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EULAR evidence based recommendations for the management of fibromyalgia syndrome

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ABSTRACT

Objective: To develop evidence based recommendations for the management of fibromyalgia syndrome (FMS).

Methods: A multidisciplinary task force was formed representing eleven European Countries. The design of the study including search strategy, participants, interventions, outcome measures, data collection and analytical method was defined at the outset. A systematic review was undertaken with the keywords 'fibromyalgia', 'treatment or management' and 'trial'. Studies were excluded if they did not utilise the ACR classification criteria, were not clinical trials, or included patients with chronic fatigue syndrome or myalgic encephalomyelitis. Primary outcome measures were change in pain assessed by visual analogue scale (VAS) and fibromyalgia impact questionnaire (FIQ). The quality of the studies was categorised based on randomisation, blinding and allocation concealment. Only the highest quality studies were used to base recommendations on. When there was insufficient evidence from the literature, a Delphi process was used to provide basis for recommendation.

Results: One hundred and forty six studies were eligible for the review. Thirty nine pharmacologic intervention studies and 59 non-pharmacologic were included in the final recommendation summary tables once those of a lower quality or with insufficient data were separated. The categories of treatment identified were antidepressants, analgesics, and 'other pharmacological' and exercise, cognitive behavioural therapy, education, dietary interventions and 'other non-pharmacological'. In many studies sample size was small and the quality of the study was insufficient for strong recommendations to be made.

Conclusion: Nine recommendations for the management of FMS were developed using a systematic review and expert consensus.

INTRODUCTION

Fibromyalgia syndrome (FMS) is a common rheumatologic condition characterised by chronic widespread pain and reduced pain threshold, with hyperalgesia and allodynia. Associated features include fatigue, depression, anxiety, sleep disturbance, headache, migraine, variable bowel habits, diffuse abdominal pain and urinary frequency [1][2]. Although the precise pathogenesis remains unknown, peripheral and central hyperexcitability at spinal or brainstem level [3][4][5], altered pain perception [6] and somatisation [7][8] have been hypothesised and demonstrated in some patients.

The American College of Rheumatology (ACR) classification criteria for FMS [9] are the most commonly used in clinical and therapeutic research. The healthcare utilisation by patients with FMS is high averaging over \$2000 per patient per year [10], but it has been shown that positive diagnosis and management can reduce healthcare utilisation [11].

Although effective treatments are available [12][13][14] no guidelines exist for management of FMS. The objectives were to ascertain the strength of the research evidence on effectiveness of treatment of FMS and develop recommendations for its management based on the best available evidence and expert opinion to inform healthcare professionals.

METHODS

Participants

A multidisciplinary taskforce was formed consisting of 19 experts in FMS representing eleven European Countries.

Search strategy

A systematic search of Medline, PubMed, EmBASE, PsycINFO, CINAHL, Web of Sciences, Science Citation Indices, Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews using the key words: “fibromyalgia”, “treatment or management” and “trial” for all publications till the end of December 2005 was carried out. A manual search of the bibliographies of trials was undertaken to verify that all published trials were identified.

Inclusion criteria

Included studies had to be clinical trials using the American College of Rheumatology 1990 classification criteria for FMS [9] to select patients. Studies including patients with Chronic Fatigue Syndrome or Myalgic Encephalomyelitis, were excluded unless they were divided into separate comparator groups for analysis.

Assessment of literature

A ‘checklist’ method [15] was used to assess quality of each study. Data was tabulated using a customised data-extraction form. This included number of patients in each arm, randomisation and blinding status. Previous reviews have identified two main outcome measures: pain assessed by visual analogue scale (VAS) and function

assessed by the Fibromyalgia Impact Questionnaire (FIQ) [16][17]. The main measure of effect was the between group difference calculated from the mean change between the pre- and post- treatment values in these outcome measures. Where possible, effect size for the 'best' treatments in each category was calculated (averaged if there was more than one trial). Rosnow and Rosenthal's modified version of the Cohen's d calculation was used [18]. The thresholds used for interpretation were: values >0.2 = small, >0.5 = medium and >0.8 = large. The number needed to harm (NNH) was also calculated if possible, using withdrawal due to adverse event as the event. Additional information included; recruitment population; duration of disease, treatment and assessment; number of tender points; and myalgic score. Other outcome measures considered were also tabulated. If required data were recorded, but not presented, or not presented in a suitable format, the author was contacted wherever possible. If data was only provided in graphical format, this was extracted where possible. Data extraction was verified by a second committee member to ensure accuracy. Any discrepancies were re-evaluated.

