Review

Biology and therapy of fibromyalgia

Evidence-based biomarkers for fibromyalgia syndrome

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Abstract

Researchers studying fibromyalgia strive to identify objective, measurable biomarkers that may identify susceptible individuals, may facilitate diagnosis, or that parallel activity of the disease. Candidate objective measures range from sophisticated functional neuroimaging to office-ready measures of the pressure pain threshold. A systematic literature review was completed to assess highly investigated, objective measures used in fibromyalgia studies. To date, only experimental pain testing has been shown to coincide with improvements in clinical status in a longitudinal study. Concerted efforts to systematically evaluate additional objective measures in research trials will be vital for ongoing progress in outcome research and translation into clinical practice.

Introduction

Fibromyalgia (FM) is a chronic condition characterized by widespread pain and tenderness on examination, along with symptoms of nonrestorative sleep, fatigue, and cognitive difficulties. Recent familial studies have suggested an underlying genetic susceptibility on which environmental factors trigger the expression of symptoms [1,2]. Despite the myalgias that patients experience, no abnormality in muscle has been reliably found [3]. Instead, aberrant pain and sensory processing probably caused by alterations in the central nervous system function are being consistently recognized in FM and related syndromes. Investigations into the autonomic nervous system and the hypothalamic–pituitary–adrenal axis also suggest a role of these stress–response systems in vulnerability to FM or in symptom expression in FM.

Our improved understanding of FM has stimulated the search for biomarkers to be used to identify individuals susceptible to the syndrome, for the diagnosis of FM, for objective measures of disease activity, or as surrogate endpoints of clinical trials. Using an expert panel from the FM workshop of the Outcome Measures in Rheumatology (OMERACT), a list of potential objective measures was first developed. Studies evaluating the measures were then methodically compiled by systematic review of the literature using a search for FM and the specific objective measure of interest. The databases searched included MEDLINE (1966 to 2006), PubMed (1966 to 2006), CINAHL (1982 to 2006), EMBASE (1988 to 2006), Healthstar (1975 to 2000), Current Contents (2000 to 2006), Web of Science (1980 to 2006), PsychInfo (1887 to 2006), Science Citation Indexes (1996 to 2006), and/or Cochrane Collaboration Reviews (1993 to 2006). The resulting published studies were used as the basis for the review.

Genetics

Increasing evidence supports a genetic predisposition to FM. First-degree relatives of individuals with FM display an eightfold greater risk of developing the syndrome than those in the general population [1]. As such, a genetic study using multicase families has been completed that identified an HLA linkage not yet replicated [4].

Polymorphisms in the serotonergic 5-hydroxy tryptamine 2A receptor (T/T phenotype), the serotonin transporter, the dopamine 4 receptor and the catecholamine *o*-methyl transferase enzyme have also been evaluated in patients with FM [5-10]. Notably, these polymorphisms all affect the metabolism or transport of monoamines, compounds that have a critical role in both sensory processing and the human stress response. With the exception of the catecholamine *o*-methyl transferase finding and the dopamine-4-receptor gene polymorphism, however, which have not been replicated or

DNIC = diffuse noxious inhibitory control; ERP = event-related potential; FM = fibromyalgia; fMRI = functional magnetic resonance imaging; IL = interleukin; SPECT = single-photon emission computed tomography.

Table 1

Genetics in fibromyalgia

Reference	Year of study	Number of subjects	Number of control individuals	Objective measure	Findings
Bondy and colleagues [5]	1999	168 FMS	115	5-HT2A, T102C polymorphism	Different from control, but not significant for specific allele
Gürsoy and colleagues [6]	2001	58 FMS	58	5-HT2A, T102C polymorphism	Not significant
Gürsoy and colleagues [7]	2003	61 FMS	61	COMT haplotype	Over-representation of LL variant (low activity). Similar to migraine and TMD
Offenbaecher and colleagues [8]	1999	62 FMS	110	5-HTT	One positive for over-representative SS genotype, one negative study. Suggestion that any association might be related to comorbid psychology
Gürsoy [9]	2002	53 FMS	60 mentally healthy	5-HTT	
Yunus and colleagues [4]	1999	40 multicase families		HLA	Linkage to HLA
Buskila and colleagues [10]	2004			Dopamine D_4 receptor polymorphism	Decrease in the frequency of the seven-repeat allele in exon III of the D_4 receptor gene associated with fibromyalgia. Finding associated with low novelty-seeking personality

COMT, catecholamine *o*-methyl transferase; FMS, fibromyalgia syndrome; 5-HT2A, serotonergic 5-hydroxytryptamine 2A receptor (T/T phenotype); 5-HTT, serotonin transporter; TMD, temporomandibular disorder.

refuted, the other findings initially noted were generally not found in subsequent studies [4-10]. In some cases, the findings in FM were found when all individuals with this disorder were studied, but not when individuals free of psychiatric comorbidities were studied, suggesting that some of the above findings may track more closely with psychiatric comorbidity than inherent features of FM. Other candidate genes evaluated but not shown to be associated with FM are presented in Table 1.

Evoked (experimental) pain measures

Even before the establishment of the American College of Rheumatology criteria for FM in 1990, which require both widespread pain and tenderness, investigators have used psychophysical pain testing to learn more about the nature of this condition. In fact, the early findings that the tenderness in FM was detectable throughout the body, rather than just confined to areas of tender points or muscle, was a hallmark finding that led investigators to believe this was a central nervous system pain amplification syndrome [11]. These measures are only relatively objective since they require patient self-report, but tender points do clearly measure a phenomenon that is independent from spontaneous, clinical pain.

Numerous experimental pain studies have evaluated methods of quantifying the sensory experience of pain. Various groups using an assortment of devices that produce several stimuli have assessed the pain threshold and have attempted to quantify the pain experience in FM. A review of the investigated modalities gives the greatest support for the use of the tender point intensity/index, pressure pain thresholds, or heat pain thresholds as objective measures of the degree of hyperalgesia (increased pain to normally painful stimuli) and allodynia (pain in response to normally nonpainful stimuli) of an individual. Another consistent finding has been an absence of descending endogenous analgesic activity in FM.

Tender point count

The American College of Rheumatology criteria for FM require that an individual has a certain degree of tenderness. A tender point count is performed by applying 4 kg pressure manually to 18 predefined tender points, and then asking the patient whether these areas are tender. A positive response is considered a tender point; if an individual has 11 tender points or more, this element of the case definition is satisfied.

