Overactive lifestyle in patients with fibromyalgia as a core feature of bipolar spectrum disorder

A. Alciati[1], P. Sarzi-Puttini[2], A. Batticciotto[2], R. Torta[3], F. Gesuele[4], F. Atzeni[2], J. Angst[5]

[1]Department of Clinical Neurosciences, Villa San Benedetto Menni, Hermanas Hospitalarias, FoRiPsi, Albese con Cassano, Como, Italy;
[2]Department of Internal Medicine, Rheumatology Unit, Luigi Sacco University Hospital, Milan, Italy;
[3]Clinical and Oncologic Psychology Unit, University of Turin, Turin, Italy;
[4]Department of Psychiatry, Luigi Sacco University Hospital, Milan, Italy;
[5]Zurich University Psychiatric Hospital, Zurich, Switzerland.

Alessandra Alciati, MD
Piercarlo Sarzi-Puttini, MD
Alberto Batticciotto, MD
Riccardo Torta, MD
Felice Gesuele, D. Psych
Fabiola Atzeni, MD, PhD
Jules Angst, MD

Please address correspondence to:
Dr Alessandra Alciati,
Department of Clinical Neurosciences,
Villa San Benedetto Menni,
22032 Albese con Cassano,
Como, Italy.
E-mail: alessandra.alciati@libero.it

Received on November 16, 2012; accepted in revised form on November 26, 2012.

Clin Exp Rheumatol 2012; 30 (Suppl. 74): S122-S128

Key words: bipolar spectrum disorders, fibromyalgia, hypomania, prevalence

Competing interests: none declared.

ABSTRACT

Objectives. *To test the hypothesis that the premorbid overactivity previously described in subjects with fibromyalgia is a core feature of the manic/hypomanic symptoms characterising bipolar spectrum disorders.*

Methods. *110 consecutive patients with fibromyalgia were assessed for bipolar spectrum disorders using both categorical and dimensional approaches. The first was based on a version of the DSM-IV SCID-CV interview, modified to improve the detection of bipolar spectrum disorders, the second on the hypomania symptom checklist HCL-32, which adopts a dimensional perspective of the manic/hypomanic component of mood by including subsyndromal hypomania.*

Results. *Both DSM-IV and Zurich criteria diagnosed high rates of bipolar spectrum disorder in patients with fibromyalgia (70% and 86.3%, respectively). Individuals with a major bipolar spectrum disorder (bipolar II disorder) and with a minor bipolar spectrum disorder (subthreshold depression and hypomania) did not differ in their demographic and clinical aspects.*

Hypomanic symptom counts on the HCL-32 confirmed high estimates of the bipolar spectrum, with 79% of subjects with fibromyalgia scoring 14 (threshold for hypomania) or above.

Conclusion. *Overactivity reported in previous studies may be considered a core feature of hypomanic symptoms or syndromes comorbid with bipolar spectrum disorders.*

Major and minor bipolar spectrum disorders are not associated with differences in demographic or clinical characteristics, suggesting that fibromyalgia rather than being related specifically to depression is related to bipolar spectrum disorders and in particular to the hypomania/overactivity component.

Introduction

Fibromyalgia syndrome (FMS) is a diffuse musculoskeletal pain disorder, accompanied by tenderness on examination at specific anatomic sites known as tender points (TP), fatigue and non-restorative sleep (1-6). This condition may qualify as "somatoform disorders" within the DSM approach. In addition to somatic symptoms, many patients with FMS have serious mood disturbance with a lifetime history of major depression in 50–70% of cases (7, 8), and current depression in 14–36% (9, 10).

Despite intensive research, major gaps in our understanding of the pathogenesis of FMS and the relationship with the psychiatric comorbidity remain. Several studies have shown that the lifestyle premorbidly adopted by patients with fibromyalgia has been characterised by high self-reported "overactivity" (11, 12). Overactivity patterns may not only precede the illness but may persist after illness onset in the form of periodic outbursts of activity followed by prolonged periods of rest (13).The "overactive" lifestyle in patients with fibromyalgia has been operationalised as high "action-proneness" and considered as a cognitive and behavioural tendency toward direct action (12). The hypothesis that fibromyalgia subjects retrospectively idealise their premorbid lifestyle or attitude towards activity has not been supported by subsequent studies; the patients' self-descriptions are strongly confirmed by their significant others (13). The high "action-proneness" and the associated "overactive" lifestyle have been considered one of the factors that make people more vulnerable to fibromyalgia and also contributes to the onset and perpetuation of the illness. It has been suggested that the paths from such high "action-proneness" or "overactivity" to chronic fatigue and pain may involve psychological as well as physiological aspects (neuroendocrine and immunological alterations) (12).