Categorising evidence

Due to the large variability in outcome measures and assessments data could not be pooled to perform a formal meta-analysis. Therefore studies were classified according to their randomisation and blinding level. The highest quality study (randomized controlled trial) for each treatment class was used as a basis for the recommendations. The ranking was graded as (with 1 being highest):

1. Randomised controlled double-blind trials
2. Randomised, blinded crossover trials
3. Randomised single blind trials
4. Randomised open trials / Non-randomised single blind
5. Non-randomised open trials

Evidence for each recommendation was categorised according to study design and strength of each recommendation was classified according to the criteria previously published [19].

The recommendations were discussed at a final committee meeting and via email for a consensus to be reached. Delphi exercise was used to base recommendations on when limited evidence was found by systematic review. Agreement on the included recommendations was unanimous.

Publication Bias Analysis

Abstracts published between 2002 and 2005 inclusive in *Annals of Rheumatic Disease, Pain, Arthritis & Rheumatism* and *Journal of Musculoskeletal Pain* were reviewed to guard against non-inclusion of any negative studies that had not been fully published. If available, data was extracted. Any contradictory data would be included when forming the recommendations.

Future research plan

The committee proposed that these recommendations should be reviewed and updated in 4 years time, to see if a) quality of trials and reporting in FMS had improved and b)

if there was new evidence to suggest recommendation of new treatments, or to alter the recommendations of treatments already included.

RESULTS

Research evidence identified

In the preliminary search, 508 studies were identified. Table 1 demonstrates how these were shortlisted.

No. rejected	Reason	Total
	Total identified	508
171	Not relevant	337
72	Reviews	265
29	Not ACR criteria	236
20	Not clinical trials	216
19	Abstracts	197
8	No pain or function assessments	189
5	Follow-up data only	184
4	FMS combined for analysis	180
		Eligible clinical trials
19	Data recorded, but not given	161
4	Non-English language - translations reveal to be ineligible	157
12	Non-English language – translations not available	145
+1	Identified from bibliographies	146

Table 1. Study breakdown from initial literature search.

The 146 eligible clinical trials included 59 pharmacological and 87 non-pharmacological (including multidisciplinary). Studies were further subdivided into treatment interventions and the highest quality studies from each intervention were selected to be the basis for recommendations, (table 2).

Intervention		Total no.	No. omitted	No. included	Quality of studies included	Reasons for excluding
Analgesics	Systemic	6	3	3	2=1, 1=2 (crossover)	1=too few subjects, 2=no control
	Topical	3	1	2	Both = 1	No control + combined FMS & MFP
Antidepressants	Tricyclic antidepressants	8	2	6	4=1, 2=2 (crossover)	Single blind
	Selective serotonin reuptake inhibitors	5	1	4	3=1, 1=2 (crossover)	No control
	Dual re-uptake Inhibitors	5	2	3	All=1	No control
	5HT2/3 Antagonists	10	6	4	3=1, 1=2 (crossover)	No control
	Monoamine oxidase inhibitors	4	2	2	Both=1	1=data not clear, 1=quasi randomised, single blind
Others	Triiodothyronine	3	0	3		
	Individuals	16	4	12	5=1, 4=2, 3=5	No results
Exercise	Pool-based	2	0	2	1=3, 1=4	-
	Aerobic	11	1	10	4=3, 6=4	No results
	Strength	4	1	3	1=3, 2=4	Open, not randomised
	Mixed	4	3	1	4	2=open not randomised, 1=no data
Education / CBT	Education	2	0	2	4	-
	Education +Exercise	8	1	7	1=3, 7=4	No control
	CBT	2	0	2	5	-
	CBT + Exercise	5	2	3	1=3, 2=4	Open, not randomised
	Combination	8	8	0		Low quality & limited data
Dietary		7	3	4	1=1, 1=4, 2=5	No data
Others	Physiotherapy	4	2	2	1=3, 1=4	No data & no control
	Balneotherapy	4	0	4	All=4	-
	Laser/light	2	0	2	Both=3	-
	Acupuncture	4	1	3	1=1, 1=3, 1=4	No data
	Magnets	2	0	2	Both=1	-
	Homeopathy	3	3	0	-	No data
	Individuals	14	3	11	2=1, 1=3, 3=4, 3=5	No data

Table 2. Breakdown of the short listed studies to base recommendations on, and those eliminated from further analysis.