The apparent close link between tenderness and FM has been well studied in both clinical trials of new therapies and in mechanistic studies. In a number of longitudinal randomized, placebo-controlled trials, improvements in clinical pain have corresponded with a significant change in tender point counts or in the tender point index [12-14]. In contrast, other studies did not show a correspondence between improvements in clinical pain and tender point counts [15-20].

The discrepancies between studies could either be because the therapies did not improve tenderness or because tender points are not a good measure of tenderness. Both factors are likely to play a role since, in certain studies where multiple measures of the pain threshold were used, tender point counts did not significantly improve whereas other measures did [21,22]. Moreover, other studies have shown that tender points are not a pure measure of tenderness. For example, there is a strong correlation between tender point counts and measures of distress in population-based studies [23]. Tender points have also been demonstrated to be biased by cognitive and emotional aspects of pain perception, whereas other measures of tenderness are much less so (see below) [24]. Improvements in tender point counts in some previous FM trials therefore possibly occurred because of improvements in distress, rather than because of inherent improvements in pressure pain threshold. Finally, tender points are often not continuously distributed in samples; rather, most people have either very few or nearly 18 tender points. As such, many investigators do not feel that tender point counts are useful to assess tenderness, and have instead turned to psychophysically and statistically superior measures.

Pressure pain thresholds

Directly measuring pressure pain thresholds is an alternative method of documenting tenderness. Devices that measure pressure pain thresholds have been used to demonstrate a left-shift and lowered pressure pain thresholds in patients with FM compared with control individuals, and this finding is noted anywhere in the body, both at tender points and in areas previously considered control points (Table 2). These findings suggest to many investigators that the term control points should be abandoned, or replaced by a term such as high-threshold tender point, since FM patients are just as tender in these regions relative to healthy control individuals.

Many of these studies initially used commercial devices or dolorimeters to deliver continuously increasing pressure via blunt probes. These measures were found to be sensitive to psychophysical and psychological biases, however, slightly similar to tender point counts using digital palpation (reviewed in [25]). For instance, the rate of increase of stimulus pressure, controlled by the operator, and patient distress were both shown to influence the pain threshold [24,26]. To minimize the bias, more sophisticated paradigms using random delivery of pressures have been developed and investigated [27,28] (Table 3). Random delivery may be less sensitive to certain influences, but it is not free of bias. For instance, in a study by Petzke and colleagues, FM patients reported higher pain during random delivery than during ascending – possibly due to a perceived lack of control [28].

A recent longitudinal study compared the three different evoked measures – tender point counts, the dolorimeter (ascending pressure paradigm), and the multiple random staircase (random pressure paradigm) – with clinical reports of pain improvement [21]. Although both clinical pain measures improved during the course of the study involving acupuncture, only one of the evoked measures – the multiple random staircase measure, which presented stimuli to individuals in an unpredictable fashion – improved after treatment. These results suggest that, of the different methods, the random stimuli paradigm may be more likely to systematically change over time. Interpretation of the results is nonetheless limited and will need to be reproduced and examined using other treatment modalities.

Heat, cold, and electrical stimuli

In addition to the heightened sensitivity to pressure noted in FM, other types of painful stimuli also are judged more painful by these patients. A decreased heat pain threshold in FM patients as compared with control individuals has been shown by multiple groups [28-30] (Table 4). A reduced cold pain threshold has been reported by one group in two different studies [30,31]. Sensitivity to warmth and the ability to detect electrical stimuli do not appear to be discriminative measures at this time.

Diminished diffuse noxious inhibitory control

In the process of understanding altered evoked pain sensitivity present in FM, evaluation of the intrinsic analgesic systems has uncovered another potential biomarker: diminished diffuse noxious inhibitory control (DNIC). DNIC testing in both animals and humans involves testing the pain threshold at baseline, and then administering an acutely painful stimulus that leads to a systemic analgesic effect, presumably by activating endogenous analgesic systems.

Several studies by different groups, using different conditioning stimuli (the acute noxious stimulus) and test stimuli (the stimulus used to measure pain threshold at baseline and following the acute, noxious stimulus), have indicated a deficiency of DNIC in individuals with FM. Diminished DNIC was observed in four cross-sectional studies by different groups that used variable test and conditioning stimuli [31,32-34] (Table 5). Diminished DNIC has also been noted in other types of chronic pain; that is, temporomandibular disorder and hip osteoarthritis [35,36]. The normalization of DNIC after hip osteoarthritis surgery suggests it may be an objective measure of chronic pain that can change over time with treatment [36].

Functional neural imaging

Functional neural imaging enables investigators to visualize how the brain processes the sensory experience of pain. The primary modes of functional imaging that have been used in FM include functional magnetic resonance imaging (fMRI), single-photon emission computed tomography (SPECT), and positron emission tomography.

fMRI studies evaluating pain processing have the strongest current evidence of the functional imaging studies, because

