Naturalistic 6-month antidepressants follow-up in patients with fibromyalgia: impact on somatic and mood spectrum symptoms

C. Carmassi[1], A. Ciapparelli[1], A. Cappelli[1], V. Dell'Oste[1], C.A. Bertelloni[1], C. Foghi[1], G. Amatori[1], V. Pedrinelli[1], L. Bazzichi[2], L. Dell'Osso[1]

[1]*Psychiatric Clinic, Department of Clinical and Experimental Medicine, University of Pisa;*
[2]*Rheumatology Clinic, Department of Clinical and Experimental Medicine, University of Pisa, Italy.*

Claudia Carmassi, MD, PhD
Antonio Ciapparelli, MD
Andrea Cappelli, MD
Valerio Dell'Oste, MD
Carlo Antonio Bertelloni, MD
Claudia Foghi, MD
Giulia Amatori, MD
Virginia Pedrinelli, MD
Laura Bazzichi, MD
Liliana Dell'Osso, MD

Please address correspondence to:
Andrea Cappelli,
Department of Clinical and Experimental Medicine,
University of Pisa,
Via Roma 67,
56126 Pisa, Italy.
E-mail: andrea.cappelli1990@gmail.com

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ABSTRACT

Objective. *Literature shows high rates of comorbidity between fibromyalgia (FM) and mood disorders, especially major depressive disorder (MMD), reported in more than half of the cases. Consistently, patients with FM also present high rates of mood spectrum symptoms, despite scant data are still available on the relationship with antidepressant treatment outcomes. The present study was aimed at exploring the clinical outcome of patients with FM-MDD comorbidity naturalistically treated with antidepressant drugs, besides the relationships between* mood spectrum *symptoms and the treatment response.*

Methods. *A total sample of 40 patients with FM and MDD, who started a treatment with an antidepressant drug, was recruited at the Rheumatology Unit of the University of Pisa, Italy. Patients were evaluated at baseline and after 1 (T1) and 6 months (T2) of the treatment with an antidepressant drug. Assessments included: the Mood Spectrum-Self Report (MOODS-SR) for mood spectrum symptoms, the Short Form Health Survey (SF-36) for the global functioning and the Clinical Global Impression (CGI) for the clinical severity and improvement. All instruments were administered at baseline and the SF-36 and CGI were repeated at T1 and T2.*

Results. *Twenty-eight (70%) patients reported an improvement at the CGI at T2. At T1 and T2 the CGI item-1 and most of the SF-36 domain scores significantly improved with respect to the T0, with the exception of the "role physical" and "role emotional" subscales. Improved patients reported higher scores in the energy depressive MOODS-SR domain. Furthermore, correlations emerged between several MOODS-SR domains and the CGI or SF-36 subscales scores at T0.*

Conclusion. *Our results corroborate previous findings on the role of antidepressant drugs in the management not only of MDD symptoms, but also of the painful component of FM. FM patients should be investigated for* Mood Spectrum *symptomatology considering its prominent role on the manifestations of the disorder and treatment outcome.*

Introduction

Fibromyalgia (FM) is a severe chronic condition characterised by deep and diffuse musculoskeletal pain, hyperalgesia and allodynia in the absence of articular inflammation. The detrimental role of FM on health-related quality of life, and its high prevalence rates in the general population ranging from 2% to 7%, contribute to define the disease a relevant problem for the healthcare systems in the western countries (1-7). A major issue in the management of FM is due to its heterogeneous clinical presentations and its plethora of symptoms encompassing fatigue, stiffness, irritable bowel syndrome, headaches, dizziness, fluid retention, paresthesia and restless legs, besides mood fluctuations, sleep problems, depressive symptoms and cognitive disturbance (8-12). Current treatments, in fact, hardly act on the different symptomatic dimension of the disease like chronic pain, fatigue, sleep and mood fluctuations (2). Specifically, the fibromyalgic pain is recognised as difficult to treat as only a minority of patients experiences a clinically relevant benefit from the various pharmacological options (8-13). Antidepressants, such as tricyclic antidepressants (TCA), selective serotonine reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs), are widely prescribed in FM clinical practice, despite great controversies are still debated on their efficacy for this condition (13,

14). Some of the current guidelines from multiple agencies, including the Food and Drug Administration (FDA), encourage the use of multiple agents to target the specific symptoms of FM including antidepressant drugs (15). Conversely, the European Medicines Agency (EMA) denied clinically relevant effects for these drugs, on the basis of a lack of robust evidence of efficacy, and because the adverse effects profile was considered to outweigh the benefits (16, 17).

