Manic spectrum symptoms are correlated to the severity of pain and the health-related quality of life in patients with fibromyalgia

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ABSTRACT

Objective. *We aimed at investigating the impact of lifetime manic spectrum symptoms on the severity of pain and the health-related quality of life (HRQoL) in patients with fibromyalgia (FM).*

Methods. *One hundred and sixty-seven patients with FM, assessed according to the ACR criteria, were consecutively enrolled. Psychiatric diagnoses were carried out following the Diagnostic and Statistical Manual for Mental Disorders (DSM-IV-TR). The severity of pain and the HRQoL of FM patients was measured by means of the Fibromyalgia Impact Questionnaire (FIQ) and the Medical Outcomes Study Short Form-36 Health Survey (MOS SF-36); the mood spectrum symptomatology by means of the Mood Spectrum-Self Report (MOODS-SR).*

Results. *A high rate of lifetime manic symptoms was detected and resulted as related to the Pain Visual Analogic Scale ("pain VAS") of the FIQ and the FIQ total scores as well as to the "bodily pain", and to the physical and mental component summary scores of the MOS SF-36, both in the whole sample (n=167) and in FM patients without bipolar disorder (n=160).*

Conclusion. *Our results highlight the need to pay more attention to manic spectrum symptoms and features in FM patients, because of their relationship with the severity of pain and with a worse HRQoL.*

Introduction

Fibromyalgia (FM) is a chronic, non-articular rheumatic condition characterised by diffuse aching, pain or stiffness in the muscles or joints, and the presence of tenderness on examination at specific, predictable anatomic sites known as tender points (TPs) (1). According to the American College of Rheumatology (ACR), FM is defined by the following criteria: a) widespread pain of at least 3 months' duration; b) tenderness of at least 11 of the 18 specific TPs on examination (2). FM has been related to a more severe disability in daily activities than other rheumatic conditions, besides having a negative impact on almost all aspects of the health-related quality of life (HRQoL) (3-7).

Despite extensive research, the pathogenesis of pain in FM syndrome is not completely understood (8, 9) and increasing interest has been devoted to the role of psychiatric comorbidity (10, 11). A growing body of literature has investigated psychiatric comorbidity in patients with FM, reporting prevalence rates ranging between 35.7% and 87.6% (10-14), with major depression (MD) being the most frequently reported diagnosis, at rates of 20%-80% (10-19). In contrast, fewer studies investigated bipolar disorders (BD) comorbidity in FM patients, reporting rates ranging between 1.3% and 12.8% (20, 21), in spite of the fact that, recently, Goldstein *et al*. (22) demonstrated that BD patients are significantly more likely to report the presence of pain compared to subjects without BD or to subjects with MD or anxiety disorders. Moreover, a significant number of manic symptoms have been reported in FM patients (23), independently of a diagnosis of BD, but no data is available on their impact on the severity of pain.

There is agreement on the negative impact of comorbid mental disorders, particularly of MD and anxiety disorders, on the HRQoL in FM patients (10, 11, 24-26), while, to the best of our knowledge, no data has been reported on the impact of Axis I BD or subthreshold manic symptoms comorbidity on the HRQoL in FM patients.

Within the framework of an Italo-American collaboration, a questionnaire based on a dimensional approach to mood psychopathology that explores the full spectrum of mood phenomenology was developed and validated (Mood Spectrum-Self Report [MOODS-SR]) (27). This instrument focuses on manic and depressive symptoms and features, including isolated/atypical symptoms, traits, and lifestyles that may characterise the temperamental mood dysregulations, present throughout the lifespan both in fully syndromal and subthreshold mood disturbances.

Thus, by using the MOODS-SR, the aim of the present study was to determine the impact of lifetime manic spectrum symptoms on the severity of pain and on the HRQoL in FM patients either with or without comorbid BD.

Material and methods

Subjects

A sample of 167 patients with a diagnosis of FM was consecutively recruited at the Dipartimento di Medicina Interna, Unità di Reumatologia of the University of Pisa. Eligible subjects included new and continuing patients, of at least 18 years of age, who met the 1990 American College of Rheumatology criteria for diagnosis of FM (2).

Exclusion criteria were: the presence of any inflammatory cause of the pain, concomitant rheumatic diseases, neurologic complications or pregnancy, ongoing antidepressant treatment.