Table 2

Pressure pain thresholds in fibromyalgia

Reference	Year of study	Number of FM patients	Number of control individuals	QST	QST method	Findings
Staud and colleagues [102]	2005	11	12	PPT: affected and CP	ASC	Decreased PPT (opposite of HC) after exercise
Sandberg and colleagues [103]	2005	19	19 HC, 7 TM	PPT: TP	ASC	FM, TM with decreased PPT
Montoya and colleagues [104]	2005	12	12	PPT, ERP	ASC	No difference (trend toward FM with decreased PPT). HC with decreased PPTs with repeat stimuli in one session. Decreased PPT for left hand versus right hand. FM decreased PPT in second assessment period (after EEG)
Laursen and colleagues [105]	2005 2005	10 FM/whiplash, 10 RA, 10 CLBP, 10 endometriosis	41	PPT: TP and CP	ASC	FM/whiplash, RA, endometriosis, CLBP with decreased PPT. Correlation between pressure hyperalgesia at lowest PPT sites and physical function impairment and mental health found
Landis and colleagues [51]	2004	37	30	PPT: TP and CP	ASC	FM women with decreased PPT. PPT correlated with sleep spindle incidence and duration
Landis and colleagues [106]	2004	33	37	PPT: TP	ASC	FM women with decreased PPT
Maquet and colleagues [107]	2004	20	50 females, 50 males	PPT: TP	ASC	HC with decreased intraindividual variation (FM w/24%). HC females with decreased PPT compared with HC males. FM with decreased PPT compared with HC females. No difference between dominant and nondominant hands. PPT reproducibility and discrimination optimal at gluteal and knee
Geisser and colleagues [108]	2003	20	20	PPT: TP and CP	ASC	FM with decreased PPT (more statistically significant than HPT). Catastrophizing correlated with decreased PPT. Depression associated with increased PPT
Yoldas and colleagues [47]	2003	11	10	PPT and ERP	ASC	FM reduced P300 amplitude, correlated well with PPT
Ernberg and colleagues [109]	2003	18	n/a	PP: over masseter	ASC	No difference (trend toward decreased PPT after antagonist)
Carli and colleagues [110]	2002	145 (FM, CFS, WP, MPTE, MP)	22	PPT: CP and TP, HPT, CPT, cold pressor test, ischemic tourniquet test	ASC	FM with decreased PPT (CFS, MPTE), HPT (CFS), cold pressor test (CFS), ischemic tourniquet test (CFS, MPTE, WP, MP) than HC
Hedenberg-Magnusson and colleagues [111]	2002	18	15 masseter myalgia	PPT: over masseter	ASC	Decreased PPT after treatment in both groups. Correlated with symptoms
Ernberg and colleagues [112]	2000	12	12 HC, 12 RA	PPT: masseter	ASC	FM with decreased PPT
Graven-Nielsen and colleagues [113]	2000	15 FM ketamine responders	Placebo	EPT, PPT: TA muscle, PPT and pain tolerance: 3 TPs	ASC	Increased PPT at TA muscle, pain pressure tolerance after ketamine compared with placebo. Noted improvement in symptoms
Ernberg and colleagues [114]	2000	12	12	PPT	ASC	FM with no significant increase in pain or decrease in PPT. HC with increased pain and decrease in PPT after infusion
Ernberg and colleagues [115]	1999	18	10 HC, 17 local myalgia	PPT, pain tolerance: masseter	ASC	FM with decreased PPT associated with higher fraction of masseter to serum serotonin levels

Continued overleaf

Table 2

Continued

Reference	Year of study	Number of FM patients	Number of control individuals	QST	QST method	Findings
Kosek and Hansson [30]	1997	10	10	PPT	ASC	FM decreased PPT
Kosek and colleagues [31]	1996	10	10	PPT	ASC	FM decreased PPT
McDermid and colleagues [116]	1996	20	20 HC, 20 RA	PPT: TP and CP	ASC	FM decreased PT compared with RA, HC. RA decreased PT compared with HC
Kosek and colleagues [117]	1995	16	n/a	PPT at cream site	ASC	No difference in PPT after EMLA cream
Tunks and colleagues [118]	1995 1995	6	6 myofascial 6 pain controls, 6 HC	PPT: TP and CP	ASC	FM and myofascial pain was discriminated from HC by dolorimetry and palpation
Wolfe and colleagues [119]	1995	391	n/a	TPC, dolorimetry	ASC	PPT and TPC correlate with symptoms, but TPC correlates better
Gibson and colleagues [29]	1994	10	10	PPT: TP and CP	ASC	FM decreased PPT at CT and TP, but data not clearly shown
Lautenbacher and colleagues [120]	1994	26	26	PPT: CP and TP	ASC	FM decreased PPT
Granges and Littlejohn [121]	1993	60	60	PPT: TP and CP	ASC	FM decreased HPT, PPT, CPT in CP and TP
Lautenschlager and colleagues [122]	1991	47	n/a	PPT: TP and CP	ASC	Body diagram correlated better with dolorimetric findings than visual analog scale

ASC, ascending; CFS, chronic fatigue syndrome; CLBP, chronic low back pain; CP, control point; CPT, cold pain threshold; CT, cold perception threshold; EEG, electroencephalography; EMLA, local anesthetic cream; EPT, electrical pain threshold; ERP, event-related potential; FM, fibromyalgia; HC, healthy control individuals; HPT, heat pain threshold; MP, diffuse multiregional pain; MPTE, multiregional pain associated with at least 11 tender points; n/a, not applicable; PPT, pain pressure thresholds; QST, quantitative sensory testing; RA, rheumatoid arthritis; TA, tibialis anterior; TM, temporal mandibular disorder; TP, tender point; TPC, tender point count; WP, widespread pain.

they corroborate this left-shift in stimulus–response function (that is, hyperalgesia/allodynia) noted in FM. Specifically, several areas of the brain consistently show greater activation in FM patients than in control individuals given the same objective stimulus intensity – especially the secondary somatosensory cortex, insula and the anterior cingulate cortex. These findings have been noted in five cross-sectional studies by two different groups, using both pressure and heat stimuli [37,38] (Table 6). In the study by Giesecke and colleagues, the clinical pain intensity corresponded with an increase in the evoked regional cerebral blood flow [37]. The resting regional cerebral blood flow was evaluated by a third group in a longitudinal study using fMRI, and showed change after drug treatment [39]. These studies have also been useful in identifying differences in pain processing in individuals with and without psychological comorbidities, showing for example that depression does not seem to be influencing the magnitude of neuronal activation in sensory pain regions such as the secondary somatosensory cortex, whereas cognitive factors such as catastrophizing did influence the sensory intensity of pain [37,40].

Positron emission tomography imaging in FM has been reported in only a few studies with inconclusive results. The only positive study is a recent one showing there may be altered dopaminergic activity in FM [41].

SPECT imaging has been studied in four cross-sectional studies by different groups that consistently found reduced regional cerebral blood flow in the right thalamus of patients with FM (three of the four studies) [42-45]. No correlation between symptoms and findings were noted in the SPECT studies.

The consistent abnormalities seen in fMRI and SPECT studies suggest either of these methods might be useful to use as a biomarker, but longitudinal studies showing that improvements in symptoms coincide with normalization of functional imaging findings would be necessary to establish this role. The advantages of fMRI imaging over positron emission tomography and SPECT include the less invasive nature and the higher temporal and spatial resolutions of fMRI. Disadvantages of fMRI include the cost and prac-

