

# Methodological approach to depressive symptoms in fibromyalgia patients

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## ABSTRACT

**Objective.** Depression is a common comorbid condition in fibromyalgia (FM) and a major contributor to poor quality of life and disability. However, depression can be difficult to assess in patients with FM due to overlapping symptoms between the two conditions. This review aims to present the most used rating scales for depression in FM patients by discussing their potential drawbacks. Moreover, we aimed to discuss the possible approach to mood symptoms in FM patients according to the mood spectrum model.

**Methods.** We included the main scales that have been used previously to assess depression in FM according to the literature data. Then, we reviewed the studies exploring the prevalence and the impact of sub-threshold mood symptoms on FM patients.

**Results.** Rating scales for depression such as the Hamilton Rating Scale for Depression, the Hospital Anxiety and Depression Scale, the Center for Epidemiologic Studies Depression Scale, the Beck Depression Inventory, the Montgomery Asberg Depression Rating Scale and the Zung Self-Rating Depression Scale have been largely used. However, almost all these instruments could suffer from a criterion contamination bias by somatic symptoms of chronic pain patients. Many studies have shown a critical role of sub-threshold mood psychopathology on worsening quality of life, disability and pain in FM patients. Specific questionnaires (Mood Spectrum Self-Report [MOODS-SR]) for subsyndromal phenomenology have been validated and used also in patients with medical diseases.

**Conclusion.** The need of a careful screening of depressive symptoms and of their proper management is primary

in FM. In our opinion instruments like MOODS-SR are particularly suitable for screening FM patients because they allow to recognise also sub-threshold mood symptoms with minimal contamination by somatic conditions.

## Introduction

Fibromyalgia (FM) is a chronic, non-articular rheumatic condition characterised by widespread 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, 2). 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 (3). FM has been related to a more severe disability in daily activities and to a more negative impact on almost all aspects of the health-related quality of life (HRQoL) than other rheumatic conditions, including rheumatoid arthritis (RA) (4-6).

A growing body of literature has investigated the prevalence of different psychiatric disorders in patients suffering from FM. Major depression (MD) emerges as the most frequently reported diagnosis with a lifetime prevalence of about 90% for depressive symptoms and 62-86% for major depressive disorder (MDD) (7-11). At any point in time, the best estimate of co-occurrence of depressive symptoms in FM is 40% (12). The high frequency of depressive symptoms in FM patients permits to speculate that FM should be considered within the "affective spectrum disorder" (13). Indeed, the hypothesis that depressive symptoms can be simply interpreted as a reaction to a chronic and

disabling disorder is not supported by the evidence that the percentage of FM patients with depressive symptoms is significantly higher than that found in other comparably severe chronic diseases (6). On the contrary, bipolar disorder (BD) seems to be less frequent in FM patients, with a prevalence rate between 1.3% and 19% (7, 8, 14). However, BD patients seem to suffer more frequently from pain syndromes than patients with MD (15).

There is agreement on the negative impact of comorbid mental disorders, particularly of MD and anxiety disorders, on the severity and course of FM. High levels of depression and anxiety in patients with FM were found to be associated with more physical symptoms and poorer functioning than pain controls (16). Furthermore, the number of reported medical symptoms in patients with FM has been positively associated with current and past depressive and anxiety disorders (17). Mood and anxiety disorders are associated with functional disability in patients with FM (17-20) and psychological disturbance is a predictor of persistence of pain associated with FM (21). These data underline the need of careful screening of depressive symptoms and of their proper management in FM patients.