Sensitivity Analysis

Effect size and NNH for the interventions recommended were calculated where possible (table 3).

Pharmacological			
Intervention	Effect size (95% confidence interval)		NNH
	Pain	Function	
Amitriptyline	1.033 (-0.393, 2.458) [20][21][22][23]	0.51 (-12.847, 13.868) [22] [24]	45.56 (-36.06, 127.17)
Dual re-uptake	0.341 (-0.644, 1.323) [25][26]	0.438 (-2.77, 3.647) [25] [27]	9.91 (6.87, 12.96)
MAOIs	0.822 (-0.024, 1.669) [22] [23]	Can't calculate	24.29 (2.93, 37.14)
SSRIs	0.824 (-0.417, 2.064) [22] [28][29]	0.536 (-7.323, 8.395) [22] [28][29]	8.25 (5.8, 10.7)
Tramadol	0.657 (-0.276, 1.589) [30][31]	0.189 (-6.312, 6.689) [30][31]	35 (only one study)
Tropisetron	0.799 (-0.884, 2.482) [32]	Can't calculate	27.47 (only one study)
Pramipexole	0.736 (-0.556, 2.028) [33]	0.606 (-7.073, 8.285) [33]	-21 (only one study)
Non-pharmacological			
Pool based Exercise	0.437 (-0.659, 1.532) [34][35]	0.495 (-1.68, 2.67) [34]	-8 (one study)
Balneotherapy	1.408 (0.684, 2.133) [36][37][38]	2.085 (-5.334, 9.979) [36] [38]	Can't calculate
Aerobic Exercise	0.377 (-0.794, 1.549) [39][40][41][42][43]	0.062 (-5.174, 5.297) [39][40][41][42]	-13.5 (one study)
Strength training	2.225 (1.159, 3.292) [44][45]	1.031 (-29.197, 31.259) [44] [46]	16.15 (one study)

Table 3. Effect size calculated using modified Cohen's d method for recommended treatments where data available.

EULAR Recommendations

From these tables the following recommendations were made (table 4).

Recommendation	Level of Evidence	Strength
General		
Full understanding of fibromyalgia requires comprehensive assessment of pain, function, and psychosocial context. Fibromyalgia should be recognised as a complex and heterogeneous condition where there is abnormal pain processing and other secondary features.	IV	D
Optimal treatment requires a multidisciplinary approach with a combination of non-pharmacological and pharmacological treatment modalities tailored according to pain intensity, function, associated features such as depression, fatigue and sleep disturbance in discussion with the patient.	IV	D
Non-Pharmacological Management		
Heated pool treatment with or without exercise is effective in fibromyalgia.	IIa	B
Individually tailored exercise programmes including aerobic exercise and strength training can be beneficial to some patients with fibromyalgia.	IIb	C
Cognitive behavioural therapy may be of benefit to some patients with fibromyalgia.	IV	D
Other therapies such as relaxation, rehabilitation, physiotherapy and psychological support may be used depending on the needs of the individual patient.	IIb	C
Pharmacological Management		
Tramadol is recommended for the management of pain in fibromyalgia.	Ib	A
Simple analgesics such as paracetamol and other weak opioids can also be considered in the treatment of fibromyalgia. Corticosteroids and strong opioids are not recommended.	IV	D
Antidepressants: amitriptyline, fluoxetine, duloxetine, milnacipran, moclobemide and pirlindole, reduce pain and often improve function, therefore they are recommended for the treatment of fibromyalgia.	Ib	A
Tropisetron, pramipexole and pregabalin reduce pain and are recommended for the treatment of fibromyalgia.	Ib	A

Table 4. EULAR Recommendations for the management of fibromyalgia.

Assessment of Recommendations

There was no weighting in terms of order of the recommendations. √ denotes recommendation derived from expert opinion.