Table 3

Pain pressure thresholds and fibromyalgia (FM): part 2

Reference	Year of study	Number of FM patients	Number of control individuals	QST	QST method	Findings
Petzke and colleagues [123]	2005	43	28	PPT: CP	ASC and random	FM patients report greater pain intensity but less relative unpleasantness compared with HC
Giesecke and colleagues [124]	2004	16	11 HC, 11 CLBP	PPT: CP	ASC and random	FM and CLBP with decreased PPT
Giesecke and colleagues [125]	2003	97	n/a	PPT: CP	ASC and random	FM subgroups: high and low tenderness. High or low control over pain correlated with cognitive and mood factors
Petzke and colleagues [28]	2003	43	28	PPT: CP, suprathreshold	ASC and random	FM decreased PPT, suprathresholds. Ratings from random method were consistently higher than those of the ASC method, possibly due to perceived lack of perceived control
Petzke and colleagues [24]	2003	39 FM, 6 CWP, 3 regional	28 no pain, 3 pain	PPT: CP and TP	ASC and random	Random method independent of psychological state. ASC correlated more with psychological state
Gracely and colleagues [126]	2002	16	16	PPT: CP	ASC and random	FM with decreased PPT
Chang and colleagues [27]	2000	11 IBS + FM	11 IBS, 10 HC	PPT: TP and CP	ASC and random	In random method, IBS + FM with more decreased PPT than IBS, but not HC. IBS with higher PPT than HC. In ASC, IBS similar PPT to HC
Bendtsen and colleagues [127]	1997	25	25	PPT: TP and CP, suprathreshold	Random	FM with left shift in response function for stimuli applied to tender point (trapezius m) only, no difference in CP compared with HC

ASC, ascending; CLBP, chronic low back pain; CP, control point; CWP, chronic widespread pain; HC, healthy control individuals; IBS, irritable bowel syndrome; PPT, pain pressure thresholds; QST, quantitative sensory testing; TP, tender point.

ticability as well as the inability to perform receptor–ligand studies that are possible with positron emission tomography and SPECT.

Event-related potentials

Cerebral potentials evoked by noninvasive stimulation provide a unique opportunity to investigate the functional integrity and magnitude of brain processing pathways. Expressing the ability of the human brain to discriminate, classify, and memorize the significance of exogenous stimuli, event-related potentials (ERPs) have been used as a marker of cognitive function in patients with psychiatric and neurological disorders. The electrical waveforms generated can be divided into late and early components, and the waveforms are designated by their polarity (P-positive, N-negative) and latency (timing of peak) after stimulus onset. Additionally, the amplitude – the size of the voltage difference between the component peak and a prestimulus baseline – is also quantified. Auditory, somatosensory, and visual ERPs have been evaluated in patients with FM in a few studies.

Among the ERPs evaluated to date, the P300 potential (most commonly generated by an auditory consciously attended stimuli) appears to be the most promising to differentiate FM patients from control individuals. The P300 wave is a late cortical neuropsychological event, the latency of which reflects the information processing speed and the amplitude of which expresses memory functions. A reduced P300 amplitude during an auditory discriminated-task paradigm has been significantly noted in FM patients as compared with control individuals in three cross-sectional studies by two different groups [46-48] (Table 7). All three studies also evaluated the P300 latency, but only the largest study by Alanoglu and colleagues noted an increase in P300 latency, a finding that may have not been found in the prior studies due to lack of power [46]. In the one of these three studies by Ozgocmen and colleagues that performed ERPs before and after treatment, 8 weeks of sertraline treatment led to an increase in the P300 magnitude [48].

These studies generally failed to show an association between the ERP findings and symptom severity, although

Table 4

Heat pain threshold, cold pain threshold, and electrical stimuli in fibromyalgia

Reference	Year of study	Number of FM patients	Number of control individuals	QST	QST method	Findings
Petzke and colleagues [28]	2003	43	28	HPT, suprathreshold	ASC and RAN	FM decreased HPT, suprathresholds. Pain ratings from RAN were consistently higher than ASC, possibly due to perceived lack of perceived control
Gibson and colleagues [29]	1994	10	10	WT and HPT	ASC and RAN	FM decreased HPT, no difference in WT
Staud and colleagues [102]	2005	11	12	Suprathreshold: affected and CP	ASC	Increased thermal pain ratings after exercise (opposite of HC)
Geisser and colleagues [108]	2003	20	20	HPT, WT	ASC	FM with decreased HPT. Higher intensity and unpleasantness for non-noxious stimuli
Kosek and Hansson [30]	1997	10	10	CT, WT, CPT, HPT	ASC	FM decreased CT in forearm. FM decreased CPT and HPT. No difference in WT
Lautenbacher and Rollman [34]	1997	25	26	HPT	ASC	FM had decreased HPT
Kosek and colleagues [31]	1996	10	10	CT, WT, CPT, HPT	ASC	FM decreased HPT, CPT. FM had decreased WT *only* at TP
Lorenz and colleagues [128]	1996	10	10	HPT	ASC	FM decreased HPT
Lautenbacher and colleagues [120]	1994	26	26	HPT	ASC	FM decreased HPT, no difference in WT
Lautenbacher and Rollman [34]	1997	25	26	Electrical	ASC	No difference in electrical detection/PT
Lautenbacher and colleagues [120]	1994	26	26	Electrical – CP and TP	ASC	FM decreased electrocutaneous *only* at TP, not control points
Arroyo and Cohen [129]	1993	10	10	Electrical detection, suprathreshold	ASC	No difference in electrical detection, FM decreased electrical tolerance

ASC, ascending; CP, control point; CPT, cold pain threshold; CT, cold perception threshold; FM, fibromyalgia; HC, healthy control individuals; HPT, heat pain threshold; PT, pain threshold; QST, quantitative sensory testing; RAN, random; TP, tender point; WT, warmth perception threshold.

Table 5

Diffuse noxious inhibitory controls (DNIC) in fibromyalgia (FM)

Reference	Year of study	Number of FM patients	Number of control individuals	Test stimuli (noxious stimuli)	Heterotopic conditioning noxious stimuli	Findings
Julien and colleagues [32]	2005	30	30 HC, 30 CLBP	Water bath, cold, noxious	Water bath, cold, noxious	Diminished DNIC in FM patients, not CLBP
Staud and colleagues [33]	2003	11	22 females, 11 males	Wind up	Water bath, heat, noxious	Diminished DNIC in female HC and female FM patients
Kosek and Hansson [30]	1997	10	10	CT, WT, HPT, CPT	Tourniquet	Diminished DNIC in FM patients
Lautenbacher and Rollman [34]	1997	25	26	Electrical pain threshold	Thermode tonic cold thermal, noxious and non-noxious	Diminished DNIC in FM patients
				Electrical detection		No difference

CLBP, chronic low back pain; CT, cold perception threshold; CPT, cold pain threshold; HC, healthy control individuals; HPT, heat pain threshold; WT, warmth perception threshold.