The Ethics Committee of the Azienda Ospedaliero-Universitaria Pisana approved all recruitment and assessment procedures. All patients were asked about their preparedness to participate in the study and underwent a psychiatric assessment after a routinely scheduled appointment. Eligible subjects provided written informed consent after receiving a complete description of the study and having an opportunity to ask questions.

The diagnosis of FM was made according to the ACR criteria by a rheumatologist. For each patient, the count and the tenderness at TPs were evaluated by means of the Fisher dolorimeter. The rheumatologist advanced the instrument at a rate of 1 kg/s, and the patient was instructed to say when this procedure became painful. The pressure was then stopped, and the threshold measurement was recorded in kg/cm^2.

The myalgic score was the sum of the dolorimetry results for all 18 TPs. The TP count was determined by the number of TPs that had a threshold of 4 kg/cm^2. Each positive TP had a pain score between 0 and 3.

Psychiatric diagnoses were made using the Structured Clinical Interview for the DSM-IV Axis I disorders (SCID-I/P) (28), administered by psychiatrists trained and certified in the use of the study instrument at the Dipartimento di Psichiatria, Neurobiologia, Farmacologia e Biotecnologie of the University of Pisa, Pisa, Italy. The following questionnaires were also administered: the MOODS-SR lifetime version (27), the Fibromyalgia Impact Questionnaire (FIQ) (29) and the Medical Outcomes Study Short Form-36 Health Survey (MOS SF-36) (30). Sociodemographic data were collected using interviewer-administered questionnaires. A structured interview format was used to record sex, age, educational level, marital status, employment and duration of illness.

The MOODS-SR is a validated questionnaire for the assessment of mood spectrum symptomatology. It includes 161 items coded as present/absent, for one or more periods of at least 3-5 days across the lifespan. Items are organised into three manic and three depressive domains exploring mood, energy, and cognition, plus a domain that investigates disturbances in rhythmicity and vegetative functions. Each domain score corresponds to the sum of the items answered as "present". The sum of the scores in the three manic domains constitutes the "manic component" (62 items), while that of the depressive domains constitutes the "depressive component" (63 items). In accordance with the aim of the present study, the manic and depressive components of the MOODS-SR were explored. The instrument can be downloaded from the web site: www.spectrum-project.net.

The FIQ is a brief self-administered instrument, designed to evaluate the overall impact of FM over many dimensions of the HRQoL (physical functioning, work status, depression, anxiety, sleep, pain, stiffness, fatigue, and well-being). It consists of 10 items and is scored from 0 to 100, with the latter number being the worst case. The pain dimension is measured by a Visual Analogical Scale (VAS), in which patients reported the severity of pain as a score ranging from 0 (corresponding to "absence of pain") to 10 (corresponding to "very severe pain"). We considered the FIQ total score to explore the global impact on the HRQOL, and the "pain VAS" to explore the severity of pain.

The MOS SF-36 is a self-administered questionnaire used to assess general health status and the HRQoL. It consists of 36 items, 35 of which are aggregated into 8 multi-item scales that measure: Physical Functioning (PF; extent to which health limits physical activities); Role Physical (RP; extent to which physical health interferes with work or other daily activities); Bodily Pain (BP; intensity of pain and effect on normal work); General Health (GH; personal evaluation of health, current and outlook); Vitality (V; feeling energetic); Social Functioning (SF; extent to which physical health or emotional problems interfere with normal social activities); Role Emotional (RE; extent to which emotional problems interfere with work or other daily activities), and Mental Health (MH; general mental health, including depression, anxiety, behavioural and emotional control, general positive affect). The sum of the first four scales represents the mental component summary (MCS) score while the sum of the other four represents the physical component summary (PCS) score. Subscale raw scores are standardised and range from 0 to 100, where 0 is worst and 100 the best possible health status. We considered the MCS and PCS scores to explore the global impact on the HRQOL, and the BP scale to explore the intensity of pain and its specific impact on work activity.

Statistical analyses

Pearson's correlations were used to investigate the presence of relationships between MOODS-SR depressive and manic component total scores, and

the variables describing the severity of pain and the HRQoL ("pain VAS" and FIQ total score; MCS, PCS and BP scores of the MOS SF-36) of FM patients, either with (n=167) or without (n=160) BD.