√ *Full understanding of fibromyalgia requires comprehensive assessment of pain, function, and psychosocial context. Fibromyalgia should be recognised as a complex and heterogeneous condition where there is abnormal pain processing and other secondary features.*

This is based on expert opinion. It is important to recognise that FMS is a heterogeneous condition comprising a range of symptoms and features, effective management must take all of these factors into account. The nociceptive system also has connections with the stress regulating, immune, and the sleep system in the limbic brain. It is these links that probably lead to the 'syndrome' incorporating numerous symptoms and features.

√ *Optimal treatment requires a multidisciplinary approach with a combination of non-pharmacological and pharmacological treatment modalities tailored according to pain intensity, function, associated features such as depression, fatigue and sleep disturbance in discussion with the patient.*

This is a logical progression from the first recommendation. It represents general practice, but is based solely on expert opinion. As FMS is polysymptomatic, lacking one treatment that acts on all symptoms, a multidisciplinary approach tailored to the needs of the individual is often required. This may need to include self-management via patient education [47][48] [49]. Only two multidisciplinary trials were short-listed in the summary tables for further analysis [50][51]. Other reviews have supported the use of multidisciplinary treatment [47][48], but highlighted the lack of high quality trials in this area [48] [52].

Heated pool treatment with or without exercise is effective in fibromyalgia.

Heated pool treatment or balneotherapy was reported to be effective in improving pain and function. Three of 5 trials included exercise in the intervention [34][35] [38] (two positive for function and two for pain). Of those without exercise, two were positive for pain and function [34] [36]. In the third trial only the heated pool treatment group improved in pain, but no comparison was made to the control. Function was not assessed [37]. Drop out for adverse events was very low. Sample sizes ranged from medium to large. Three of the studies restricted the use of medications, (not stated in the remaining two). The fairly high quality of this small number of studies with positive results has led to this recommendation and there is agreement with previous reviews [47][48].

√ *Individually tailored exercise programmes including aerobic exercise and strength training can be beneficial to some patients with fibromyalgia.*

This is based largely on expert opinion with a combination of some experimental evidence and previous reports.

For aerobic exercise the majority of trials were open (7/11). The best quality were a randomized, assessor blind 12 week study by Richards et al. 2002, with large sample size [53], and a smaller randomised single blind study by Valim et al 2003 [42]. Valim et al. reported an improvement in VAS pain and FIQ compared to control. Richards et al. did not report significant between group improvements in either of our chosen outcome measures although the FIQ score did improve more in the treatment group, and significant between group improvements were seen at 12 months follow-up. All three strength training studies were randomised but only one single blind. This had no significant between group differences in pain or function, although both improved in the exercise group only [44].

In general the quality of studies among exercise trials was considerably variable. Blinding and/or control was frequently inadequate. Those that did show some differences in favour of exercise used usual activity and care for their controls [40] [41] (with the exception of Valim et al. who had a stretching control group [42]). The majority of exercise studies asked for participants not to change their medication intake whilst on the trial (9),

Although evidence in the literature was poor, the committee felt that given the safety and benefit of exercise to general health exercise should be included as a recommendation. The poor quality of the trials and our predetermined outcome measures were likely precluding positive outcomes from being shown. In previous reviews, exercise has been recommended [12] [16][17] [47][48] with aerobic exercise gaining the most support. It is likely that different forms of exercise would suit different subgroups of patients, hence these programmes should be tailored to the individual.

√ ***Cognitive behavioural therapy may be of benefit to some patients with fibromyalgia.***

This is based on expert opinion. The only two studies identified for our review with pure cognitive behavioural therapy (CBT) were of poor quality; neither had a control group, both allowed patients to remain on their usual medication and only one used either of our predetermined outcome measures.

This is another area in which the poor quality of trials has masked what experts believe to be a realistic reflection of possible benefits. Whilst previous review work has also been hampered by the inadequacy of research in this field, strong evidence has been reported for CBT with positive results for pain & function [47].

√ ***Other therapies such as relaxation, rehabilitation, physiotherapy and psychological support may be used depending on the needs of the individual patient.***

This is based on expert opinion and some experimental evidence. Two studies of moderate quality were identified for physiotherapy. An open study [54] for connective tissue massage which had larger subject numbers (25 control and 23 treated) and lasted 10 weeks, reported improvement in both pain and function compared to control. Other relaxation and rehabilitation techniques are recommended

due to expert opinion. Clinical trial evidence is lacking in these areas although reviews report some benefits [47].