Bipolar illness is a mood disorder characterised by the succession of depressive episodes and excited periods. Both bipolar I and bipolar II forms are defined by the presence of at least one depressive episode but are distinguished by the intensity of the excited periods: in bipolar I disorder there is severe mania, while in bipolar II disorder excitement is less severe (hypomania).

In recent decades the boundaries of bipolar disorder have gradually been expanded to include subsyndromal and atypical forms of hypomania. All forms of bipolar disorders are now best conceptualised as a continuum, ranging from the minor, normal forms of hyperthymic temperament to the most severe cases of delusional mania and together defined as the bipolar spectrum disorders (14, 15). The correct definition and accurate detection of hypomania are key to the identification of bipolar spectrum disorders. Nevertheless, hypomanic symptoms are underdiagnosed in clinical practice because they are rarely experienced by the subjects themselves as pathological, being often associated with enhanced productivity and masked by the natural diurnal and annual rhythms of mood (16).

Several studies (17-19) suggest that overactivity (increased goal-directed activities) is a core feature of hypomania, arguing in favour of upgrading it to the same priority level as mood enhancement in the diagnosis of hypomania. Overactivity is an observable behaviour, which is easier to remember than mood change and which frequently prompts patients' memories of a concurrent mood change.

Our hypothesis is that the overactive lifestyle described in the literature in subjects with fibromyalgia represents a core feature of hypomania, often in its subsyndromal or atypical forms. In order to test this hypothesis we assess the prevalence of the entire bipolar spectrum, using both a modified version of the Structured Clinical Interview for DSM-IV Axis I Disorders-Clinician Version Mood Disorder module (SCID-CV) and a hypomanic symptom count based on a validated 32-item hypomania symptom checklist (HCL-32) (16), which adopts a dimensional perspective of the manic/hypomanic component of mood. According to a "spectrum" approach we consider not only threshold-level manifestations of mood disorders, but also atypical, subthreshold features and symptoms that may occur throughout the patient's lifetime in isolation or as part of a temporally circumscribed clinical syndrome. We hypothesised that the prevalence of bipolar spectrum disorders would be higher in patients with fibromyalgia than in the general population.

Methods

Subjects

A consecutive series of 110 subjects with fibromyalgia attending the Rheumatology Department of L. Sacco University Hospital entered the study from May 2010 to May 2011. The patients underwent a detailed medical history and a thorough clinical examination by an experienced rheumatologist. Enrolment in the study was conditional on meeting American College of Rheumatology criteria (20) for fibromyalgia, including widespread pain for at least 3 months distributed through both sides and both upper and lower parts of the body. In addition, pain had to be present in 11 out of 18 specified sites (tender points) detected by a pressure of 4 kg/cm applied for a few seconds.

Subjects were excluded from the study if they had a) an inflammatory cause of pain, b) clinically significant current or previous hepatic, renal, cardiac, neurological, endocrine or malignant diseases. The study was accepted by the University Hospital L. Sacco Ethics Committee. After complete explanation of the study, written informed consent was obtained from all subjects. It was conducted in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans.

Psychiatric diagnoses

Psychiatric diagnoses were based on data collected with the Structured Clinical Interview for DSM-IV Axis I Disorders-Clinician Version, Mood Disorder module (SCID-CV) (21) in a cross-sectional, single assessment by two experienced clinicians (A.A. and F.G.). The SCID-CV was modified in a semi-structured way because the possibility of changing the wording of sentences allows improvements and checks on the level of understanding by each patient. The SCID-CV was also modified as suggested by Benazzi and Akiskal (22) in order to improve the detection of bipolar II disorder (BIP-II). In particular, the skip-out instruction for the SCID-CV stem question on mood was not followed. The systematic probing for all past hypomanic symptoms, regardless of the patient's answer to the mood screening question, can elicit hypomanic features that would otherwise be ignored by the strict adherence to the SCID. In addition, the DSM-IV-TR 4-day minimum duration of hypomania required for a diagnosis of BIP-II was not adhered to, and patients with hypomania lasting at least 1 day were included, on the basis of studies showing close similarities in diagnostic validators between bipolar II disorder with short periods of hypomania (of 1-3 days) and DSM-IV-TR bipolar disorder (17, 22).

