

TENS is based on electrically induced analgesia. The mechanisms involved are reviewed by Minor and Sanford.[65] The major biophysical effect is probably due to stimulation of afferent nerves that transmit or inhibit noxious inputs from the spinal cord to the brain related to the gate-control theory.[66] Justin reviewed the role of TENS as treatment for chronic pain, and concluded that the clinical response is variable and unpredictable.[67] However, in 1991, Johnson showed that some patients do gain significant benefit without serious adverse effects.[68] TENS is generally most useful in more localised cases of pain, which limits the usefulness of the method in generalised pain as fibromyalgia. Nevertheless, some patients with fibromyalgia do profit from low frequency treatment with TENS.

Berman and coworkers[69] critically reviewed published reports on the effectiveness of acupuncture in the treatment of fibromyalgia. All randomised or quasi-randomised controlled trials, or cohort studies of patients with fibromyalgia who were treated with acupuncture, were selected for analyses. The methodological quality, sample characteristics, type of acupuncture treatment, and outcome were evaluated. Seven studies were reviewed, of which only one was of high methodological quality. In this study, Deluze and coworkers[70] reported a 3-week, double-blind, randomised trial of electro-acupuncture in patients with fibromyalgia. They concluded that the limited amount of high quality evidence suggests that real acupuncture is more effective than sham acupuncture for improving symptoms of patients with fibromyalgia. However, further high quality randomised trials are needed to provide more firm data on the possible efficacy of acupuncture in fibromyalgia.

3.3 Bio-Feedback

Bio-feedback is a therapeutic approach in which feedback is given by different methods to facilitate control of physiological processes such as muscle tension and frequency of breathing. Only a few studies have been performed in patients with fibromyalgia. Ferraccioli and coworkers[71] studied 12 patients who received auditory feedback of muscle tension in the scalp. The authors reported a 50% clinical improvement in nine patients at 6 months. In a study by Buckelew and coworkers,[72] improved self-efficacy, reduced disease severity and increased physical activity were found in patients with fibromyalgia treated with bio-feedback. However, these patients underwent a multi-disciplinary approach that also included relaxation training and structured exercise programmes. Although only a limited number of studies have been undertaken, the method seems to have a positive therapeutic effect and further studies should be encouraged.

3.4 Cognitive Behavioural Therapy

A biopsychological perspective is partly adopted in assessing fibromyalgia. This perspective emphasises the psychological dimensions of chronic pain and has led to the development of psychological management strategies. The purpose of cognitive behavioural therapy is to teach individuals the skills necessary to control pain and disability.[73] Morley and co-workers[74] provided a review and meta-analysis of 25 randomised, controlled trials of cognitive behavioural therapy and behaviour therapy for chronic pain in adults. It was concluded that the studies provide sufficient evidence to claim that cognitive behavioural therapy and behavioural therapy in adults with chronic pain is effective.

There has been a growing interest in the use of formal self-management training programmes for patients with fibromyalgia. Sandstrøm and Keefe[75] reviewed studies that have tested the efficacy of two types of programmes, those emphasising training in coping skills and those emphasising training in physical exercise. Taken together, the studies reviewed suggested that formal self-management programmes such as coping skills training or exercise may play an important role in the control of fibromyalgia symptoms. However, it was also concluded that not all individuals with fibromyalgia responded to such programmes. Additional research is clearly needed to explore fully how cognitive behavioural therapy should best be applied in order to achieve optimal effects.

4. Drug Therapy

Because of an incomplete understanding of the aetiopathogenetic processes of fibromyalgia, conventional drug therapy is mostly based on empirical research.[76] However, the evolving contours of the pathogenic mechanisms of fibromyalgia have encouraged an increased use of drugs applied in other medical conditions. Several experimental studies have already been conducted and may hopefully initiate a new generation of drugs for fibromyalgia. An overview over studies in which conventional drugs are applied in the treatment of fibromyalgia is given in table I.[77-105] Most of the studies are presented in more detail in the following text.