The gold standard for the diagnosis of mood disorders at present is represented by the criteria of the Diagnostic and Statistical Manual, Fourth Edition (DSM-IV), of the American Psychiatric Association. Some instruments such as the Mini International Neuropsychiatric Inventory (MINI) (22) and the Structured Clinical Interview for DSM-IV (SCID) (23) are largely used for psychiatric diagnosis according to DSM criteria. However, in clinical practice and research studies, particularly in epidemiological studies, surveys, and treatment trials measuring severity of depressive symptoms, use of DSM-IV criteria often is not feasible or useful because the clinical reality of psychopathological conditions among the general population or in clinical settings may not be optimally reflected, and because their use necessarily requires dedicated and trained operators. The official nomenclature provides a useful

but incomplete characterisation of psychopathology. Some individuals experience substantial impairment from certain isolated symptoms or sub-threshold symptom clusters. The current system of categorisation does not take into account the continuum between the criterion symptoms of a disorder and clinically significant prodromic, residual, atypical and subclinical characteristics. To date scarce information is available about the prevalence and impact of sub-threshold mood symptoms in FM patients, which are quite common in the general population and in psychiatric patients (24-26).

Several rating scales for screening and/or assessment of severity of depression are available and have been used widely to assess depression also in patients suffering from other diseases. However, there are several methodological difficulties in assessing depressive symptoms in FM, and it is unclear which scales are suitable for the assessment of depression in this patient group. Moreover, the variability of depression prevalence reported in FM patients could reflect the heterogeneity of methods/instruments used for assessment. Only a minority of studies have used DSM criteria to diagnose depression in FM populations, while most consider FM patients depressed only on the basis of cut-off points for clinical significance of different rating scales. These problems and their impact on the use of scales to assess presence and severity of depression in patients with FM are recognised and discussed. The aim of this article is to present the most used rating scales for depression in FM patients by discussing their potential drawbacks. Moreover, we aimed to discuss the possible approach to mood symptoms in FM patients according to the mood spectrum model, which in our opinion, could be particularly suitable in FM patients because these patients often have atypical/attenuated depressive symptoms that are more difficult to investigate with the scales used so far for FM.

### Methods

We included in this paper the main scales that have either been used previously to assess depression in FM

or, according to literature review and expert evaluation, have potential utility in FM based on their content and their clinimetric evidence from studies in depressed patients without FM. We limited our assessment to depression-specific scales, as assessment of all multidimensional scales that include assessment of depression was beyond our scope. Medline on PubMed was searched for all listed publications up to September 2012. For each scale, a search was conducted for the terms "Fibromyalgia" and the name of the scale. We decided to present only the rating scales used at least twice in studies on FM patients. Only published or in press peer-reviewed papers were considered. In the second part of the manuscript we reviewed the studies investigating the prevalence and the clinical significance of sub-threshold mood symptoms in FM patients by means of a specific questionnaire for the assessment of mood spectrum symptomatology, the Mood Spectrum Self-Report (MOODS-SR) (27).

### Results

FM is a complex disorder with numerous symptoms occurring along with widespread pain and tenderness. Consensus exists for a core set of 9 symptom domains that should be evaluated in all treatment trials. Depression is included in this set, together with pain intensity, physical function, patient global impression of change, cognitive dysfunction (fibrofog), fatigue, multidimensional function/health-related quality of life (HRQoL), sleep disturbance and tenderness (28). However, there are no accepted standards for assessments to evaluate these domains. In two studies, which pooled data from FM treatment trials, support was found for construct validity of self-report questionnaires also for depression (29, 30). The most used rating scales for depression in the examined trials were the Hamilton Rating Scale for Depression (HRSD) (31), the Hospital Anxiety and Depression Scale (HADS) (32), the Center for Epidemiologic Studies Depression Scale (CES-D) (33) and the Beck Depression Inventory (BDI) (34); the HRSD and CES-D were found to

**Table I.** Rating scales for depressive symptoms in fibromyalgia patients.

	Total items	Somatic items	S/T ratio	Cut-offs	Self-reported
HRSD	21	5	0.24	<7: normal; 7-17 mild; 18-24 moderate; >24 severe	no
HADS	14	0	0	<7: normal; 8-10 suggestive; >10 probable	yes
CES-D	20	3	0.15	<16: normal	yes
BDI	21	6	0.28	<10: normal; 10-18 mild; 19-29 moderate; >30 severe	yes
MADRS	10	3	0.30	<7: normal; 7-19 mild; 20-34 moderate; >35 severe	no
ZSDS	20	8	0.40	<50: normal; 50-59 mild; 60-69 moderate; >70 severe	yes
MOODS-SR	161	23 (optional)	0.14	>22/63 (depressive component): depressive spectrum	yes