Definition of the bipolar spectrum

In addition to DSM-IV-TR diagnoses, we applied the broadest definition of the bipolar spectrum (Zurich criteria), (17) comprising the bipolar spectrum subtypes as follows:

Major bipolar spectrum

1. Bipolar I disorder (BIP-I): major depressive episode associated with a manic syndrome.
2. Bipolar II disorder (BIP-II): major depressive episode associated with a) a hypomanic syndrome or b) a subsyndromal hypomanic episode (both defined below).

Minor bipolar spectrum

3. Minor bipolar disorder (MinBP): dysthymia, minor depression or recurrent brief depression associated with a) a hypomanic syndrome, or b) hypomanic symptoms only (subsyndromal hypomanic episode).
4. Pure hypomania (PureHyp): a) a hypomanic syndrome without any diagnosis of depression, or b) hypomanic symptoms only (subsyndromal hypomanic episode) lasting at least 1 day.

Hypomanic syndrome was defined according to the Zurich criteria (17): 1)

euphoria, irritability, or overactivity; 2) patients have themselves experienced problems or received comments from others that something must be wrong with them (consequences); 3) patients presented at least three out of seven signs and symptoms of DSM-IV hypomania.

Subsyndromal hypomanic episode was defined as an episode of at least two hypomanic symptoms, which did not meet DSM-IV criteria for hypomania (number of symptoms below DSM-IV cut-off, or mood changes not present, or duration of ≥1 day) and did not have consequences (17, 23).

Recurrent brief depression was diagnosed according to ICD-10. Minor depression was diagnosed according to the Zurich definition, which required three to four of nine DSM-III-R criterial symptoms, with a minimum duration of 2 weeks. Minor bipolar disorders and pure hypomania were also defined as minor affective spectrum conditions.

Hypomania Symptom Checklist

All past hypomanic symptoms, with overactivity (increased goal-directed activity) considered as a stem criterion on a par with euphoria and irritability, were systematically assessed using the Italian version of the Hypomania Symptom Checklist (HCL-32) (24). The HCL-32 is a self-administered, paper and pencil inventory consisting of 32 yes/no items used in psychiatric and general medical practice to identify possible symptoms of hypomania in patients with depressive episodes and designed to help clinicians diagnose bipolar II and minor bipolar disorders (16). Results of a study in non-clinical adult samples (25) suggest that the HCL-32 can also be useful as a screening tool in nonclinical samples as well. The analyses of the HCL responses in this paper are restricted to the checklist of hypomanic items (*i.e.* they do not cover the other questions in the HCL-32 regarding consequences, etc.).The total HCL-32 score was obtained by summing all items rated "yes". We used a cut-off score of 14, found to yield the best combination of sensitivity (true bipolars) (80%) and specificity (true non-bipolars) (51%) in distinguishing between bipolar disorder and major depressive disorders (MDD) in a study of Italian and Swedish patients (16).

A number of studies (26, 27) have revealed, across cultures, a two-factor structure of hypomania, also present in the HCL-32 (25, 28).The first factor (F1), defined as *active-elated*, is an indicator of hypomanic symptoms related to the *sunny, bright expression* of bipolarity, such as increased activity, energy, social contacts and communication. The second factor (F2), *risk-taking/irritable*, includes the more negative, problem-causing symptoms of hypomania (irritability, impulsivity, substance abuse) (25).

Headache and fibromyalgia

A frequently reported symptom, which is not comprised in the definition of fibromyalgia but may further increase the patient's disability, is headache, which was found in 70 to 76% of patients with fibromyalgia (29). The comorbidity between migraine and bipolar disorders, with a preferential association with bipolar II disorder, is well documented in numerous epidemiological and clinical studies (30). All patients were asked if they had repeatedly suffered from headaches in their lives. The International Classification of Headache Disorders version 2 (ICDH-II) (Headache Classification Subcommittee of the International Headache Society, 2004) was applied to each patient who complained of headache, but in this paper headache has been considered dichotomously only (yes/no).