4.1 Conventional Treatment

Unfortunately, the results from empirical research are rather discouraging, as only a few drugs have proved partially effective. Drugs frequently administered in fibromyalgia are nonsteroidal antiinflammatories (NSAIDs), analgesics, sedatives, antidepressants and selective serotonin reuptake inhibitors (SSRIs). Opioids are only occasionally administered in patients with severe symptoms and are only poorly studied in this context. However, opioids are generally not recommended in fibromyalgia because of the high risk of abuse. As there is a large body of evidence that fibromyalgia is a central pain state, opioids should be studied in the context of fibromyalgia. However, as opioids have a considerable abuse potential, treatment involving such drugs should be individualised and avoided in patients with a history of substance abuse. Sys-

Table I. Studies of pharmacological treatment in patients with fibromyalgia

Drug (dosage in mg/day)	No. pts	Duration (wks)	Comparator drug (c)	Better than c?	Reference
NSAIDs					
Naproxen (1000)	15	6	Placebo	no	77
Ibuprofen (600)	20	3	Placebo	no	78
Ibuprofen (2400)	17	6	Placebo	no	79
Tenoxicam (20)		8	Placebo	no	80
Ibuprofen (2400) + alprazolam (3)	52	6	Placebo	yes	79
Tenoxicam (20) + bromazepam (3)		8	Placebo	no	80
Analgesics					
Paracetamol (acetaminophen) (160) + caffeine (32) + carisoprodol (200)	43	8	Placebo	yes	81
Paracetamol (acetaminophen)			NSAIDs	no	82
Tramadol (100)	12		Placebo	?	83
Tramadol (50-400)	69	3	Placebo	yes	84
Sedatives + anxiolytics					
Cyclobenzaprine (10-40)	120	12	Placebo	yes	85
Cyclobenzaprine (10-40)	40	6	Placebo	no	86
Cyclobenzaprine (20-40)	9	4	Placebo	no	87
Cyclobenzaprine (10-30)	208	4/26	Placebo	yes/no	88
Bromazepam (3)		8	Placebo	no	79
Alprazolam (0.5-3.0)	17	6	Placebo	no	78
Zopiclone (7.5)	41	12	Placebo	no	89
Zopiclone (7.5)	33	8	Placebo	no	90
Zolpidem (5-15)	16		Placebo	no/yes	91
Corticosteroids					
Prednisone (15)	20	2	Placebo	no	92
Antidepressants					
Monoamine oxidase inhibitors (400-600)	130	12	Placebo	no	93
Fluoxetine (20)	42	6	Placebo	no	94
Citalopram (20-40)	23	8	Placebo	no	95
Citalopram (20-40)	40	18	Placebo	yes/no	98
Fluoxetine (20) + cyclobenzaprine (10)	21	12	Cyclobenzaprine	yes	96
Fluoxetine (20) + amitriptyline (25)	19	6	Placebo	yes	97
Sertraline (50)	40	12	Amitriptyline 25mg	equal	99
Amitriptyline (10-50)	59	9	Placebo	yes	100
Amitriptyline (25)	15	6	Placebo	yes	77
Amitriptyline (10-50)	36	5	Placebo	yes	101
Amitriptyline (10-50)	23	3	Placebo	yes	102
Amitriptyline (10-50)	208	24	Placebo	no	88
Trigger-point injection					
Lidocaine injections	58		Dry needling	yes	103
Lidocaine injections	18	2	Stretching	yes	104
Lidocaine injections + stretching				yes	105

NSAIDs = non-steroidal anti-inflammatories; **?** indicates results not clear.

temic corticosteroids are also sometimes employed in conventional treatment as are trigger-point injections.

4.1.1 Nonsteroidal Anti-Inflammatories

The possible pain reducing effects of NSAIDs in fibromyalgia have been evaluated in several placebo-controlled studies.[77-80] Naproxen, ibuprofen and tenoxicam were no more efficient than placebo. These negative results are hardly surprising, as inflammatory mechanisms do not appear to be involved in the pathogenesis of fibromyalgia.

4.1.2 Analgesics

Surprisingly, rather few controlled trials of the use of analgesics to control pain in patients with fibromyalgia have been undertaken, and to our knowledge only two studies of paracetamol (acetaminophen)[81,82] and no studies of aspirin (acetylsalicylic acid) have been undertaken. Tramadol, a relatively new analgesic in most countries, is a combined opioid analogue, norepinephrine inhibitor and serotonin-releasing drug. In one study, completed in 1998 by Biasa and coworkers,[83] 12 patients received injections with tramadol 100mg or placebo. The results gave no clear information of the possible effects of this drug. Another study of tramadol concluded that tramadol provided pain relief in patients with fibromyalgia who tolerated the drug.[84] Further studies are awaited.