HRSD: Hamilton Rating Scale for Depression; HADS: Hospital Anxiety and Depression Scale; CES-D: Center for Epidemiologic Studies Depression Scale; BDI: Beck Depression Inventory; MADRS: Montgomery Asberg Depression Rating Scale; ZSDS: Zung Self-Rating Depression Scale; MOODS-SR: Mood Spectrum Self-Report.

S/T ratio: somatic to total items ratio. Low values suggest better suitability for detection of depressive symptoms in patients with somatic diseases (low risk for criterion contamination by overlapping symptoms).

be more sensitive to change of depressive symptoms during treatment of FM patients than BDI. Beyond these FM treatment trials, other instruments commonly used in multiple studies assessing depression in FM patients are the Montgomery Asberg Depression Rating Scale (MADRAS) (35) and the Zung Self-Rating Depression Scale (ZSDS) (36).

#### *Hamilton Rating Scale for Depression (HRSD)*

The interviewer-rated HRSD is the most widely used and accepted measure for evaluating the severity of depression (31). Although it does not cover DSM-IV criteria completely, it has acceptable discriminant validity, high sensitivity and high specificity (37). The HRSD contains 21 ratings measured on three (0 to 2) or five (0 to 4) point scales. The ratings cover depressive symptoms during the past few days or a week. Intensity and frequency of symptoms are considered; ratings are based on a synthesis of both. The first 17 items are used in scoring the instrument, whereas the final four items provide more detail on the clinical characteristics of the depression. The items included depressed mood; feelings of

guilt; suicide; early, middle and late insomnia; work and activities; inhibition; agitation; psychic anxiety and somatic anxiety; gastrointestinal somatic symptoms; general somatic symptoms; sexual symptoms (sexual dysfunction and alterations of menstruation); hypochondria; weight loss and insight. The additional items in the 21-item version are diurnal variation, depersonalisation and derealisation, paranoid symptoms and obsessive-compulsive symptoms. A total score sums the item responses and ranges from 0 to 52 points with rising severity of depression. Hamilton did not specify cutting points, but it is generally agreed that scores lower than 7 indicate an absence of depression, scores of 7 to 17 represent mild depression, 18 to 24 moderate, and 25 or above represent severe depression. Several authors have criticised its emphasis on somatic items, which are indicators of more severe depression. It may mean that the HRSD exaggerates depression in patients with physical illness and intercurrent depression (38, 39).

#### *Hospital Anxiety and Depression Scale (HADS)*

The HADS is a short self-rated scale yielding sub-scores for depression and

anxiety. It was developed and found to be a reliable instrument for detecting states of depression and anxiety in the setting of a medical hospital outpatient clinic (32). It includes seven items reflecting anxiety and seven reflecting depression. Each item was answered by the patient on a four point (0–3) response category so the possible scores ranged from 0 to 21 for anxiety and 0 to 21 for depression. A score of 0 to 7 for either subscale could be regarded as being in the normal range, a score of 11 or higher indicating probable presence of the mood disorder and a score of 8 to 10 being just suggestive of the presence of the respective state. Further work indicated that the two subscales, anxiety and depression, were independent measures (40). The depression subscale is weighted toward the emotional aspects of depression (emphasising anhedonia rather than sadness) and does not include physical and cognitive symptoms, or suicidal ideation. Its validity has been criticised as it excludes items at the end of the severity spectrum of depression, including suicidal ideation, psychotic features and vegetative symptoms. Nevertheless, sensitivity and specificity for DSM criteria for major depressive disorder and other depression scales were reported as good (41). Moreover, the exclusion of symptoms of depression such as fatigue and insomnia or hypersomnia makes the HADS a useful tool for the detection of anxiety and depression without confounding by somatic symptoms of physical disorder (42).