Multiple regressions and covariance analyses were used to evaluate the influence of the manic component on each dependent variable ("pain VAS", FIQ, MCS, PCS and BP scores).

All data are presented as mean±SD.

The data were analyzed using the Statistical Package for the Social Sciences (SPSS Inc., Chicago 2006), version 14.0.

Results

All patients (n=167) were women, with a mean age of 50.9±12.4 years. Demographic and clinical characteristics of the sample are reported in Table I.

According to the DSM-IV-TR (APA, 2000) criteria, lifetime Axis I mental disorders were diagnosed in 135 (80.8%) FM patients: 94 (56.3%) with MD, 6 (3.6%) with BD, 25 (15%) with panic disorder, 9 (5.4%) with generalised anxiety disorder and 1 (0.6%) with obsessive-compulsive disorder.

High mean scores on the depressive and manic components of the MOODS-SR were found in the whole sample (n=167, 21.59±14.45 and 16.52±9.79, respectively). The most frequently endorsed (at least 50%) MOODS-SR manic items are reported in Table II.

Table III (panel a) shows Pearson's correlations: the MOODS-SR depressive component resulted as related to the "pain VAS" score of the FIQ and the FIQ total score as well as to the MCS and BP scores of the MOS SF-36, while the MOODS-SR manic component resulted as related to the FIQ, "pain VAS", MCS, PCS and BP scores.

Because of the evident interaction found between the MOODS-SR depressive and manic components (r=0.618, p=0.000), we isolated the effect of the manic component on the HRQoL variables by conducting statistical analyses on the group of FM patients with low depressive component scores, selected on the basis of the first quartile (score ≤9). The Pearson's correlation between the manic component and the BP score was r=-0.308, p=0.039, and this relationship was confirmed by a multiple regression analysis which included BP score as a dependent variable and the manic and depressive components as well as their product as independent variables: the manic component resulted as the only significant predictor of BP score (b=-2.163, t=-2.707, p=0.010, r^2=0.167).

Finally, we compared the groups of FM patients with low and high manic component scores, selected on the basis of the first quartile (score ≤9), utilizing a covariance analysis and including the depressive component as covariate. We observed a significant difference between the two groups on the BP scale (38.83±17.28 *vs*. 26.39±19.33,

Table I. Demographic and clinical characteristics of the sample (n=167).

Age	50.9 ± 12.4
Ethnic origin	Italian (100%)
Education	
Low	94 (56.3)
High (high school and graduate)	73 (43.7)
Marital status	
Unmarried (single, separated, or divorced)	44 (25.5)
Married	123 (74.5)
Work status	
Housewife	60 (35.9)
Employed	74 (44.3)
Unemployed	7 (4.2)
Retired	26 (15.6)
Number of tender points	14.7 ± 2.9
Duration of illness	87.8 ± 107.9
"duration of illness/age"	13.83% ± 15.37%

Age: years, mean (±SD); education, marital status, work status: n (%); number of tender points, "duration of illness/age": mean (±SD); duration of illness: months, mean(±SD).

Table II. MOODS-SR manic items endorsed by at least 50 % of FM patients without bipolar disorder (n=160).

Item n.	In the course of your life, including when you were a child, have you ever had periods of at least 3-5 days in which:	positive answers
29	…you felt persistently good or high?	n=121; 75.5%
31	…even the smallest thing could make you very enthusiastic?	n=109; 68.1%
37	…you were warm, extroverted and sociable and it was very easy to introduce yourself to others or to make new friends?	n=96; 60%
111	…you were particularly sensitive to the forms and harmony in nature?	n=96; 60%
74	…you found your interest shifting frequently from one thing to another and were easily distracted so that, for example, it was hard to finish a newspaper or magazine article or to watch a television program from beginning to end?	n=85; 53.3%
77	…you felt vigorous, much livelier than usual and full of energy?	n=83; 51.8%
38	You were the kind of person to whom others were attracted because of your confidence, enthusiasm and energy?	n=83; 51.8%

Table III. Pearson's correlations between the MOODS-SR depressive and manic components and the FIQ, MCS, PCS and BP scores of the MOS SF-36 in the whole sample (panel a, n=167) and in FM patients without bipolar disorder (panel b, n=160).