However, specific factors in FM may be related to different responses to the treatment with these drugs. For example, it is plausible that in patients with FM and comorbid psychiatric disorders, the use of antidepressants presents a more advantageous risk/benefit ratio, besides better results in reducing pain (18). Although prevalence of psychiatric comorbidities in FM varies among studies, it represents a relevant problem in the field. Literature, in fact, shows higher psychiatric disorders rates among fibromyalgic patients than in general population (6, 19). Particularly, several studies were focused on the comorbidity between FM and mood disorders, including both major depressive disorder (MDD) (19-21) and bipolar disorder (BD) (22). The lifetime prevalence of depressive disorders in FM patients ranges from 25% far to 80%, depending on the instruments and diagnostic criteria used (19-21, 23, 24). The prevalence and intensity of depressive symptoms are consistently higher in FM patients than in healthy controls (19, 25-28). Furthermore, manifestations of depression are usually associated to FM severity, pain intensity, cognitive impairment, poorer treatment outcome, high disability and decline in socioeconomic status (29-32). Improving depressive manifestations in FM could determine also an increase in levels of patients social and physical functioning, hence in reduced economic burden related to the disease (30). Interestingly, in a clinical double-blind trial on 350 subjects with FM-MDD comorbidity, Marangell *et al*. found that a portion of the effect of the antidepressant duloxetine on pain was mediated by mood symptoms reduction (18).

Some Authors described also a great number of manic features in patients with FM. Carta *et al*. reported higher manic features in a sample of 148 fibromyalgic female patients than in healthy controls (33). In a previous study, some of us reported high symptoms of mania in patients with FM, regardless the diagnosis of BD (22). In general, mood disorders and chronic pain represent mutual predictors of the development of each other in a complex bidirectional relationship. Chronic pain, in fact, was associated to worse course and outcome of both MDD and BD, determining higher rates of recurrences and functional impairment (34).

The role of mood symptoms on the response to the treatment with antidepressants for FM is still an ongoing issue in the field, with no conclusive data yet. Our hypothesis was that the clinical improvement of FM severity after antidepressants treatment would be related to mood symptoms levels at baseline. Thus, the aim of the present study was to investigate the antidepressant treatment response in a sample of patients with FM and MDD and the relationship between lifetime *Mood Spectrum* symptoms, FM severity and antidepressant outcome.

Materials and methods

Study sample

A total sample of 40 patients with diagnoses of FM and MDD was consecutively recruited at the Rheumatology unit of the Azienda Ospedaliera Universitaria Pisana (A.O.U.P., Pisa, Italy). Eligible subjects included new and continuing patients, aged at least 18 years old, meeting the 2010 American College of Rheumatology criteria for diagnosis of FM (35), and the DSM-5 criteria for MDD (36), who started a therapy with a naturalistic treatment with an antidepressant. Exclusion criteria were the presence of any inflammatory cause of the pain, concomitant rheumatic diseases, neurologic complications or pregnancy, ongoing antidepressant treatment, and the presence of other psychiatric disorders. All patients underwent a psychiatric assessment after a routinely scheduled appointment. Each patient received a psychopharmacological treatment with SSRIs (particularly Citalopram, Escitalopram, Fluoxetine, Paroxetine or Sertraline), or TCA (particularly Amitryptiline or Clomipramine) at daily equivalent dose to Citalopram 20 mg. Furthermore, all patients received a motivational interview and the indication to mild-moderate aerobic exercise. Patients were evaluated again after 1 (T1) and 6 (T2) months of treatment from the baseline evaluation (T0).

Eligible subjects provided written informed consent after receiving a complete description of the study and having an opportunity to ask questions. The study was conducted in accordance to Helsinki Declaration and received the approval of the Ethics Committee of Area Vasta Nord Ovest Toscana, Italy.