4.1.3 Sedatives and Anxiolytics

Cyclobenzaprine is a commonly prescribed centrally acting muscle relaxant which is structurally similar to tricyclic antidepressants (TCAs) and differs from amitriptyline by only one double bond.[106] In 1988, Bennett and coworkers found significantly reduced pain in patients with fibromyalgia after administration of cyclobenzaprine.[85] However, the majority of later studies were unable to demonstrate beneficial results for the use of sedatives and anxiolytics,[79,80,86-88] except for the combination of alprazolam and ibuprofen which demonstrated a small beneficial effect. Because of the high risk of abuse and marginal effects, these drugs can not be recommended as first choice agents in the treatment of fibromyalgia, and should only be used after careful consideration on an individual patient basis. The short-acting nonbenzodiazepine sedatives zolpidem and zopiclone improved sleep but failed to reduce pain in three studies of patients with fibromyalgia,[89-91] and may thus be administered to patients with severe sleep disturbances. Their lack of analgesic effects, however, limits their role in the therapy of fibromyalgia.

4.1.4 Corticosteroids

In 1985, Clark and coworkers[92] entered 20 patients with fibromyalgia in a double-blind, crossover study to compare the effects of prednisolone versus placebo. Visual analogue scales (VAS) for pain, morning stiffness, fatigability, sleep disturbances and TP examination were assessed at baseline, and the end of weeks 2 and 4. Overall there was no improvement while taking prednisolone, indeed most measured variables showed a trend towards deterioration. This study is of a special importance, since it clearly demonstrated that corticosteroids should not belong to the therapeutic spectrum of fibromyalgia. In patients with fibromyalgia responding favourably to corticosteroids, the diagnosis should be thoroughly reconsidered.

4.1.5 Monoamine Oxidase Inhibitors

In 1998, Hannonen and coworkers[93] compared moclobemide with amitriptyline and placebo. Moclobemide is a reversible inhibitor of the monoamine oxidase A and inhibits the deamination of serotonin, norepinephrine and dopamine in the synaptic cleft. It acts as an antidepressant. The response criteria in this study were weak and 74% of the amitriptyline-treated group responded, while 49 and 54%, respectively, responded favourably to placebo and moclobemide. There appears to be no good reason for prescribing this drug to patients with fibromyalgia.

4.1.6 Selective Serotonin Reuptake Inhibitors

As SSRIs also interfere with serotonin metabolism, several clinical trials to explore their possible effect on fibromyalgia have been undertaken. Three double-blind, placebo-controlled studies with two different agents have been conducted.

Wolfe and coworkers[94] evaluated fluoxetine versus placebo, whereas Nörregaard and coworkers[95] and Andenberg and coworkers[98] explored the possible effects on pain of citalopram. The first two studies did not reveal any significant pain reduction in patients with fibromyalgia. The study of Andenberg did not demonstrate any significant effect on a VAS on pain, but demonstrated, however, significant differences in pain rating on Fibromyalgia Impact Questionnaire.

Cantini et al.[96] evaluated fluoxetine in combination with cyclobenzaprine and amitriptyline. In contrast to single-agent treatment, the combination of cyclobenzaprine and fluoxetine was superior. In a double-blind crossover designed study with four arms (amitriptyline; fluoxetine; amitriptyline and fluoxetine, placebo) there was a statistically significant improvement compared with the placebo treated group for both amitriptyline and fluoxetine. When used in combination, amitriptyline and fluoxetine produced significantly better results than either drug alone, as measured by the Fibromyalgia Impact Questionnaire and by a VAS for pain, global well-being and sleep.[97] Celiker[99] compared sertraline 50mg with amitriptyline 25mg and found equal statistical improvement in all study parameters (VAS pain, sleep, fatigue, stiffness and TP). Thus, SSRIs still do not have an obvious place as a single agent treatment in patients with fibromyalgia. In depressed patients with fibromyalgia, however, it may have a role when administered in combination with amitriptyline.