Panel a MOODS-SR	FIQ	VAS dolore	BP	MCS	PCS
depressive component	r=0.318 p=0.000	r=0.241 p=0.002	r=-0.232 p=0.003	r=-0.557 p=0.000	NS
manic component	r=0.240 p=0.002	r=0.202 p=0.010	r=-0.252 p=0.001	r=-0.277 p=0.000	r=-0.196 p=0.011
Panel b MOODS-SR	FIQ	VAS dolore	BP	MCS	PCS
depressive component	r=0.332 p=0.001	r=0.251 p=0.001	r=-0.223 p=0.05	r=-0.538 p=0.001	NS
manic component	r=0.247 p=0.002	r=0.208 p=0.009	r=-0.220 p=0.005	r=-0.267 p=0.01	r=-0.155 p=0.05

F=7.233, p=0.008) and the PCS (35.79±8.43 *vs*. 31.30±8.09, F=9.023, p=.003).

In order to verify the same conditions in the absence of Axis I BD, we repeated the same statistical procedures excluding the six patients with BD from the total sample (n=160). We found overlapping significances for every analyses previously conducted (Pearson's correlations on the whole sample: Table III, panel b; Pearson's correlations on FM patients with low depressive component scores: r=-0.304, p=0.045; multiple regression model on FM patients with low depressive component scores: b=-2.194, t=-2.755, p=0.009, r^2=0.177; covariance analysis on FM patients with low and high manic component scores: 39.78±18.22 *vs*. 27.66±19.26, F=5.428, p=0.021 and 35.46±8.37 *vs*. 32.09±8.02, F=3.634, p=0.058 at the BP and PCS scores, respectively).

Discussion

The results of the present study, in line with data in the literature (10-14, 20, 21, 31), show high rates of MD and a percentage of 3.6% of BD in FM patients. Not surprisingly, and in agreement with previous reports (10, 11, 24-26), we found a positive correlation between the number of lifetime depressive symptoms and higher severity of pain and worse HRQoL. Furthermore, our results demonstrated a relevant number of lifetime manic symptoms both in the whole sample and among patients without a history of BD. In both cases, an increase in the number of lifetime manic spectrum symptoms was also found to be associated to a higher severity of pain and a worse HRQoL. In particular, FM patients without lifetime or current BD who endorsed at least 9 MOODS manic items (out of a total of 62) reported lower scores on the "physical component" as well as on the "bodily pain" subscale of the MOS SF-36, showing a negative impact on overall physical heath as well as on the severity of pain and its effect on work activity. To the best of our knowledge, only Carta *et al*. (23) previously explored manic symptoms in FM patients, and our results show for the first time the impact of lifetime subthreshold manic symptoms on the HQRoL of these patients. It's noteworthy that these data are confirmed regardless of whether patients had current or past episodes of MD.

Failure to recognise subthreshold expression of mania has been reported both in clinical settings and epidemiologic studies, contributing to the frequent under-diagnosis of BD (32-35). There are several reasons for the low rate of recognition of subthreshold mania, including the lack of subjective suffering, ego-syntonicity, enhanced productivity and assertiveness, which makes it difficult to convince these individuals that their feelings and behaviour could be harmful. Judd and Akiskal (36), in a recent reanalysis of the Epidemiological Catchment Area data, found that in the general population subsyndromal manic symptoms are not "benign" because in the general population they resulted as being associated with an increased need of assistance for mental health problems. Moreover, in a non-psychiatric clinical sample, lifetime subthreshold manic symtpoms at baseline resulted as associated to the development of depression during interferon treatment (35). Thus, these data highlight the need to systematically assess the lifetime subthreshold manic symptoms in FM patients without BD.

In view of this, it is also noteworthy to recall that even the off-label use of antidepressants is nowadays very common in a non-psychiatric setting like the rheumatologic one, since their efficacy and good tolerability have been demonstrated in FM patients (31, 37), independently of the presence of depression. As manic symptoms have long been associated with the risk of switching into a full-blown manic or hypomanic episode, particularly during antidepressant treatment, this is another important reason to identify subthreshold manic symptoms during treatment evaluation in order to avoid the possible switch in patients with a bipolar "diathesis"

The results of the present study should be interpreted keeping in mind some limitations. First, since this is a cross-sectional study, the use of a lifetime assessment of the subthreshold manic symptoms (MOODS-SR) cannot permit us to establish whether they preceded or co-occurred at the moment of the evaluation of the severity of pain and the HRQoL. A second limitation is the limited sample size, that did not allow us to perform subgroup analyses investigating the impact on the other components of the HRQoL assessments.

