

# Psychiatric problems in fibromyalgia: clinical and neurobiological links between mood disorders and fibromyalgia

A. Alciati<sup>1</sup>, P. Sgiarovello<sup>2</sup>, F. Atzeni<sup>2</sup>, P. Sarzi-Puttini<sup>2</sup>

<sup>1</sup>*Hermanas Hospitalarias, FoRiPsi, Department of Clinical Neurosciences, Villa San Benedetto Menni, Albese con Cassano, Como, Italy;*

<sup>2</sup>*Rheumatology Unit, L. Sacco University Hospital of Milan, Italy*

## SUMMARY

**Objective.** To review the literature addressing the relationship between mood disorders and fibromyalgia/chronic pain and our current understanding of overlapping pathophysiological processes and pain and depression circuitry.

**Methods.** We selectively reviewed articles on the co-occurrence of mood disorders and fibromyalgia/chronic pain published between 1990 and July 2012 in PubMed. Bibliographies and cross references were considered and included when appropriate.

**Results.** Forty-nine out of 138 publications were retained for review. The vast majority of the studies found an association between depression and fibromyalgia. There is evidence that depression is often accompanied by symptoms of opposite polarity characterised by heights of mood, thinking and behaviour that have a considerable impact on pharmacological treatment. Recent developments support the view that the high rates of fibromyalgia and mood disorder comorbidity is generated by largely overlapping pathophysiological processes in the brain, that provide a neurobiological basis for the bidirectional, mutually exacerbating and disabling relationship between pain and depression.

**Conclusions.** The finding of comparable pathophysiological characteristics of pain and depression provides a framework for understanding the relationship between the two conditions and sheds some light on neurobiological and therapeutic aspects.

**Key words:** *Depression, fibromyalgia, pain, comorbidity.*

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## ■ INTRODUCTION

As more is learned about fibromyalgia (FM), the role of psychosocial factors becomes increasingly recognised to the extent that the condition is now viewed as the result of a complex interaction between biological, psychological and social factors. The growing attention towards the psychiatric disorders associated with FM is also related to consistent findings that unrecognised and untreated psychopathologies can significantly increase pain-related dysfunction and interfere with successful treatment (1). The reciprocally close relationship between FM and psychopathology is further supported by the observation that pain hinders the remission of psychiatric disorders; for example, in the case of major

depressive episode, pain delays treatment response (2) and is a significant risk factor for relapse (3).

Previous research has shown that FM is closely associated with a number of psychiatric disorders and psychopathological aspects. In a sample of 115 fifteen females with FM, 77.3% had psychiatric illnesses diagnosed using the Structured Clinical Interview for DSM-IV (SCID I and II), with 34.8% having a mood disorder and 32.2% an anxiety disorder (4). The prevalence of mood and anxiety disorders is more than three times higher in FM patients than in the general population, and match the prevalence rates of other pain illnesses such as rheumatoid arthritis (RA) (5) and chronic back pain (6) in some studies, but not in all (7). The frequency of mood disorders

Corresponding author:  
Alessandra Alciati

Department of Clinical Neurosciences  
Villa San Benedetto Menni  
22032 Albese con Cassano, Como, Italy  
E-mail address: [alessandra.alciati@libero.it](mailto:alessandra.alciati@libero.it)

in patients with FM has led to consideration of common pathophysiological pathway that may explain the neurobiological mechanism that makes them mutually exacerbating and disabling.

In this review, we first describe a selected sample of current research studies of the association between mood disorders and FM/chronic pain, and then consider investigations into the cerebral pathophysiological pathways that may help to shed some light on the neurobiological basis of the pain/psychopathology interaction.

## ■ METHODS

We searched the literature entered in PubMed from 1990 to July 2012 using the terms “mood disorder,” “depression” “major depression,” “bipolar disorder,” “chronic pain,” “fibromyalgia”, and “comorbidity.” The reference lists of selected articles were reviewed for additional papers of interest that were missed by the computerised database search. Each article was reviewed, and those providing any clinical or pathophysiological information concerning the overlapping of FM/chronic pain and mood disorders were included.