#### *Center for Epidemiologic Studies Depression Scale (CES-D)*

The CES-D is a 20-item, self-report depression scale derived from other depression scales as a screening instrument for depression in older adults with physical illness and in the general population (33). It was designed to cover the major symptoms of depression identified in literature, with an emphasis on affective components: depressed mood, feelings of guilt and worthlessness, feelings of helplessness and hopelessness, psychomotor retardation, loss of appetite and sleep disorders. Items refer to the frequency of

symptoms during the past week. Each question uses a 0 to 3 response scale except for questions 4, 8, 12, and 16 that were worded positively and their scores are reversed. Question scores are then summed to provide an overall score ranging from 0 to 60. Scores of 16 or more are commonly taken as indicative of depression (43). It has been used extensively in epidemiological studies. It has medium cognitive complexity, similar to the HADS (44). It is strongly weighted to the assessment of depressed mood and depressive thinking, and somatic symptoms are under-represented. It has acceptable construct validity (45, 46) and discriminant validity (no depression vs. major depressive disorder) (47, 48), but it may lack utility in distinguishing between gradations of severity within the clinical range of depression (minor vs. major depression) (49).

#### *Beck Depression Inventory (BDI)*

The BDI is one of the most used self-rated instruments for major depression in clinical practice. There are three versions of the BDI. The original 1961 instrument was revised in 1978, and revised again in 1996 to form the BDI-II (50). The modifications brought the instrument in line with DSM-IV diagnostic criteria and responded to other criticisms of the instrument. The BDI-I evaluates 21 symptoms of depression, 15 of which cover emotions, four cover behavioural changes and six somatic symptoms. A potential disadvantage of the inclusion of somatic items in the BDI is that it may lead to false-positive results among patients with physical problems, above all for patients with pain (51). Therefore, in version II, the assessment of physical appearance, weight loss, somatic concern and difficulty on the job were replaced by agitation, difficulty in concentrating, loss of energy and feelings of uselessness. Each symptom is rated on a four-point intensity scale and scores are added together to give a total ranging from 0 to 63. Scores of less than 10 indicate no or minimal depression, 10 to 18 indicate mild-to-moderate depression, 19 to 29 indicate moderate-to-severe depression, and scores of 30 or more

indicate severe depression (52). Scores on the BDI-II tend to be about three points higher than the BDI-I. BDI has been used both to measure severity of depression and as a screening instrument in more than 2,000 studies (53); it has been shown to correlate with biological markers of depression (54) and to be sensitive to change in severity of depressive symptoms (55).

#### *Montgomery Asberg Depression Rating Scale (MADRS)*

The Montgomery-Asberg Depression Rating Scale (MADRS) is used by clinicians to assess the severity of depression among patients in whom a diagnosis of depressive illness has been made. It is designed to be sensitive to change resulting from treatment (35, 56). Standard rating scales such as the HRSD do not seem sensitive enough to detect these differences (57). The 10 items include apparent sadness, reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts and suicidal thoughts. The score of each item varies between 0 and 6 points, and to assign the score, the clinician can use information from sources other than the patient. Ratings can be added to form an overall score (range 0 to 60). Snaith *et al.* proposed the following cutting-points: scores of zero to six indicate an absence of symptoms; seven to 19 represent mild depression; 20 to 34 moderate; and 35 to 60 indicate severe depression (58). It has an advantage over the HAM-D in that it is not contaminated by items that evaluate anxiety, although it continues to maintain several somatic or vegetative items that make it difficult to administer to patients with predominantly physical symptomatology.