In conclusion, the results of the present study suggest that lifetime manic spectrum symptoms are associated to more severe pain and impairment of HRQoL in FM patients, even in the absence of comorbid BD.

References

1. BENNETT RM, SMYTHE HA, WOLFE F: Recognizing fibromyalgia. *Patient Care* 1989; 23: 60-83.
2. WOLFE F, SMYTHE HA, YUNUS MB *et al*.: The American College Of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee. *Arthritis Rheum* 1990; 33: 160-72.
3. WOLFE F, HAWLEY DJ: Measurement of the quality of life in rheumatic disorders using the EuroHRQoL. *Br J Rheumatol* 1997; 36: 786-93.
4. MARTINEZ JE, FERRAZ MB, SATO EI, ATRA E: Fibromyalgia versus rheumatoid arthritis: a longitudinal comparison of the quality of life. *J Rheumatol* 1995; 22: 270-4.
5. BERGMAN S: Psychosocial aspects of chronic widespread pain and fibromyalgia. *Disabil Rehabil* 2005; 27: 675-83.
6. PINCUS T, MACLEAN R, YAZICI Y, HARRINGTON JT: Quantitative measurement of patient status in the regular care of patients with rheumatic diseases over 25 years as a continuous quality improvement activity, rather than traditional research. *Clin Exp Rheumatol* 2007; 25: 69-81.
7. MAS AJ, CARMONA L, VALVERDE M, RIBAS B, EPISER STUDY GROUP: Prevalence and impact of fibromyalgia on function and quality of life in individuals from the general population: results from a nationwide study in Spain. *Clin Exp Rheumatol* 2008; 26: 519-26.
8. STAUD R, RODRIGUEZ ME: Mechanisms of disease: pain in fibromyalgia syndrome. *Nat Clin Pract Rheumatol* 2006; 2: 90-8.
9. BAIO P, BRUCATO A, BUSKILA D *et al*.: Autoimmune diseases and infections: controversial issues. *Clin Exp Rheumatol* 2008; 26: 74-80.
10. EPSTEIN SA, KAY G, CLAUW D *et al*.: Psychiatric disorders in patients with fibromyalgia. A multicenter investigation. *Psychosomatics* 1999; 40: 57-63.
11. CIAPPARELLI A, BAZZICHI L, CONSOLI G *et al*.: The impact of psychiatric comorbidity on health-related quality of life in women with fibromyalgia. *Clin Neuropsychiatry* 2008; 5: 1-8.
12. THIEME K, TURK DC, FLOR H: Comorbid