## ■ RESULTS

Three hundred and twelve studies were initially identified as being potentially relevant, of which the full articles of 138 studies were selected and reviewed. Of these, 49 were finally identified as focusing on the relationship between mood disorders and FM/chronic pain, the overlapping pathophysiological processes, and the circuitries of pain and depression.

### *Mood disorders*

The vast majority of studies and reviews have assessed the role of depression in chronic pain and FM. It has long been known that major depression is highly prevalent in patients with FM, with the rates of current depressive disorders ranging from 28.6% to 70%, and the life time

rates ranging from 62% to 86% (8, 9), the differences being due to differences in the diagnostic assessment of depression and/or sampling bias. The close relationship between the two disorders is further supported by the fact that FM is the second most frequent general medical condition associated with major depressive disorder, with an odds ratio (OR) of 3.4 (10).

Depressive symptoms beyond formal diagnosis of major depressive disorder are also frequent in FM patients, with a prevalence of about 40% as shown in a community study of almost 45,000 subjects (11). An even higher rate has been recently reported by Aguglia (12), who found clinically significant depressive symptoms (as indicated by a Hamilton Rating Scale for Depression (HAM-D) score of >7) in 83.35% of the FM patients referred to a Rheumatology Unit.

Over the last few years, converging evidence has been collected that FM patients have high rates of symptoms in the domain of the manic/hypomanic component of bipolar disorder, which are characterised by heights of mood, thinking or activity. Carta (13) detected manic symptoms in 59% of FM patients, approximately double the rate found in a control sample of healthy subjects. These findings were confirmed by the study of Dell’Osso (14), who found a high rate of lifetime manic symptoms that proved to be related to the severity of pain and its effect on working activities, as well as to a negative impact on overall physical health.

In a recent study, we found a high rate (88%) of so-called “soft bipolar spectrum disorders” in patients with FM: *i.e.* disorders in which hypomania or hypomanic symptoms are associated with major or minor depression, or occur in the absence of any depressive condition (15). These findings suggest that hypomanic symptoms (and only secondarily depressive symptoms) may be the core expression of mood disorders in FM. In the light of these observations, the over-active behaviour that has been frequently reported (16) to be characteristic of FM patients can be seen as a manifestation of an hypomanic height of activity (goal-directed over-activity).

Probably related to the high prevalence of bipolar spectrum disorder, a prospective study of a cohort of 1269 female patients with FM found that the risk of suicide was ten times higher than in the general population (17) and a large-scale community study (the NIMH Epidemiologic Catchment Area Program) has shown that subjects with sub-syndromal manic/hypomanic symptoms had a four times higher suicide attempt rate than a comparative group with no mental disorders (18). The high rate of hypomanic symptoms has an important clinical impact given the increasing off-label use of antidepressants to control pain (regardless of the presence of depression) in non-psychiatric settings. The correct detection of the manic/hypomanic component of mood dysregulation that leads to a diagnosis in the realm of bipolar disorders is crucial, because the treatment of bipolar disorder is different from that of recurrent major depression.

Controlled data suggest that there is a risk for inducing mania in patients with a bipolar spectrum disorder who are treated solely with antidepressants (19). Furthermore, their long-term use may have negative consequences such as a poor treatment response (20) or the induction of rapid cycling (21) a severe form of bipolar disorder characterised by four or more episodes of mania or depression in one year. For these reasons, the treatment of bipolar illness classically includes the use of so-called 'mood stabilisers' (lithium and specific anticonvulsants) and atypical antipsychotic agents during both the acute and maintenance phases. Antidepressants should never be used alone, but always together with a mood stabiliser or an atypical antipsychotic agent. Although all of the latter seem to be effective against acute mania, only aripiprazole, olanzapine and quetiapine have sufficient data documenting their efficacy in preventing relapse in acute responders (22).