4.1.7 Tricyclic Antidepressants

TCAs such as amitriptyline, clomipramine, dosulepin (dothiepin) and doxepin inhibit the reuptake of serotonin and norepinephrine at the neuronal terminals. The prevailing hypothesis is that mechanisms involving serotonin and norepinephrine mediate clinical analgesia through descending systems originating in the brainstem and influence the dorsal horn of the spinal cord.

Several double-blind, controlled studies of amitriptyline versus placebo have been undertaken in patients with fibromyalgia. The first study was published in 1986 by Carette and coworkers[100] who found that both amitriptyline and placebo significantly improved morning stiffness and pain compared with baseline scores. Similarly, Goldenberg and coworkers[77] found amitriptyline superior to placebo in a 6-week trial using outcome parameters such as patient and physician global assessment, pain, sleep problems, fatigue on awaking and TP score. These favourable results of amitriptyline therapy were confirmed by Scudds in 1989[101] and by Jaeschke in 1991.[102] In 1994, Carette and coworkers followed 208 patients over 6 months who were treated with amitriptyline and cyclobenzaprine. Because of a higher than expected placebo response, long-term efficacy could not be demonstrated.[88]

In conclusion, the beneficial short-term effects of amitriptyline appear well documented and at the present it may represent the drug of choice in fibromyalgia. However, further long-term studies are warranted before the role of amitriptyline in fibromyalgia is finally defined.

4.1.8 Trigger-Point Treatment

Trigger-point injection may reduce pain originating from concomitant trigger-points in selected patients with fibromyalgia who also experience myofascial pain syndrome. A trigger-point is a localised painful spot in a taut band of muscle fibre producing localised and referred pain on palpation. These trigger-points may be injected with lidocaine or be manipulated with dry needling, spray and stretch techniques.[107] Less postinjection soreness may be achieved by applying lidocaine instead of dry needling.[103] Hong and coworkers[104] performed a study comparing injections with spray and stretch. They found injections more favourable as the patients still had significant pain relief 2 weeks after injection.

This method has clear limitations, as a high number of patients with fibromyalgia possess several trigger-points. This treatment ought to be reserved for patients with pronounced trigger-points of which the most bothersome should be chosen for injection. The results are optimal when combined with stretching and physical therapy.[105]

4.2 Future Drug Therapies

This category comprises both drugs already in use but in other therapeutical fields, and experimental drugs. An overview is given in table II.[108-129]

4.2.1 Antiepileptic Drugs

Antiepileptic drugs (AED) have been administered in different chronic pain conditions for a long time.[108] To our knowledge, no study exists that was designed to evaluate the possible effects of such drugs in patients with fibromyalgia. Several newer AED with an improved tolerability have recently been introduced. Gabapentin shows the greatest potential in the management of chronic pain and may exert an indirect effect via a second order neurone, such as Wide Dynamic Range neurones. No published double-blind, placebo-controlled trials have evaluated gabapentin in the treatment of pain syndromes.

4.2.2 Calcitonin

Calcitonin (salmon calcitonin) has analgesic properties and is commonly used to treat osteoporotic fractures. Besette and coworkers[109] performed a placebo-controlled study in patients with fibromyalgia using calcitonin 100IU subcutaneously. After 4 weeks there were no significant differences between the two treatment groups.

4.2.3 Ademetionine

Ademetionine (S-adenosylmethionine) is an anti-inflammatory drug with analgesic and antidepressant effects. Jacobsen and coworkers[110] investigated the efficacy of oral ademetionine 800 mg/day versus placebo for 6 weeks in 44 patients

Table II. Studies of possible future pharmacological agents for use in patients with fibromyalgia