depression and anxiety in fibromyalgia syndrome: relationship to somatic and psychological variables. *Psychosom Med* 2004; 66: 837-44.
13. RAPHAEL KG, JANAL MN, NAYAK S, GALLAGHER RM, SCHWARTZ JE: Psychiatric comorbidity in a community sample of women with fibromyalgia. *Pain* 2006; 124: 117-25.
14. NÄRING GW, VAN LANKVELD W, GEENEN R: Somatoform dissociation and traumatic experiences in patients with rheumatoid arthritis and fibromyalgia. *Clin Exp Rheumatol* 2007; 25: 872-7.
15. BENJAMIN S, MORRIS S, MCBETH J MACFARLANE GJ, SILMAN AJ: The association between chronic widespread pain and mental disorder: a population-based study. *Arthritis Rheum* 2000; 43: 561-7.
16. MICHIELSEN HJ, VAN HOUDENHOVE B, LEIRS I, VANDENBROECK A, ONGHENA P: Depression, attribution style and self-esteem in chronic fatigue syndrome and fibromyalgia: is there a link? *Clin Rheumatol* 2006; 25: 183-8.
17. PATTEN SB, BECK CA, KASSAM A, WILLIAMS JV, BARBUI C, METZ LM: Long-term medical conditions and major depression: strength of association for specific conditions in the general population. *Can J Psychiatry* 2005; 50: 195-202.
18. ERCOLANI M, TROMBINI G, CHATTAT R *et al*.: Fibromyalgic syndrome: depression and abnormal illness behavior. Multicenter investigation. *Psychother Psychosom* 1994; 61: 178-86.
19. NORDAHL HM, STILES TC: Personality styles in patients with fibromyalgia, major depression and healthy controls. Ann Gen *Psychiatry* 2007; 9; 6: 9.
20. ARNOLD LM, HUDSON JI, HESS EV *et al*.: Family study of fibromyalgia. *Arthritis Rheum* 2004; 50: 944-52.
21. ARNOLD LM, HUDSON JI, HESS EV *et al*.: Comorbidity of fibromyalgia and psychiatric disorders. *J Clin Psychiatry* 2006; 67: 1219-25.
22. GOLDSTEIN BI, HOUCK PR, KARP JF: Factors associated with pain interference in an epidemiologic sample of adults with bipolar I disorder. *J Affect Disord* 2009; Feb 7.
23. CARTA MG, CARDIA C, MANNU F *et al*.: The high frequency of manic symptoms in fibromyalgia does influence the choice of treatment? *Clin Pract Epidemiol Mental Health* 2006; 2: 36.
24. WALKER EA, KEEGAN D, GARDNER G, SULLIVAN M, KATON WJ, BERNSTEIN D: Psychosocial factors in fibromyalgia compared with rheumatoid arthritis: I. Psychiatric diagnoses and functional disability. *Psychosom Med* 1997; 59: 565-71.
25. MACFARLANE GJ, MORRIS S, HUNT IM *et al*.: Chronic widespread pain in the community: the prevalence of psychologic symptoms and mental disorder on healthcare seeking behaviour. *J Rheumatol* 1999; 26: 413-9.
26. WHITE KP, NIELSON WR, HARTH M, OSTBYE T, SPEECHLEY M: Chronic widespread musculoskeletal pain with or without fibromyalgia: psychological distress in a representative community adult sample. *J Rheumatol* 2002; 29: 588-94.
27. DELL'OSSO L, ARMANI A, RUCCI P *et al*.: Measuring mood spectrum: Comparison of interview (SCI-MOODS) and self-report (MOODS-SR) instrument. *Compr Psychiatry* 2002; 43: 69-73.
28. FIRST MB, SPITZER RL, WILLIAMS JBW, GIBBON M: Structured Clinical Interview for DSM-IV-Patient Edition (SCID-P). Washington, DC: American Psychiatric Press; 1995.
29. SARZI-PUTTINI P, ATZENI F, FIORINI T *et al*.: Validation of an Italian version of the Fibromyalgia Impact Questionnaire (FIQ-I). *Clin Exp Rheumatol* 2003; 21: 459-64.
30. MCHORNEY CA, WARE JE JR, LU JF, SHERBOURNE CD: The MOS 36-item Short-Form Health Survey (SF-36): III. Tests of data quality, scaling assumptions, and reliability across diverse patient groups. *Med Care* 1994; 32: 40-66.
31. ARNOLD LM: Management of fibromyalgia and comorbid psychiatric disorders. *J Clin Psychiatry* 2008; 69: 14-9.
32. ANGST J: Epidemiology of the bipolar spectrum. *Encephale* 1995; 6: 37-42.
33. AKISKAL HS: The prevalent clinical spectrum of bipolar disorders: beyond DSM-IV. *J Clin Psychopharmacol* 1996; 16: S4–S14.
34. CASSANO GB, DELL'OSSO L, FRANK E *et al*.: The bipolar spectrum: a clinical reality in search of diagnostic criteria and an assessment methodology. *J Affect Disord* 1999; 54: 319-28.
35. DELL'OSSO L, PINI S, MAGGI L *et al*.: Subthreshold mania as predictor of depression during interferon treatment in HCV+ patients without current or lifetime psychiatric disorders. *J Psychosom Res* 2007; 62: 349-55.
36. JUDD LL, AKISKAL HS: The prevalence and disability of bipolar spectrum disorders in the US population: re-analysis of the ECA database taking into account subthreshold cases. *J Affect Disord* 2003; 73: 123-31.
37. UÇEYLER N, HÄUSER W, SOMMER C: A systematic review on the effectiveness of treatment with antidepressants in fibromyalgia syndrome. *Arthritis Rheum* 2008; 59: 1279-98.