Ninety percent of the studies considered in an evidence-based review (24) concluded that atypical antipsychotic agents have an analgesic effect in pain conditions ranging from headache and cancer pain to chronic lower back pain and FM. Four still-unpub-

lished double-blind controlled studies have recently evaluated the efficacy of quetiapine alone or as an add-on in the treatment of FM. Two of these have been presented at congresses, and both suggested that quetiapine could be an effective treatment for FM (25).

A positron emission tomography study of 19 healthy male volunteers provides theoretical support for the clinical view that antipsychotic agents (which share the capacity to antagonise dopamine D2 receptors) may have analgesic properties because it showed that people with relatively few available D2 receptors in the forebrain are likely to have a higher tonic level of pain suppression (26). Moreover, some anticonvulsant agents may improve both bipolar mood disorders and pain. Pregabalin is an anticonvulsant with demonstrated effects on key symptoms of FM such as pain, sleep and fatigue, and has been approved for its management in the United States (27). It has also been observed that pregabalin improves anxiety, a condition that frequently co-occurs with bipolar disorders (28). Valproate and carbamazepine, which are used during both the acute and maintenance phases of bipolar disorder, all have U.S. Food and Drug Administration (FDA) indications for the treatment and/or prophylaxis of some painful conditions (*e.g.*, migraine or trigeminal neuralgia, neuropathic pain and FM) (29).

### ***Effect of mood on pain processing***

The effect of mood on pain processing in FM patients is an important area of study, for both theoretical and practical reasons. A number of findings support the presence of a sensory-discriminative dimension of pain processing that modulates its intensity and spatio-temporal characteristics, and an affective-motivational dimension associated with its negative valence and unpleasantness (30).

The results of various studies converge to suggest that mood selectively alters the affective dimension of pain, as demonstrated by Rainville (31) who showed that pain unpleasantness was more affected by emotions than pain intensity in a group

of healthy volunteers. A functional magnetic resonance imaging (fMRI) study has endorsed these findings by showing that the extent of depressive symptoms and the presence of comorbid major depression are associated with the magnitude of neuronal activation in the brain regions that process the affective-motivational dimension of pain, and not its sensory-discriminative aspects (32). This finding is supported by some clinical studies, which found that self-rated depressive symptoms, anxiety and catastrophising did not correlate with the ratings of clinical and experimental pain in FM patients. However, depressive symptoms and anxiety can lead to a poor perception of physical health and significantly impair the health-related quality of life. (33, 34). In a sample of 500 patients with musculoskeletal pain, 54% reported pain only, 20% pain and depression, 3% pain and anxiety, and 23% pain, depression and anxiety. This last group experienced the greatest pain severity and pain-related disability, with more than twice the number of disability days due to their pain (*i.e.* 42.6 days in the previous three months *vs* the 18.1 days of those without concurrent clinical depression or anxiety) (35).

### ***Neural correlates of the relationship between depression and pain***

The relationship between depression and the affective dimension of pain is not surprising because the brain areas involved in regulating mood significantly overlap with those processing the emotional aspects of pain.

The brain system that has been most frequently implicated in the pathophysiology of depression is the extended medial prefrontal network (also called the 'medial network'), a group of ventrally located regions whose core components include the ventromedial prefrontal cortex, and the ventral and posterior regions of the cingulate cortex (36). These brain structures are highly activated during conditions in which healthy subjects attend to their internal emotions or rest passively, a state that frequently focuses on autobiographical thoughts and memories (37), and become

deactivated in response to demanding cognitive tasks that require an external focus of attention (38, 39).

In agreement with research indicating that effective disengagement from self-referential and negative affective processing is impaired in depressed patients (40), fMRI studies assessing brain responses during emotion processing (41) and cognitive/executive tasks (42) have shown that patients with major depression fail to reduce activity in the medial prefrontal regions, and that this impairment is linked to the severity of their depressive symptoms. Another recent study (43) has shown that, even in response to painful stimuli, patients with major depression fail to deactivate a region involving the subgenual-pregenual anterior cingulate cortex (ACC) and adjacent medial prefrontal areas, with abnormal persistence of activity during pain stimulation.