Table 6

Neural imaging in fibromyalgia (FM)

Reference	Year of study	Number of FM patients	Number of control individuals	Neural imaging	Description	QST	Findings
Giesecke and colleagues [37]	2005	7	7 MDD/FM, 7 HC	fMRI	QST evoked rCBF association to depression	Pressure pain MRS	Clinical pain intensity – associated with increased rCBF of insula bilaterally, contralateral ACC, prefrontal cortex. Symptoms of depression – not associated with increased rCBF of SI, SII; associated amygdala and contralateral anterior insula
Gracely and colleagues [40]	2004	15 high catastrophizers	14 low catastrophizers	fMRI	QST evoked rCBF association to catastrophizing	Pressure pain MRS	Both low and high with increased rCBF in contralateral insula, SI, SII, inferior parietal lobule and thalamus, ipsilateral S1, cerebellum, posterior cingulate gyrus, and superior and inferior frontal gyrus. High catastrophizers with unique activation in contralateral anterior ACC, contralateral ipsilateral lentiform
Giesecke and colleagues [124]	2004	16	11 HC, 11 CLBP	fMRI	QST evoked rCBF	Pressure pain MRS	In CLBP and FM patients, QST (equal pressure) increased rCBF of contralateral SI and SII, inferior parietal lobule, cerebellum, and ipsilateral SII. In HC, QST (equal pressure) activation of contralateral SII. Equal evoked equal pain associated with similar activation
Koeppe and colleagues [39]	2004	?	None	fMRI	Injection of 5-HT-3 receptor antagonist (topisetron) rCBF	n/a	In FM patients, topisetron treatment reduced rCBF of SI, contralateral posterior insula, ACC
Cook and colleagues [38]	2004	9	9 HC	fMRI	QST evoked activation of rCBF	Nonpainful and painful heat, 47°C	In FM, nonpainful heat increased rCBF in prefrontal, supplemental motor, insular, and ACC as compared with HC. In FM patients, painful heat increased activity in contralateral insular cortex as compared with HC
Gracely and colleagues [126]	2002	16	16 HC	fMRI	QST evoked activation of rCBF	Pressure pain MRS, neutral site	Common areas of evoked equal pain increased rCBF including contralateral SI, inferior parietal lobule, SII, superior temporal gyrus (STG), insula, putamen, and ipsilateral cerebellum. Decreased rCBF in ipsilateral SI. In HC, QST (equal pressure) activated ipsilateral STG and precentral gyrus
Yunus and colleagues [130]	2004	12	7 HC	PET	Resting rCBF	n/a	No difference
Chang and colleagues [131]	2003	10 IBS + FM	10 IBS	PET	QST evoked activation of rCBF	Noxious visceral and somatic pressure	In IBS patients, noxious visceral stimuli evoked increased rCBF increase in middle subregion of the ACC. In IBS + FM patients, somatic stimuli evoked greater rCBF in middle subregion of the ACC extending to ACC and the thalamus

Continued overleaf

Table 6

(Continued)

Reference	Year of study	Number of FM patients	Number of control individuals	Neural imaging	Description	QST	Findings
Wik and colleagues [132]	2006	8	None	PET	QST evoked activation of rCBF	Acute pain	In FM patients, frontal and parietal cortical activation during acute pain compared with rest (as expected). Reduced rCBF in retrosplenial cortex (evaluative processing)
Wood and colleagues [41]	2007	11	11 HC	PET	QST evoked binding of D2/D3 ligand	Nonpainful and painful saline injection	In FM patients, lack of dopamine release in basal ganglia compared with HC during painful stimuli. In HC, amount of dopamine release correlated with amount of perceived pain; in FM patients, no such correlation observed
Adiguzel and colleagues [42]	2004	14	None	SPECT	Amitriptyline (3 months) resting rCBF	n/a	Increased rCBF in bilateral hemithalami after amitriptyline. No correlation between symptoms and findings
Gur and colleagues [45]	2002	19	20 HC	SPECT	Resting rCBF	n/a	Increased rCBF in caudate nucleus. FM patients with less depression had increased uptake in pons
Kwiatek and colleagues [43]	2000	17	22 HC	SPECT	Resting rCBF	n/a	Reduced rCBF in right thalamus and potine tegmentum, no reduction in left thalamus, or caudate nucleus. No correlation between symptoms and findings
Mountz and colleagues [44]	1995	10	7 HC	SPECT	Resting rCBF	n/a	Reduced rCBF in bilateral hemithalami and caudate nucleus correlated with low pain threshold No correlation between symptoms and findings

ACC, anterior cingulate cortex; CLBP, chronic low back pain; fMRI, functional magnetic resonance imaging; HC, healthy control individuals; 5-HT-3, 5-hydroxytryptamine 3; IBS, irritable bowel syndrome; MDD, major depression disorder; MRS, multiple random staircase; n/a, not applicable; PET, positron emission tomography; QST, quantitative sensory testing; rCBF, regional cerebral blood flow; SI, somatosensory cortex I; SII, somatosensory cortex II; SPECT, single-photon emission computed tomography.

there was an association noted with the total myalgic score. Although the change in the P300 potential after sertraline treatment was attractive, the authors agreed that – given the corresponding significant clinical improvement in pain, fatigue, or depression – the mechanism for the change remained unclear, and they acknowledged it may represent regression to the mean. Larger studies by different groups with an attention to standardizing methods are essential prior to mainstream use of this marker.

In contrast to auditory potentials, there are few and varied studies evaluating somatosensory and visual ERPs. The assorted protocols used in the studies investigating somatosensory and visual ERPs may have contributed to the lack of consistently demonstrated differences in FM and normal individuals. The lack of an established standardized methodology makes direct comparison difficult and may limit the evidence of reproducibility.

Sleep and activity

In addition to pain, other symptoms very commonly seen in FM include disturbed sleep and poor function. Sleep logs and polysomnography have consistently confirmed patient reports of hypersomnolence [49,50]. Using polysomnography, investigators have correlated hypersomnolence with poor sleep quality by demonstration of fewer sleep spindles, an increase in the cyclic alternating pattern rate, or poor sleep efficiency [51-53]. Sleep abnormalities are rarely shown to correlate with symptoms in FM, however, and many investigators anecdotally feel as though even identifying and treating specific sleep disorders often seen in FM patients (for example, obstructive sleep apnea, upper airway resis-

Table 7

Evoked potentials in fibromyalgia (FM)

Reference	Year of study	Number of FM patients	Number of control individuals	Evoked potential	Paradigm	EP evaluated	Findings
Alanoglu and colleagues [46]	2005	34	22	Auditory	Auditory discriminated task paradigm	P300 wave	FM reduced P300 amplitude and prolonged latency. No correlation between EP findings, pain scores, and quality of life measurements
Yoldas and colleagues [47]	2003	11	10	Auditory	Auditory discriminated task paradigm	P300 wave	FM reduced P300 amplitude, but no difference in potential latency. P300 latency negatively correlated with total myalgic scores and the control point scores. P300 amplitude correlated with PPT and total myalgic scores. No correlation in amplitude or latency with depression or anxiety.
Ozgocmen and colleagues [48]	2003	13	10	Auditory	Auditory discriminated task paradigm ~ before and after sertraline treatment (8 weeks)	P300 wave	FM reduced P300 amplitude, but no difference in potential latency at baseline. Sertraline treatment resulted in increase in potential amplitude by 8 weeks without change in latency. No correlation between EP findings, fatigue and pain scores, but correlated to total myalgic scores

EP, evoked potential; PPT, pain pressure thresholds.

tance, restless leg or periodic limb movement syndromes) does not necessarily lead to improvements in the core symptoms of FM.