#### *Zung Self-Rating Depression Scale (ZSDS)*

The ZSDS is a short self-rated scale that assesses psychological and somatic symptoms of depression. The ZSDS comprises 20 items; ten are worded positively and ten negatively. For each item, respondents indicate the frequency with which they experience the symptom or feeling, either

at the time of testing or in the previous week (36). Item scores are added to form a total ranging from 20 to 80, with higher scores indicating increasing depression. Most guidelines for interpreting results suggest that index scores of less than 50 are within the normal range, scores of 50 to 59 indicate minimal or mild depression, 60 to 69 moderate-to-marked depression, and scores above 70 indicate severe depression (59-62). There are a large number of somatic items. Therefore, to adjust for an expected higher baseline score in elderly patients seen in medical settings, it has been recommended that the cut-off score be raised from 50 in the general population to 60 or greater in this population (63). It has been widely used to screen for (36, 64, 65) and measure severity of depression (66). It is more easily comprehended than the HADS, CES-D, and BDI (44). Specific criticisms of the SDS include its focus on assessing the frequency rather than the severity of symptoms. In fact, most clinical ratings of depression rate severity, and this may contribute to the low agreement between the Beck or Hamilton and the Zung scales. Like the BDI, the SDS correlates highly with anxiety scales, suggesting that they may measure a broader state than depression alone (67).

#### *Drawbacks of rating scales for depression in chronic pain patients*

The main criticism of rating scales commonly used to assess depression in chronic pain patients is the criterion contamination by somatic items (68). Most self-report measurements of depression are affected by items that elicit a response due to symptoms associated with the disease rather than emotional distress. These symptoms include fatigue, difficulty in performing everyday activities, listlessness, loss of appetite and sleep disturbances. Patients with chronic pain can acquire a clinically significant score on most depression measures by endorsing items concerning such symptoms. These symptoms are all attributed by patients to pain rather than mood, and have been shown to be associated with pain rather than mood measures (51).

Despite their hopelessness and fear for the future, patients with pain may score below agreed cut-off points for clinical significance on cognitive and affective components. For example Wedding *et al.* (2007) investigated the prevalence of somatic and affective depressive symptoms with the BDI in 213 hospitalised cancer patients (69). They reported that female patients, patients with solid tumour and those with functional limitations had significantly higher BDI mean scores than others but all differences were related to higher scores in somatic and not in affective items. Therefore, they concluded that most alterations in the BDI in cancer patients are related to somatic and not to affective symptoms and may be attributed not to depression but to severity of the underlying disease. Trentini *et al.* (2005) reported a higher score in a group of elderly adults (60+ years) compared to younger adults (<60 years) in the somatic items subscale but not in the affective items subscale; this translated into a significant higher total BDI (70). Previously, the criterion contamination drawback in the assessment of depression was found also in different studies on patients suffering from rheumatoid arthritis (RA) by using either the BDI (71) and the CES-D (72). Pincus *et al.* (1996) in their study suggested that the HADS, developed specifically for use with patients from a range of medical conditions, should be relatively free of criterion contamination by somatic items (71). Also the psychiatric DSM-IV interview gives the instruction: "Do not include symptoms that are clearly due to a general medical condition", leaving the subjective decision of inclusion or exclusion of symptoms in the hands of the interviewer. This results in a confusing approach to depression assessment in the clinical complexity of chronic pain patients.

### Mood spectrum model

In the last few years, a growing interest has been focused on sub-threshold psychopathology as it seems to produce a negative impact on the quality of life and functioning. In particular, sub-threshold symptoms of depression, which occur in community sam-