Instruments and assessments

Enrolled subjects were investigated by means of the Short Form Health Survey (SF-36) (37), for the global functioning, the Clinical Global Impression (CGI) (38) for the clinical improvement and the Mood Spectrum - Self Report (MOODS-SR) (39), for lifetime *Mood Spectrum* symptoms. All instruments were administered at baseline and, SF-36 and CGI, repeated at T1 and T2. A structured interview format was used to collect socio-demographic and clinical data.

The SF-36 is a self-administered questionnaire that measures general health status and the health-related quality of life. It consists of 36 items, 35 of which are aggregated into domains that assess: *Physical Functioning*; *Role Physical*; *Bodily Pain*; *General Health*; *Vitality* (feeling energetic); *Social Functioning*; *Role Emotional*, and *Mental Health*. The sum of the first four scales evaluates the *physical component summary* score of the SF-36. The sum of the latter four assesses the *mental component summary* score. Subscale raw scores are standardised and range from 0 to 100, with 0 being the worst and 100 the best possible health status.

The CGI provides an overall clinician-determined summary measure that takes into account all available information, including knowledge of the patient's history, psychosocial cir-

cumstances, symptoms, behaviour, and the impact of the symptoms on the patient's ability to function. The CGI actually comprises two companion one-item measures evaluating the severity of psychopathology from 1 to 7 (*severity scale*) and the change from the initiation of treatment on a similar seven-point scale (*improvement scale*). In accordance with the aim of the present study CGI score was related to the severity of FM. Furthermore, on the basis of CGI score at T2, patients were divided in not improved (*improvement scale* 4 or more) and improved (*improvement scale* 3 or less).

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.

Statistical analysis

All statistical analyses were carried out using the Statistical Package for Social Science, version 25.0 (SPSS Inc.). Basic statistics were used to describe the demographic and clinical characteristics of the sample. In order to examine the efficacy of the antidepressant treatment, CGI and SF-36 scores at T0, T1 and T2 were compared by means of the Freedman test. A student t-test was computed to compare MOODS-SR domains scores between improved and not-improved (distinguished by the CGI *improvement scale*) patients at T2. Finally, Pearson correlation coefficient was calculated to investigate the associations between MOODS-SR and the SF-36 domains scores or CGI *severity scale* at T0. All tests were two-tailed and a p-value <0.05 was considered statistically significant.

Table I. Socio-demographic characteristics of the total sample (n=40).

Age (Years)		mean ± SD 52.18 ± 13.38 n (%)
Marital status	• Unmarried	5 (12.5%)
	• Married	27 (67.5%)
	• Divorced	3 (7.5%)
	• Widow/widower	5 (12.5%)
Work status	• Employed	17 (42.5)
	• Unemployed	17 (42.5)
	• Retired	6 (15%)
Education	• Low (≥8 years)	17 (42.5%)
	• High (≥13 years)	23 (57.5%)

Table II. Comparison of SF-36 and CGI scores at T0, T1 and T2 in the total sample (n=40).

	T0 mean ± SD	T1 mean ± SD	p*	T2 mean ± SD	p*
SF-36					
Physical functioning	51.1 ± 23.1	57.8 ± 26.4	**0.023**	57.6 ± 27.7	**0.037**
Role physical	21.2 ± 29.1	37.5 ± 39.2	**0.010**	33.1 ± 42.1	0.092
Bodily pain	32.0 ± 16.5	39.3 ± 17.7	**0.012**	42.2 ± 19.0	**<0.001**
General health	35.5 ± 19.7	44.1 ± 18.0	**0.007**	42.2 ± 17.8	**0.008**
Vitality	33.3 ± 18.5	40.0 ± 19.2	**0.009**	40.5 ± 19.9	**0.009**
Social functioning	53.7 ± 28.3	64.3 ± 25.0	**0.005**	65.6 ± 24.1	**0.003**
Role emotional	51.6 ± 41.3	50.8 ± 44.0	0.876	48.3 ± 40.6	0.876
Mental health	50.4 ± 23.4	58.8 ± 24.4	**0.009**	59.1 ± 21.5	**0.013**
CGI	3.0 ± 1.0	2.47 ± 0.8	**0.009**	2.25 ± 0.8	**<0.001**

*with respect with T0.