Actigraphy

A method of motion assessment that infers sleep and wakefulness from the presence of limb movements, actigraphy is increasingly being used as a surrogate marker for both sleep and activity. The actigraph typically combines a movement detector and memory storage on a watch-like device. The device can be worn on the wrist or the ankle continuously for long periods of time. Sleep-pattern measures available via actigraphy analyses include sleep latency, the wake time after sleep onset, and the total sleep time; sleep architecture cannot be measured, as with polysomnography. Compared with polysomnography, however, actigraphy is less expensive, less invasive, and more conducive to repeated measures, resulting in extensive use in intervention studies [54].

Actigraphy is being increasingly used in FM studies and appears promising, but has not yet proven adequately sensitive to stand alone in clinical evaluation or treatment trials [50,55,56]. As a measure of sleep quality there have been inconsistent actigraphy results, with one group noting increased levels of activity at night in FM (also noted in patients with major depression) [55] and another group noting no difference [50]. Edinger and colleagues used actigraphy as an outcome measure in an intervention trial comparing cognitive behavior therapy intervention with sleep hygiene and usual care in the treatment of insomnia [57]. Deriving an actigraphic improvement criterion, the investigators showed a greater number of patients receiving cognitive behavior therapy had clinically significant improvement in the total wake time compared with sleep hygiene therapy. No statistical difference between cognitive behavior therapy and usual care was able to be demonstrated, even though a statistical difference between the groups was shown using sleep log data in the same study.

As an objective measure of functional status, actigraphy might hold more promise as a surrogate outcome measure, because it allows the direct recording of activity levels, rather than relying on patient self-report [58]. Kop and colleagues demonstrated that although patients with FM have 36-Item Short Form health survey scores nearly two standard deviations below the population average, they have the same average activity level as a group of sedentary control individuals [58]. The FM patients had much lower peak activity levels, however, suggesting that the problems in function that FM patients report might be more due to an inability to rise to the intermittent demands of day-to-day life than due to overall reduced function.

Stress–response systems and sex hormones

The theoretical link between stress–response systems and symptom expression is supported by studies demonstrating alterations of the hypothalamic–pituitary–adrenal axis and the autonomic nervous system in FM. Probing different aspects of the stress systems is underway to uncover objective ways to identify persons at risk or to identify reproducible abnormalities. One group clearly with increased susceptibility is women. Investigators hypothesize a potential effect of sex hormones on the stress response to partly explain the female predominance seen in FM, but this connection has not yet been specifically examined in FM patients [59].

Hypothalamic–pituitary–adrenal axis

In basal and diurnal cortisol studies, the most consistently found measure is a flattened diurnal plasma cortisol level with an elevated trough, found in three of four cross-sectional studies by two out of three groups [60-62] (Table 8). Studies evaluating basal plasma cortisol levels, salivary basal and diurnal cortisol levels, and urinary cortisol levels have shown inconsistent results, but they generally demonstrate normal to reduced basal levels. Since atypical depression can show a reduced cortisol level, biopsychological factors that influence cortisol levels may be contributing to the inconsistent results currently found in the literature [63]. These factors need to be better elucidated and accounted for in future studies. Nonetheless, a flattened diurnal cortisol level is a promising objective measure.

Evaluation of other components of the hypothalamic–pituitary–adrenal axis has been relatively unrevealing. Basal and diurnal adrenocorticotropic hormone shows no difference in FM patients versus healthy control individuals [62,64,65] (Additional file 1). Provocative hypothalamic–pituitary–adrenal studies utilizing the cosyntropin test have shown inconsistent results [62,66-68] (Additional file 2).

Results of the dexamethasone suppression test have been reported in a number of studies by different groups, and the results reveal normal to high levels of cortisol following infusion of the corticosteroid [60,64,66,69,70] (Additional file 3). Depression also typically follows a pattern of resistance to the dexamethasone test, and therefore is a confounding factor in a large number of these evaluations.

Studies have also been completed to assess the cortisol response to exogenous corticotropin-releasing hormone or endogenous activators of corticotropin-releasing hormone (that is, hypoglycemia, IL-6) in FM. Investigators found normal to reduced cortisol levels in patients with FM after an increase in corticotropin-releasing hormone, but these results were not reproduced in other similar studies. Further investigation taking into account psychological factors as well as doses of different drugs will be prudent.

Autonomic reactivity

Tilt table testing and heart rate variability have been evaluated in patients with FM. The consistent and reproducible finding of lower heart rate variability in FM patients compared with control individuals (in three cross-sectional studies by two different groups) makes it a more useful measure than tilt table testing [71-73]. An abnormal drop in blood pressure or an excessive rate of syncope during tilt table testing has been noted in two out of three cross-sectional studies completed by three different groups [74-76]. One study noted no difference in normal individuals and control individuals using univariate analysis [76]. Moreover, recent findings also suggest that aberrations in heart rate variability may predispose to fibromyalgia symptoms [77,78], possibly identifying patients at risk.

Sex hormones

FM syndrome is more prevalent in women than in men, suggesting a role of sex hormones in the pathophysiology of FM [79]. To date, two studies have failed to show an association between sex hormones and pain sensitivity [79,80]. The reason for a female predominance in FM is complex and warrants further investigation.

Serologic and biochemical abnormalities

Physicians from multiple disciplines have used simple blood tests to diagnose and evaluate treatment for various diseases. Scientists have similarly evaluated a number of compounds in the serum and cerebrospinal fluid of patients with FM to find a comparable marker of disease or disease activity. Despite the effort to find easily accessible measures, no clinically suitable tests have yet been appropriately validated for FM.