ples at a higher prevalence than the full syndrome and often co-occur with chronic diseases, may further increase psychosocial dysfunction both in psychiatric and medical outpatients (24). Sub-threshold depression is linked to an increased functional disability, decreased energy, less interest in leisure, lower motivation, and problems with interpersonal relationships; there is also a major risk for more disability days, more hospitalisations and greater loss in functional status (24-26). In addition, a recent re-analysis of the Epidemiological Catchment Area data found that also sub-syndromal 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 (73). Recently, following this suggestion, a questionnaire based on a dimensional approach to mood psychopathology (74) has been developed and validated in the form of self-report or Structured Clinical Interview, that explores the full spectrum of mood phenomenology (Structured Clinical Interview for Mood Spectrum [SCI-MOODS]) (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 sub-threshold mood disturbances. Three versions are available to explore sub-threshold mood psychopathology throughout the lifespan or in the last month/week. MOODS-SR includes 161 dichotomous ("yes"/"no") items coded as present/absent, for one or more periods of at least 3-5 days across the lifespan. Items are organised into seven specific domains: three depressive domains (mood-depressive, cognition-depressive and energy-depressive), three manic domains (mood-manic, energy-manic and cognition-manic), and one independent domain (rhythmicity and vegetative functions). Mood domains explore lability and associated changes in interest directed towards family, friends, romantic relationships, work, hobbies and sports. Energy domains explore significant changes in energy levels occurring in specific situations

or times. Cognition domains explore changes in cognition associated with energy or mood dysregulation. Rhythmicity and vegetative functions probe changes in energy, physical well-being and mental and physical efficiency in relation to weather, seasons, changes in eating, sleep and sexual activities. 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). The cut-off score for the presence of manic-hypomanic spectrum or depressive spectrum is 22. The instrument can be downloaded from the web site [www.spectrum-project.org](http://www.spectrum-project.org).

Evidence on the clinical utility of mood spectrum assessment in psychiatric populations has already been provided by Cassano *et al.* (2005), who found a significant relationship between the presence of lifetime manic-hypomanic symptoms and increased suicidal risk in patients with recurrent unipolar depression (75). However, in the last years a growing interest has focused on the prevalence and impact of sub-threshold mood symptoms in non-psychiatric patients. For example a recent study reported that hepatitis-C-virus-infected subjects treated with IFN with no past history of psychiatric disorders are more likely to develop depression if they experienced sub-threshold manic-hypomanic symptoms in their lifetime, evaluated by means of MOOD-SR (76). Still according to the mood spectrum model, two studies showed that lifetime depressive spectrum symptoms negatively affects HRQoL of patients with RA (77, 78). Moreover, two recent studies focused on the impact of sub-threshold mood symptoms in FM patients. The first one found a positive correlation between the number of lifetime depressive symptoms evaluated with MOOD-SR and higher severity of pain and worse HRQoL in a sample of 167 FM patients. Further, a relevant number of lifetime manic symptoms was demonstrated 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 (79). The second one aimed at comparing the prevalence of sub-threshold mood symptoms in rheumatic patients suffering from FM and RA. The results showed that FM patients presented significantly higher scores than RA patients in MOOD-SR “mood depressive”, “cognition depressive” domains and in total depressive component. The authors speculated that this different weight of sub-threshold psychopathology in the two diseases could play a role in the worse quality of life and in the major perception of pain that characterise FM (80). The high prevalence and impact of depressive symptoms but also of sub-syndromal mood psychopathology comorbidity in FM point out the need of a careful screening for them and of their proper management in order to improve the pain symptomatology, as well as the quality of life of patients.

### Conclusions

Fibromyalgia is a complex disorder and may represent a manifestation of affective spectrum disorder. Depressive symptoms often complicate FM with a negative impact on quality of life, disability and pain. The assessment of depression is not simple in FM patients because of overlapping symptoms between the two conditions and because the most used rating scales for depression may suffer from criterion contamination by FM somatic aspects like sleep problems, fatigue, reduced activity, etc. For this reason FM management requires a multidisciplinary approach including a psychological and psychiatric evaluation by dedicated and trained specialists. In our opinion instruments like the MOODS-SR are particularly suitable to assess mood symptoms in patients suffering from medical disease and/or chronic pain like FM because they allow to recognise also sub-syndromal features and to evaluate different domains of mood phenomenology. Indeed, as previously said, rhythmicity and vegetative functions represent an independent domain of the MOOD-SR questionnaire that is

not included in the total scoring. This allows to consider emotional and cognitive mood symptomatology without (or with minimal) contamination by somatic aspects of medical conditions.

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