These findings suggest the presence of increased processing of internal somatic and visceral stimuli in major depressive patients that is consistent with enhanced self-focused attention and a reduction in the resources destined to external stimulation, including painful stimuli. Given the role of the sub-genual ACC in maintaining self-focused attention, the reduced deactivation in this region could explain the paradoxical phenomena of increased somatic complaints in depressive patients and the repeatedly described decreased pain perception during experimentally delivered painful stimulation of the skin (44).

The ACC and the regions including the parietal operculum and posterior insula (PO/PI) have also been identified as central cortical loci in regulating the emotional and behavioural reaction to pain. (45). It is thought that the ACC is a key structure that contributes to pain unpleasantness, as suggested by human observations showing that surgical ablation of the ACC significantly reduces pain unpleasantness without affecting the ability to detect the intensity or location of pain (46). The role of the ACC is further supported by the observation that specific manipulation of pain unpleasantness leads to significant changes in ACC activity, whereas the manipulation of

pain intensity mainly leads to changes in the primary somatosensory cortex (31). The ACC is not only involved in mediating the affective components of pain, but also mediates the anticipation of pain (47). In normal subjects, the uncertain expectation of painful stimulation enhances the brain responses to non-painful warm stimulation in the ACC and PO/PI (*i.e.* the expectation of painful stimulation amplifies the perceived unpleasantness of even innocuous stimulation), whereas it does not influence perceived pain intensity (48). Increased activation within the amygdale and the ACC during the anticipation of pain has been demonstrated in unmedicated subjects with current depression (49). These inappropriately large responses to anticipated pain suggest an exaggerated emotional distress or affective bias in the pain experience of patients with major depression patients, even before the actual painful stimulation occurs and even though the perception of pain intensity is not altered. This observation suggests that the difference between expected and actual body experiences may be greater in subjects with major depression. This is in line with the assumptions of cognitive models of depression that depressed patients negatively bias their expectations, perceptions and memories, and may represent a neural correlate of their hypervigilant monitoring of negative information (50).

The neuroimaging techniques used to assess the cerebral response to painful stimulation have also been used to investigate the effects of antidepressants. In comparison with untreated control subjects, patients with major depression treated with duloxetine show an improvement in core depressive symptoms that significantly correlates with a significant reduction in fMRI pain-related activations and enhanced deactivations in regions characterised by the abnormal persistence of activity during pain stimulation (34).

Decreased limbic activity also seems to contribute to the effect of cognitive behavioural therapy (CBT), a psychotherapeutic method that has been demonstrated to be effective on various forms of chronic pain (51). CBT is an approach that uses guided

discovery to identify and challenge distorted cognitions (*i.e.* catastrophism) and dysfunctional beliefs (52), and maladaptive behavioural patterns such as the avoidance used to prevent pain can be targeted by exposure-oriented interventions. The few studies that have investigated the neural correlates of CBT in pain patients have found that the clinical effect of CBT was associated with significantly decreased resting-state activity in the limbic regions, including the para-hippocampal gyrus and cingulate cortex. It is possible that the decreased limbic activity in response to CBT reflects attenuated vigilance and attention to pain as both of these measures have been found to improve after treatment (53, 54).

## ■ CONCLUSIONS

Current evidence supports the idea that depression and FM are highly inter-related, with the co-existence of both being associated with a poor prognosis and greater disability than that observed in patients with either illness alone. Recent findings have shown that depression in patients with FM is often associated with symptoms of opposite polarity, such as the heights of mood, thinking and behaviour characterising the bipolar spectrum of mood disorders. These have an important impact on the pharmacological management of FM and support the use of alternative treatments such as the use anticonvulsant or antipsychotic drugs. Although the underlying mechanism mediating the comorbidity of mood disorder and chronic pain is unknown, there is support for a model in which brain regions (including the limbic and paralimbic prefrontal cortical areas) play a role in both syndromes. These neurobiological links may provide the anatomical basis of the bidirectional relationship between pain and depression, with the symptoms of one worsening the other and/or making the other more likely to develop. Moreover, a better understanding of the relationship between pain and depression may improve current treatment options and provide targets for new treatment strategies.



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