Autoantibodies

The search for representative autoantibodies is a predictable step for a disease like FM, often evaluated by rheumatologists and coexisting with autoimmune diseases. Antiserotonin antibody, antiganglioside antibody, and antiphospholipid antibody have been shown to be different in FM patients and control individuals, but the applicability of these findings is not yet clear [81] (Table 9). Antiserotonin antibody has been shown to be increased in FM in three cross-sectional studies by two different groups [81-83]. Antiganglioside antibody and antiphospholipid antibody have each been shown to be increased in FM in two cross-sectional studies by the same group [81,82]. A different group evaluating antiganglioside antibody in a third cross-sectional study was unable to reproduce the results [83]. Antithromboplastin antibody [83], antipolymer antibody [84], and anti-68/48 kDa and anti-45kDa [85] have each been evaluated in one cross-sectional study and have shown increased levels in FM. A review of the literature demonstrates that antinuclear antibodies, antithyroid antibodies, antisilicone antibodies, and antiglutamic acid decarboxylase are not informative in FM.

Table 8

Basal and diurnal cortisol and fibromyalgia (FM)

Reference	Year of study	Number of FM patients	Number of control individuals	Measured (plasma)	Findings
McCain and Tilbe [60]	1989	20	20 RA	Plasma cortisol	Normal peak, elevated trough, flattened diurnal compared to RA
Crofford and colleagues [133]	1994	7	7	Plasma cortisol	Normal peak, elevated trough, flattened diurnal
Crofford and colleagues [61]	2004	13	12 FMS + CFS, 15 CFS	Plasma cortisol	Delay in rate of decline in FM, elevated cortisol in late period in FM, flattened diurnal, lower O/N cortisol in CFS
Adler and colleagues [62]	1999	15	13	Plasma cortisol – total and free	Normal, normal diurnal
Korszun and colleagues [134]	1999	9	9 HC, 8 CFS	Plasma cortisol	Normal
Malt and colleagues [135]	2002	22	13	Plasma cortisol	Normal
Valkeinen and colleagues [136]	2005	13 (60 years old)	13 (59 years old)	Plasma cortisol	Normal
Griep and colleagues [64]	1993	10	10	Plasma cortisol	Normal
Gur and colleagues [137]	2004	63 (<35 years old)	38 (<35 years old)	Plasma cortisol	Reduced
Gur and colleagues [63]	2004	68	46 HC, 62 CFS	Plasma cortisol	Reduced in FM with high BDI scores (>17), not in those with low BDI. Reduced in CFS
Griep and colleagues [66]	1998	40	14 HC, 28 CLBP	Plasma cortisol	Reduced
Lentjes and colleagues [138]	1997	40	14 HC, 28 CLBP	Plasma cortisol – total and free	Reduced total cortisol in FM only, Normal free cortisol in FM, CLBP
Riedel and colleagues [65]	1998	16	17	Plasma cortisol	Elevated
Catley and colleagues [139]	2000	21	22 HC, 18 RA	Salivary cortisol 6 times/day	Elevated, normal diurnal
McClean and colleagues [140]	2005	20	16	Salivary cortisol 5 times/day	Normal, normal diurnal strong relationship between current pain symptoms and cortisol levels at waking and 1 hour after waking. No relationship between fatigue and stress
Weissbecker and colleagues [141]	2006	85	n/a	Salivary cortisol 6 times/day	Flattened diurnal, greater cortisol responses to awakening in FM with history psychological, physical abuse
Dedert and colleagues [142]	2004	91	n/a	Salivary cortisol 5 times/day	Flattened diurnal on those with low religiosity
Sephton and colleagues [143]	2003	50	n/a	Salivary cortisol 5 times/day	Higher log-transformed mean salivary cortisols associated with better memory
Adler and colleagues [62]	1999	15	13	24-hour urinary cortisol	Normal
Maes and colleagues [144]	1998	?	PTSD, depression	24-hour urinary cortisol	Normal
Torpy and colleagues [145]	2000	13	8	24-hour urinary cortisol	Normal (trend toward reduced)
Crofford and colleagues [133]	1994	12	10	24-hour urinary cortisol	Reduced (no difference between depressed and non depressed)
Lentjes and colleagues [138]	1997	40	14 HC, 28 CLBP	24-hour urinary cortisol	Reduced in FM and CLBP
Griep and colleagues [66]	1998	40	14 HC, 28 CLBP	24-hour urinary cortisol	Reduced

BDI, Beck Depression Inventory; CFS, chronic fatigue syndrome; CLBP, chronic low back pain; FMS, fibromyalgia syndrome; HC, healthy control individuals; PTSD, post-traumatic stress disorder; RA, rheumatoid arthritis.

Table 9

Autoantibodies and fibromyalgia (FM)

Reference	Year of study	Number of FM patients	Number of control individuals	Objective measure	Findings
Klein and colleagues [82]	1992	50	?HC	Antiserotonin	Increased in FMS
				Antiganglioside	Increased in FMS
				Antiphospholipid	Increased in FMS
Klein and Berg [81]	1995	100	42 CFS, ?HC	Antiserotonin	Increased in CFS and FMS
				Antigangliosides	Increased in CFS and FMS
				Antiphospholipid	Increased in CFS and FMS
Werle and colleagues [83]	2001	203	64	Antiserotonin	Increased
				Antithromboplastin	Increased
				Antiganglioside	No difference
				Gm1	No difference
Wilson and colleagues [84]	1999	47	16 OA,12 RA, banked sera, 15 myositis, 30 RA, 30 SLE, 30 SSc	Antipolymer antibody	Increased in antipolymer antibodies, higher in severe versus mild
Nishikai and colleagues [85]	2001	125	114 CFS, ?psych, ?CTD	Anti-68/48 kDa	Increased in FMS and CFS
				Anti-45 kDa	Increased in FMS and CFS

CFS, chronic fatigue syndrome; CTD, connective tissue disease; FMS, fibromyalgia syndrome; HC, healthy control individuals; OA, osteoarthritis; RA, rheumatoid arthritis; SLE, systemic lupus erythmatosus; SSc, systemic sclerosis.

The nonspecific increase in antibodies to a number of antigens may be a nonspecific finding that arises from a subtle shift in immune function in this spectrum of illness. In the closely related chronic fatigue syndrome, investigators have noted a shift from a T1 to a T2 immune response, which would be expected to lead to increased production of nonspecific antibodies. Any antibody or autoantibody proposed as either a diagnostic test for FM or a biomarker of FM must therefore be carefully tested using various control individuals to ensure its authenticity.