Tramadol is recommended for the management of pain in fibromyalgia. Simple analgesics such as paracetamol and other weak opioids can also be considered in the treatment of fibromyalgia. Corticosteroids and strong opioids are not recommended.

Regarding tramadol, two randomised controlled trials were identified as eligible for the review [30][31]. One was a high quality study of large sample size and 13 weeks duration [31]. The second was preceded by an open label study and only included responders [30]. Bennett et al. reported positive effects for pain and function, and Russell et al. reported improved pain levels but no change in function. There was no difference between placebo and treated group for adverse event withdrawals (high but non-serious). Bennett et al. restricted concomitant medications, but Russell et al. disallowed sedative hypnotics only. Tramadol should be used with some caution due to the possibility of typical opiate withdrawal symptoms with discontinuation and the risk of abuse and dependence [55].

The recommendation for simple analgesics and other weak opioids is based mainly on expert opinion due to insufficient data [56].

The negative recommendation for use of strong opioids and corticosteroids is based on expert opinion. These medications have significant long-term side effects and no clinical trials were identified in FMS. Previous reviews support our recommendation [47] [57].

Antidepressants: amitriptyline, fluoxetine, duloxetine, milnacipran, moclobemide and pirlindole, reduce pain and often improve function therefore they should be considered for the treatment of fibromyalgia.

Four out of 5 trials of amitriptyline that assessed VAS pain had positive outcomes. Only two used the FIQ, one positive. However, it is important to note, that as highlighted in previous reviews [14], the only trial that lasted longer than 12 weeks did not show a significant improvement in pain compared to control [58]. Two trials assessing fluoxetine reported positive outcomes for both pain and function [22] [28]. These trials were of moderate to high quality, reasonable samples sizes and 6 and 12 weeks duration. Duloxetine improved function in two trials and pain in one [25] [27]. The milnacipran trial reported an improvement in pain [26]. These were all large, high quality trials of 12 weeks duration. Moclobemid and pirlindole were assessed in one trial each, both of high quality and with improvements in pain [21] [23]. FIQ was not assessed in either trial. For all the trials withdrawals due to adverse events were generally low and non-serious.

In general these trials excluded other medications prescribed for FMS, with the exception of paracetamol. The only exception was the Arnold et al. 2002 trial which also allowed NSAIDs [28]. Previous reviews have agreed with the recommendation of antidepressants with the strongest evidence for amitriptyline (or tricyclic antidepressants) [12] [14] [47] [57].

Tropisetron, pramipexole and pregabalin reduce pain and should be considered for the treatment of fibromyalgia.

Two tropisetron clinical trials were eligible. One had positive results for pain at a dose of 5mg [59]. Späth et al. 2004 did not report significantly positive results, but sample size was small and there was a positive trend in the treated group [32]. FIQ was only assessed in the trial by Späth et al. 2004 with negative results therefore no firm comment can be made on this outcome measure. Fäber et al. 2000 made no comment on whether concomitant medications had been controlled, but Späth et al. disallowed antidepressants, tranquilizers and sedatives. This treatment appears well tolerated. These were short term studies, so further research into longer term effects is required.

One trial for pramipexole was positive for both pain and function [33]. Frequency of mild/moderate adverse events was high and this trial did not restrict concomitant medications, although dosages were kept stable. A monotherapy trial is required for more conclusive assessment of effect.

One trial reported pregabalin 450mg reduced pain, but FIQ was not assessed [60]. Dropouts due to adverse events were largely classed mild to moderate in severity. All medications for pain and sleep disorders were restricted, with the exception of paracetamol.

These are recent studies and suggest further research into the use of these promising medications for FMS. Previous reviews have also mentioned their potential benefit [47] [57] (neither include the pramipexole study as this was not published).

DISCUSSION

These EULAR recommendations are based on expert opinion and changes in pain assessed by VAS and function assessed by the FIQ in clinical trials. Positive effects in other outcome measures were not considered, neither were pain or function if assessed by different instruments. Consequently some studies were excluded from our review due to not using these outcome measures, or not presenting the data. Although other instruments might be more sensitive in FMS it was decided that setting a standard for outcome measures was vital so that comparisons could be made fairly between trials and therefore using those most frequently reported allowed better analysis [47] [61]. Previous reviews have used different inclusion/exclusion criteria and/or assessed more or different outcome measures producing different evidence e.g. [16] [47][48].