Drug (dose)	Type of study/diagnosis	No. pts	Duration	Efficacy	Reference
Gabapentin (antiepileptic drug)	No studies in pain syndromes				108
Calcitonon (100IU SC)	Fibromyalgia		4wk	no	109
Ademetionine (S-adenosylmethionine)					
800mg orally	Fibromyalgia	44	6wk	yes	110
600mg IV	Fibromyalgia		10d	yes/no	111
Oxitriptan (5-hydroxytryptophan)					
300mg orally	Fibromyalgia	50		yes	112
300mg orally	Fibromyalgia	50	90d	yes	113
Botulinum toxin	Tension headache	10	8wk	yes	114
Capsaicin	Fibromyalgia	45		yes/no	115
γ-Hydroxybutyrate	Fibromyalgia	11		yes	116
Growth hormone	Fibromyalgia		39wk	yes	117
Nerve-growth factor	Experimental				118
Dopamine D_2-receptor agonist	Fibromyalgia	166	16wk	yes	119
Malate (12-2400mg) + magnesium (3-600mg)	Fibromyalgia	15	8wk	yes	120
NMDA-receptor antagonists					
IV	Fibromyalgia	11		yes	121
orally 250 mg/kg	Fibromyalgia	1	Long-term	yes	122
IV 0.3 mg/kg	Fibromyalgia	17		yes	123
orally 20-100mg	Neuropathic pain	21		yes/no	124
orally 50-150mg + tramadol	Clinical / fibromyalgia	46		yes/no	125
5-HT_3-receptor antagonists					
orally 5,10,15mg	Experimental	96	10d	↓ serotonin	126
orally 5,10,15 mg	Fibromyalgia	418	10d	yes	127
orally 5 mg	Fibromyalgia	30	4wk	yes	128
IV 2 mg	Fibromyalgia	24	10d	yes	129

IV = intravenous; **SC** = subcutaneously.

with fibromyalgia. Significant improvements were observed for pain at rest and fatigue. Pain during physical activity, quality of sleep and overall well-being did not show any improvement. Although Volkmann and coworkers[111] were unable to show pain reduction using ademetionine 600mg intravenously for only 10 days, the potential effect of this agent should be further delineated in fibromyalgia.

4.2.4 Oxitriptan

Oxitriptan (5-hydroxytryptophan; 5-HTP) is the intermediate metabolite of the essential amino acid L-tryptophan in the biosynthesis of serotonin, and is well absorbed after an oral dose. Therapeutic administration of oxitriptan has been shown to be effective in treating a wide variety of conditions, including fibromyalgia.[130] A double-blind, placebo-controlled study of the efficacy and tolerability of oxitriptan 300 mg/day was conducted in 50 patients with fibromyalgia.[112] All the clinical parameters studied (number of TP, anxiety, pain intensity, quality of sleep and fatigue) were significantly improved. Some of the same authors published a 90-day study with the same promising results. In addition, the efficacy was maintained throughout the whole period of treatment.[113] Further controlled studies are required to properly define the value of oxitriptan in patients with fibromyalgia.

4.2.5 Botulinum Toxin

Botulinum toxin is applied to ease muscular spasms. Recently, it has been shown that botulinum toxin also may relieve pain before relieving spasms.[131] Relja studied the efficacy on pain in ten patients with tension-type headache.[114] There was a significant decrease in muscle tenderness that lasted up to 8 weeks. This preliminary study demonstrated that an injection of botulinum toxin may be an effective treatment for patients with chronic tension-type headaches. The potential effects of this agent on pain in patients with fibromyalgia need to be investigated.

4.2.6 Capsaicin

Capsaicin is a depletor of substance P and desensitises the neuronal cell membrane, resulting in inhibition of synthesis and release of substance P.[132] McCarty and coworkers[115] investigated the efficacy and safety of capsaicin in a double-blind, vehicle-controlled study of a 0.025% capsaicin cream in 45 patients with fibromyalgia. Capsaicin-treated patients reported significantly less tenderness in TP and a significant increase in grip strength. However, there were no statistically significant differences in the visual analogue scale of pain. The most common adverse effect was transient burning or stinging at the application site. Before recommending this drug in patients with fibromyalgia, additional positive studies are needed.

4.2.7 γ-Hydroxybutyrate

γ-Hydroxybutyrate (GHB; sodium oxybate) is a naturally occurring metabolite of the human nervous system, with the highest concentrations in hypothalamus and basal ganglia. Scharf and coworkers[116] evaluated the possible effect of GHB in 11 patients with fibromyalgia. There was a significant improvement in both fatigue and pain, with an increase in slow wave sleep and a decrease in the severity of the α-anomaly (the protrusion in slow wave sleep). This is a drug of interest with a potential place in the treatment of fibromyalgia. Further controlled studies are, however, needed to finally establish the clinical improvement and the polysomnographic changes observed in this study.