Table III. Comparison of MOODS-SR domains scores between not-improved patients (n=12) and improved ones (n=28).

	Total sample mean ± SD	Not-improved patients mean ± SD	Improved patients mean ± SD	p
Mood depressive	10.7 ± 6.6	8.7 ± 6.7	11.5 ± 6.5	0.231
Mood manic	8.7 ± 4.9	7.3 ± 5.6	8.7 ± 4.7	0.430
Energy depressive	3.8 ± 3.0	2.3 ± 2.4	4.5 ± 3.0	**0.035**
Energy manic	4.3 ± 3.3	3.3 ± 3.4	4.8 ± 3.2	0.204
Cognition depressive	9.1 ± 5.9	7.5 ± 6.1	9.8 ± 5.8	0.255
Cognition manic	4.2 ± 3.2	3.6 ± 3.7	4.4 ± 2.9	0.478
Rhythmicity	12.4 ± 5.3	10.8 ± 6.0	13.1 ± 4.9	0.207
Depressive total	23.7 ± 14.4	18.5 ± 14.0	25.8 ± 14.2	0.144
Manic total	16.9 ± 9.8	14.3 ± 11.1	18.0 ± 9.2	0.288

Results

All patients were women, with a mean age of 52.18±13.38 years. More than two thirds of the sample were married, 42.5% were employed and the 57.5% presented a high school degree (>13 education years) (Table I).

Statistically significant improvement emerged at T1 and T2, with respect with T0 for the following SF-36 domains: *Role physical, Bodily Pain, General Health, Vitality, Social Functioning and Mental Health*, with the only exception of *Role Emotional* that showed a worsening. CGI Item 1 also showed a statistically significant improvement in both T1 and T2 respect to T0. No severe side effects were reported and no subjects interrupted the antidepressant treatment due to side effects.

Table IV. Pearson's correlations between CGI or SF36 subscales at T0 and MOODS-SR domains in the total sample (n=40).

	Depressive component				Manic component				Rhitmicity	MOODS-SR
	Mood	Energy	Cognitive	Total	Mood	Energy	Cognitive	Total		Total
Physical functioning	-0.145	-0.134	-0.251	-0.198	0.097	-0.123	-0.168	-0.047	-0.503**	-0.235
Role physical	-0.325*	-0.263	-0.311*	-0.334*	-0.080	-0.266	-0.094	-0.162	-0.289	-0.310*
Bodily pain	-0.222	-0.262	-0.307	-0.284	0.026	-0.124	-0.135	-0.073	-0.237	-0.237
General health	-0.256	-0.138	-0.280	-0.262	0.014	-0.212	-0.142	-0.111	-0.209	-0.209
Vitality	-0.129	-0.81	-0.185	-0.153	0.080	-0.121	0.069	0.021	-0.153	-0.123
Social functioning	-0.498**	-0.336*	-0.516**	-0.513**	-0.117	-0.382*	-0.278	-0.279	-0.513**	-0.506**
Role emotional	-0.330*	-0.074	-0.259	-0.275	-0.156	-0.266	-0.025	-0.178	-0.275	-0.290
Mental health	-0.324*	-0.270	-0.393*	-0.368*	-0.279	-0.383*	-0.359*	-0.388*	-0.368*	-0.438*
CGI	0.396*	0.461*	0.420*	0.453*	0.438*	0.317*	0.399*	0.459*	0.453*	0.481*

*p<0.05. **p<0.001.
Weak correlations; moderate correlations.

Dividing the sample between improved and not improved, on the basis of CGI scores at T2, 70% (n=28) of patients resulted "improved" after 6 months. Improved patients reported higher scores in all the MOODS-SR domains, with statistically significant difference for the *Energy Depressive* domain only (Table III).