Neuropeptides

Substance P is a neuropeptide released in spinal fluid when axons are stimulated. Four different cross-sectional studies by various groups in FM patients noted an elevation of substance P in cerebrospinal fluid [86-89]. In contrast, a normal substance P level has been noted in the cerebrospinal fluid of patients with chronic fatigue syndrome [90]. Although these results appear promising, elevated substance P is not specific for FM but rather has been shown to occur in other pain states such as chronic, daily headaches and chronic neck or shoulder pain associated with whiplash injury [91,92]. A high level of substance P therefore seems to be a biological marker of the presence of chronic pain.

Nerve growth factor and calcitonin gene-related peptide are additional neuropeptides that have been evaluated in FM. Nerve growth factor was shown in one study to have increased levels in FM and not in FM/rheumatoid arthritis overlap, therefore presenting inconclusive results [93]. Cerebrospinal fluid and serum calcitonin gene-related peptide have been studied and not found to be different in FM patients and control individuals [94,95].

Biochemicals and cytokines

The amino acid tryptophan and the cytokine IL-8 have both been shown to be different in patients compared with control individuals in a couple of studies, but neither have been evaluated in longitudinal studies [96-98]. A low tryptophan level has been found in two of three studies by three different groups [96,99,100]. IL-8 has been consistently demonstrated in three studies by two different groups [97,98,101]. Moreover, IL-8 has been shown to correlate with symptoms of FM and not to be associated with depressed FM [98]. Serum IL-6 was evaluated and found to be normal in FM patients [98,101].

Muscle abnormalities

Despite the interest and investigation for objective peripheral muscle abnormalities, the results have remained variable and have not yet been reproduced by different groups. Additionally, there is great heterogeneity in the methods evaluating for objective muscle abnormalities that render a complete review of the data beyond the scope of the present study. To dissect out possible useful objective measures, further investigations are necessary, preferably utilizing non-invasive procedures.

Table 10

Summary of findings for objective markers

Objective marker	Findings
Genetics	Polymorphisms in catecholamine *o*-methyl transferase have been noted in some ethnic groups but not others; dopamine 4 receptor findings have not been replicated or refuted as compared with other polymorphisms
Tender point counts or index	Multiple studies suggesting utility. The tender point count and the tender point index may be influenced by cognitive and emotional aspects of pain, and therefore may be biased
Pressure pain threshold	Multiple studies suggesting utility. The pressure pain threshold may be influenced by cognitive and emotional aspects of pain, which may be minimized by utilizing a random pressure paradigm
Heat and cold pain threshold	Consistently different in patients versus control individuals but not shown to be correlated with changes in clinical pain
Diminished diffuse noxious inhibitory controls	Four cross-sectional studies by different groups suggest utility. Needs further exploration with standardized methods, longitudinal studies
Functional neural imaging	Multiple studies suggesting utility. May be influenced by cognitive aspects of pain. Longitudinal studies needed
Event-related potentials	Reduced P300 amplitude has been noted in three cross-sectional studies by two different groups. Larger studies with standardized methods are necessary. Longitudinal studies needed
Sleep logs and polysomnography	Confirm reports of hypersomnolence, but no changes are pathognomonic of or specific for fibromyalgia
Actigraphy	Inconsistent measure of sleep quality. Report suggesting utility in measuring functional status. Larger, longitudinal studies needed
Hypothalamic–pituitary–adrenal axis	Flattened diurnal cortisol noted in three of four cross-sectional studies by two of three groups. Need to explore influence of biopsychosocial factors. Longitudinal studies needed
Autonomic reactivity	Lower heart rate variability noted in three cross-sectional studies by two different groups. May predispose to condition. Longitudinal studies needed
Autoantibodies	Antiserotonin antibody noted to be increased in three cross-sectional studies by two different groups. Stringent controls necessary prior to determining utility. Longitudinal studies needed
Neuropeptides	Substance P noted to be increased in cerebrospinal fluid in four cross-sectional studies by various groups. Potential nonspecific marker of chronic pain
Biochemical and cytokines	Low tryptophan and elevated IL-8 noted. Longitudinal studies needed
Muscle abnormalities	No clear and reproducible abnormality. Additional studies with standardized methods needed

Conclusion

Except for psychophysical pain testing, no objective measure has been appropriately evaluated and shown to improve with improvements in clinical status in a longitudinal study, and thus to qualify as a biomarker (see Table 10 for summary). These tests are not, however, entirely objective. Of the objective tests, those that hold the most promise as biomarkers are probably tests that directly assess elements of neural function, such as functional neuroimaging, ERPs, and DNIC. An effort by different groups to systematically evaluate these measures in research trials to obtain useful, comparable results will be vital for ongoing progress in outcome research. There will be an ongoing need to identify biomarkers for future studies that have reproducibility and predictive value, practicability, and biological and temporal relevance in FM.

This review is part of a series on
Biology and therapy of fibromyalgia
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Additional files

The following Additional files for this article are available online:

Additional file 1 is an Excel file containing a table that presents studies of basal and diurnal adrenocorticotropic hormone and fibromyalgia. See http://arthritis-research.com/content/supplementary/ar2443-s1.xls

Additional file 2 is an Excel file containing a table that presents studies of the cosyntropin test and fibromyalgia.

See http://arthritis-research.com/content/supplementary/ar2443-s2.xls

Additional file 3 is an Excel file containing a table that presents studies of the dexamethasone test and fibromyalgia. See http://arthritis-research.com/content/supplementary/ar2443-s3.xls

Competing interests

DD is a consultant for Forest Laboratories. LJC is a consultant for Pfizer, Wyeth, Lilly, and Allergan, and receives research grant support from Pfizer, Wyeth, Allergen, and Boehringer-Ingelheim. MS is a consultant to Allergan, Eli Lilly, Jazz Pharmaceuticals, Pfizer and Pierre Fabre Medicament, and is on the speaker bureaus of Eli Lilly, Grünenthal, Pfizer and Pierre Fabre Medicament. IJR is a consultant for Allergan and Grünenthal, has research grant support from Allergan, Schwartz, Grünenthal, Jazz Pharmaceuticals, and Forest Laboratories, and is on the speaker bureau for Jazz Pharmaceuticals, Pfizer, and Forest Laboratories. DJC is a consultant for Cypress Biosciences, Pfizer, Lilly, Forest Laboratories, Wyeth, Proctor and Gamble, and Takeda.

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