4.2.8 Growth Hormone

Bennett et al.[117] investigated the possible efficacy of somatropin (human growth hormone) in patients with fibromyalgia with low levels of IGF-1 using the Fibromyalgia Impact Questionnaire, TP score and global improvement. The 9-month study showed a significant improvement in all the examined parameters in the patients receiving growth hormone. Thus, despite being rather expensive, growth hormone appears promising in patients with fibromyalgia and low IGF-1 levels.

4.2.9 Nerve Growth Factor

Nerve growth factor (NGF) is reported to regulate the sprouting of sensory axons into neighbouring denervated territory and there exists selective expression of high-affinity NGF receptors (trkA re-

ceptors) on nociceptive afferents. NGF may thus function as a mediator of some chronic pain conditions including fibromyalgia. This assumption is supported by the work of Giovengo and coworkers[133] who measured higher NGF levels in the CSF of patients with fibromyalgia than in controls. McMahon and coworkers[118] have used a synthetic protein trkA-immunoglobulin (Ig)G to sequester endogenous NGF and block the survival effects of NGF on cultured sensory neurones. In this experimental study it was shown that administration of this molecule produces a sustained thermal and chemical hypoalgesia, and leads to a down-regulation of the sensory neuropeptide calcitonin gene-related peptide. Antagonists of NGF may therefore be of clinical use; however, no clinical studies have been undertaken to date.

4.2.10 Dopamine D_2-Receptor Antagonists

To consider the importance of suppressing hyperadrenergic stimuli as an inhibitor of deep, restorative sleep, the effect of adding pramipexole, a dopamine D_2-receptor antagonist was explored. A nonblind prospective trial of pramipexole was conducted in 166 consecutive patients meeting the ARC criteria for fibromyalgia. For those who tolerated the drug, mean pain score decreased from 24.5 to 11.4 with a mean dose of 1.55mg every hour. The results are promising and further studies are awaited.

4.2.11 NMDA-Receptor Antagonists

A probable pathogenic mechanism of chronic pain is sensitisation within the central nervous system that in part is mediated by the excitatory amino acids glutamate and aspartate binding to N-methyl-D-aspartate (NMDA) receptor. A number of antagonists to the NMDA receptor are antinociceptive in animal models but the substances are associated with significant dose-limiting adverse effects. Commercially available NMDA-receptor antagonists include ketamine, dextromethorphan, memantine and amantadine. The opioids methadone, dextropropoxyphene and ketobemidone are also antagonists at the NMDA receptor. The NMDA-receptor antagonists have a significant impact on the development of tolerance to opioid analgesics. Consequently, NMDA-receptor antagonists may represent a new class of analgesics and may have co-analgesic properties when used in combination with opioids.[134]

Quite a few trials on the effect of these types of drugs have been undertaken in patients with neuropathic, post-traumatic and other types of chronic pain. The results are variable. Several studies have shown substantial pain relief by administration of an NMDA-receptor antagonist,[135-141] whereas other studies have shown no or little beneficial effect.[142-144] A serious problem still to be resolved are the adverse effects. In a randomised, controlled trial of oral ketamine in patients with chronic pain,[124] only 14% of the patients had an extra analgesic response. The majority of patients complained of serious adverse effects. However, the disease spectrum of the patients in this study was highly heterogeneous, encompassing those with multiple sclerosis and post-stroke pain. An experimental study administering ketamine 0.3 mg/kg in 17 patients with fibromyalgia showed reduced muscle pain, temporal summation, and referred pain.[123] To our knowledge, only one clinical study on the effect of NMDA-receptor antagonists has been undertaken in patients with fibromyalgia.[125] The conclusion was that dextromethorphan added to tramadol may have a therapeutic role in a small subset of patients with fibromyalgia. Thus, NMDA-receptor antagonists should be evaluated in more studies including in fibromyalgia.