Table IV describes Pearson correlation coefficients between MOODS-SR domain scores and SF-36 or CGI score at T0. Particularly, moderate correlations emerged between: MOODS-SR *Rhythmicity* and physical functioning; MOODS-SR *Mood Depressive*, *Cognition Depressive*, *Rhythmicity*, *Depressive Component* and social functioning, MOODS-SR total score and mental health; MOODS-SR *Mood Manic*, *Energy Depressive*, *Cognition Depressive*, *Rhymicity*, *Depressive Component*, *Manic Component*, besides total score and CGI *severity* scale. Furthermore, other weak correlations emerged, as shown in Table IV.

Discussion

To the best of our knowledge, this is the first study aimed at examining the improvement of both physical and mental health symptoms in a sample of FM-MDD patients treated with antidepressant drugs. The results of the present study show that 70% of the whole sample improved after one month of antidepressant treatment, and this result remains after 6 months. Furthermore, the MOODS-SR scores correlated with the functional impairment severity related to FM at baseline, besides to the clinical improvement due to antidepressant treatment.

Our results corroborate previous studies reporting how antidepressant treatment in fibromyalgic patients can improve FM symptoms severity (40-42). More specifically, the pharmacological treatment can address not only depressive symptoms but also the painful component of the disorder. Our data are in agreement with other studies showing antidepressant drugs are efficacious in the management of chronic pain (43-46). Despite TCAs have been widely used in the treatment of various pain conditions for years, and Amitriptyline in particular still remains a first line choice (47), SSRIs presented inconclusive or inconsistent results in the clinical trial on chronic pain treatment. In a systematic review, Patetos *et al*. (48) suggested that SSRIs may be useful in chronic pain therapy, but literature is still inconsistent or affected by relevant methodological flaws. Conversely, there is a great amount of evidence suggesting how SNRIs, such as Duloxetine and Venlafaxine, could be effective in the treatment of chronic pain (45), but conclusive data on their utility in FM are not available yet.

It is also noteworthy that, in our sample, patients with a better outcome showed higher MOODS-SR scores at the baseline in all domains, despite only the *Energy Depressive* one presented a significant difference. This is in line with literature pointing out a clinical overlap between FM fatigue and psychomotor features of MDD. Over 75% of fibromyalgic patients suffers from chronic fatigue and this is considered a pivotal symptom of FM itself (19, 49, 51). MDD is also strongly associated with asthenia, chronic fatigue, tiredness, and decreased energy, and usually all these manifestations improved with antidepressant therapy. In a dimensional perspective, it may be possible that the presence of these depressive features are mostly associated with response to antidepressant in FM-MDD patients. Furthermore, despite there are data supporting that analgesia induced by some antidepressants is independent of their mood-related effect (52), other Authors highlighted the mediating effect of depression improvement on pain reduction after antidepressant therapy (18). We suggest that patients affected by high level of mood symptoms could benefit of a treatment with an antidepressant.

Interestingly, the Pearson's coefficient analysis showed several correlations between lifetime manic, depressive or rhythmicity symptoms and FM severity, as also reported in previous studies. Some Authors found a relationship in patients with FM between psychiatric comorbidities and the SF-36 or FM severity (53-55). This is in line with another study that showed a positive correlation between the number of lifetime depressive and manic symptoms, and a higher severity of pain and worse HRQoL (22). These evidences could highlight the impact of lifetime subthreshold symptoms on the severity of the disease.

The results of this study should be interpreted keeping in mind some limitations. First of all, a larger sample size would be necessary to confirm our findings. Second, the whole sample included women only. Third, there was no assessment for adherence to the suggested physical activity programme. Fourth, no data was recorded on concomitant other treatments, such as cognitive-behavioural therapy or physical therapy, or adherence to the suggested physical activity programme. Finally, the effect of different antidepressant drugs treatment (TCA, SSRIs) on FM was not analysed.

In conclusion fibromyalgic patients should be carefully investigated for mood symptomatology, considering the prominent role of these kind of features on the manifestations and the treatment outcome of FM. Furthermore, our data support the use of antidepressant in the management of FM, especially in patients affected by high levels of depressive symptoms. However further double-blind clinical trial on each specific molecule are still required, in order to better understand the possible advantage of these drugs on somatic, social and mental features of this multidimensional disorder.

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