The high variability in outcome measures used, reporting of results, as well as the inadequacy of methodological quality were barriers to conducting meta-analysis [12] [14] [16][17] [57] [62]. This led to difficulties in producing strict evidence based recommendations. In some areas evidence is lacking due to the poor quality of the studies, where expert opinion suggests otherwise, e.g. exercise.

Outcome measures may be decided according to desired treatment effect. Non-pharmacological interventions have previously been suggested to have a significantly better effect on function than medications [62], reflected by its wider assessment in these studies. However, if this outcome measure is not frequently assessed in pharmacological trials, results could be biased.

Guidance on how to conduct good RCTs in FMS, including standardised outcome measures and validated, sensitive instruments is important for future research.

For the treatments that were recommended, effect sizes generally range from medium to high. Although these results give an indication of the efficacy of each treatment, they should be interpreted with some caution as they were only calculated where data was available and could be biased by factors such as whether or not the outcome measure was assessed. We have not collected any information on the cost effectiveness of these treatments. Further analysis of disease duration and baseline values does not reveal any obvious pattern that would affect the outcomes of this review. Review of the abstracts published between 2002 and 2005 revealed no conflicting evidence to that derived from the published articles identified.

The assessment of strength of evidence tends to favour pharmacological studies as double blinding and placebo controls are impossible in many non-pharmacological studies. However, most non-pharmacological interventions are safe and have other health benefits. These important factors were taken into account in formulating these recommendations.

Summary

These recommendations are the first to be commissioned for FMS, although previous reviews have addressed the area [47] [62]. The standard operating procedures published by EULAR [63] were followed. They will be updated every 5 years and it is hoped that good quality clinical trials in this area will add to the evidence currently available. These recommendations should assist health care providers, with a secondary intention to incorporate information into materials for patients.

The 9 recommendations included 8 management categories, 3 of which had strong evidence from the current literature, and 3 were based on expert opinion.

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Competing Interests

The following authors have no competing interests to declare:

L. Arent-Nielsen, H. Bliddal, S.F. Carville, J. da Silva, B. Danneskiold-Samsøe, F. Dincer, K. Longley, G. McCarthy, M. Puszczewicz, P. Sarzi Puttini and A Silman.

Declarations:

Francis Blotman has been reimbursed by Laboratoires Procter and Gamble, Sanofi-Aventis, Roche and Bristol Meyers Squibb for attending medical conferences and had honorarias for speaking for Laboratoires Pierre Fabre, Servier and Roche.

Jaime Branco has been paid by Pierre Fabre and Pfizer for running educational programmes and for speaking at international conferences and reimbursed by Eli Lilly for attending international conferences.

Dan Buskila has been reimbursed by Pierre Fabre Company, the manufacturer of Milnacipran, for attending several symposiums and by Pfizer for consulting.

Ernest Choy has served on advisory panels of Pierre Fabre Medicament, Jazz Pharmaceutical, Allergan and Pfizer. Ernest Choy has also lectured in meetings organized by Pierre Fabre Medicament, Eli Lilly and Pfizer. The Rheumatology Department received a research grant from Pierre Fabre Medicament.

Chris Henriksson has participated in symposia organized by Laboratoires Pierre Fabre and received reimbursement for participation. She has also received fees for written material in proceedings from these symposia.

Karl Henriksson has participated in symposia organized by Laboratoires Pierre Fabre and received reimbursement for participation. He has also received fees for written material in proceedings from these symposia. He has held a lecture on pain mechanisms and received a fee from Pfizer.

Dr Kosek has participated as a consultant in advisory board meetings (total of 4) for the following pharmaceutical companies; Pfizer, Wyeth and Pierre Fabre. She gave a speech on a satellite symposium organized by Pfizer. She has currently research collaboration with Pierre Fabre.

Serge Perrot has been paid by Pfizer, Eli Lilly, Grunenthal, Pierre Fabre and Sanofi Aventis for running educational programmes and participating in advisory boards.

Michael Spaeth has served on advisory panels of Pierre Fabre Medicament, Jazz Pharmaceuticals and Allergan. Michael Spaeth has also lectured in meetings organized by Novartis, Pierre Fabre Medicament and Lilly.

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