4.2.12 Serotonin 5-HT_3 Receptor Antagonists

Recently, clinical studies with serotonin 5-HT_3–receptor antagonists have been performed in patients with fibromyalgia. The 5-HT_3 receptor is a ligand-gated cation channel located in the central and peripheral nervous system. The antagonists available are potent and highly selective competitive inhibitors. They are rapidly absorbed and penetrate blood-brain barrier easily. Half-lives in healthy volunteers vary from 3 to 4 hours (ondansetron, granisetron) to 7 to 10 hours (tropisetron, dolasetron). 5-HT_3 receptors are present exclusively on peripheral and central neurones. In the periphery, the receptors are located on pre- and

postganglionic autonomic neurones and on neurones of the sensory and enteric nervous system. High densities of 5-HT3 receptors are located in the brain stem, cortex and dorsal horn ganglia. The central receptors are thus concentrated in regions that are involved in integration of the vomiting reflex and pain processing. Clinical efficacy was first established for chemotherapy-induced emesis.[145]

Serotonin receptors interact with other neurotransmitter systems to play an essential role in pain processing and endogenous pain suppression as a component of the monoaminergic descending inhibitory system with projections from the brain stem to the dorsal horn. The role of the 5-HT_3 receptors in this context is still not fully understood. Overall, the findings relating to the effect of stimulation or blockade of 5-HT_3 receptors on pain reactions are inconsistent and not yet convincing.[145]

A prospective, multicenter, double-blind, parallel-group, dose-finding study exploring efficacy and tolerability of tropisetron 5, 10 and 15 mg/day in 418 patients with fibromyalgia has been conducted.[127] A bell-shaped dose-response curve appeared with the highest efficacy of 5mg once daily. Treatment was well tolerated and prolonged clinical benefits were seen. In a randomised study, Haus and coworkers[128] compared treatment results with tropisetron at 10 days and 28 days. The pain reduction was most pronounced after 10 days with further improvement up to day 28. Psychometric tests showed significant improvements in depression and anxiety score, and functional symptoms improved with prolonged tropisetron treatment. In a pilot study, Müller and Stratz[129] investigated intravenous versus oral administration of tropisetron. A more rapid and profound reduction in pain was achieved after a single intravenous injection of 2mg than with oral tropisetron 5 mg/day. In individual patients, those who had previously experienced no reduction of pain after 10 days of oral tropisetron 5 mg/day responded to intravenous therapy. A more favourable and persistent effect on pain, combined with a simultaneous significant improvement in various vegetative and functional symptoms was achieved with 5 days treatment with intravenous tropisetron 2 mg/day.

Thus, 5-HT_3–receptor antagonists are promising as pain relievers in patients with fibromyalgia. Tropisetron was first reported to be generally well tolerated, except for the not infrequent occurrence of headache and obstipation. New studies are in progress, but lately fatal cases of obstipation have been reported,[146] which unfortunately may retard new research in this otherwise promising area.

Hopefully we will know much more about the possibilities of these drugs during the next few years.

5. Conclusions

Fibromyalgia is still an enigmatic condition with unknown aetiology and a pathogenesis that is only beginning to be understood. Moreover, it is most probably a heterogeneous condition, with several pathways to the final stage of chronic pain and fatigue. The wide spectrum of treatment modalities mirrors the complexity of the condition. Traditional pharmacological treatment alone has so far been rather discouraging. TCAs and to a certain extent SSRIs are the most efficacious drugs so far with respect to improvement of pain, while zopiclone has an effect on sleep disturbances, which rather often poses a serious problem to patients with fibromyalgia. The analgesic tramadol seems promising in relieving pain and further studies with this agent are awaited with interest.

On the other hand, the development of new drugs is now in progress, represented by 5-HT_3– and NMDA-receptor antagonists, growth hormone, NGF and possibly γ-hydroxybutyrate. Unfortunately the two first drug classes mentioned have serious adverse effects, while growth hormone is very expensive. Hopefully further studies with these fields will lead to a new generation of pain-modulating medicaments suitable for fibromyalgia.

Because of the probable multifactorial aetiology, a combination of several drugs will possibly be useful in the future. Most trials of nonpharmacological treatments were associated with significant improvement in coping and also with some

pain reduction. When compared, nonpharmacological treatment appears to be more efficacious in improving self-report of fibromyalgia symptoms than pharmacological treatment alone. The optimal intervention for fibromyalgia in the future would possibly include appropriate medication as needed for sleep and pain, and combined with nonpharmacological treatment such as specific exercise, instruction in relaxation techniques, attending support groups including participation in patient education programs, and cognitive behavioural therapy.

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