Statistical analyses

Differences in demographic characteristics and clinical symptoms among the bipolar spectrum patients were analysed using the Chi-squared test for categorical variables and the independent Student's *t*-test for dimensional variables. *P*-values <0.05 were considered statistically significant. Analysis of variance was used to compare the groups and differences between means were determined by *post hoc* LSD analysis.

Profiles of single, dichotomous items of the HCL-32 were compared between major and minor bipolar spectrum individuals using Chi-squared tests. *P*-values were two-tailed, and conservatively set at 0.01 because of multiple comparisons between groups.

Results

The total sample comprised 110 patients with fibromyalgia (8 males and 102 females) with a mean age of 46.12±12.1 years. All patients were of Caucasian ethnicity and had a mean educational level of 11.6±3.37 years. The patients reported having had their first fibromyalgia symptoms an average of 10.8 years (S.D.=9.8) before our psychiatric examination, but the time to diagnosis was 7.9 years (SD=8.6).

Diagnoses

Applying DSM-IV-TR criteria, we found a lifetime major depressive episode (MDE) in 63 of the total sample of 110 patients (57.3%). Only 3 were currently depressed. Thirty of the 63 patients with MDE met criteria for DSM-IV bipolar II disorder. The remaining 33 patients with MDE were diagnosed as having bipolar disorder NOS (Table I). None of the patients received a DSM-IV-TR diagnosis of unipolar depression, bipolar I disorder or hypomanic episode without depression. A further 14 patients, without MDE, were diagnosed as having bipolar disorder NOS.

According to the Zurich classification (17), 95 of the 110 subjects with fibromyalgia (86.3%) were diagnosed as having a bipolar spectrum disorder. 63 of the 95 (66.3%) met the broader criteria for BIP-II (including brief hypomanic episodes of 1 to 3 days. 14 (14.7%) were diagnosed as having minor bipolar disorder and 18 (18.9%) hypomania only. A comparison between Zurich and DSM-IV classifications is shown in Table I.

All further analyses are based on the Zurich criteria.

The three diagnostic groups, bipolar II disorder, minor bipolar disorder and pure hypomania, did not differ with regard to demographic/clinical characteristics and health habits as shown in Table II.

There were no differences between the total HCL-32 scores of patients with bipolar II disorder, minor bipolar disorder and pure hypomania.

Table I. Diagnoses according to DSM-IV-TR and Zurich criteria.

	Major Bipolar Spectrum		Minor Bipolar Spectrum		
	MDE with hypomanic features		Minor bipolar disorder (MinBP):	Pure hypomania (PureHyp):	
	n=63		n=14	n=18	
DSM IV-TR	BIP-II n=30	BIP NOS. n=33	BIP NOS. n=14	--	--
Zurich criteria	MDE+ Zurich criteria hypomanic syndrome n=45	MDE+ hypomanic symptoms n=18	n=14	hypomanic syndrome --	hypomanic symptoms n=18

MDE: Major depressive episode; BIP NOS: Bipolar disorder Not Otherwise Specified; BIP-II: Bipolar II disorder; MinBP: Minor bipolar disorder; PureHyp: Minor bipolar disorder.

Table II. Comparison of demographic and clinical characteristics in fibromyalgia patients with bipolar spectrum disorders of differing severity.

	Major Bipolar Spectrum	Minor Bipolar Spectrum		*p*-value BIP-II/MinBP/ PureHyp	*p*-value Major/Minor BP Spectrum
	BIP-II 63 (66.3%)	MinBP 14 (14.7%)	Hypomania 18 (18.9%)		
Sex (F/M)	58/5	12/2	17/1	χ^2= 0.83 NS	χ^2= 0.05 NS
Age years (mean±SD)	46.68 ± 11.4	46.5 ± 11.5	45.6 ± 11.7	F= 0.062 NS	t= -0.263 NS
Education years (mean±SD)	11.3 ± 4.55	12 ± 4.24	11.7 + 2.95	F=0.131 NS	t= -0.069 NS
Civil status					
Married	46	9	13	χ^2=1.83 NS	χ^2= 1.1 NS
Single	12	4	3		
Separated/divorced	11	1	2		
Work					
Manager	6	3	2	χ^2=9.55 NS	χ^2= 1.45 NS
White collar	30	4	7		
Blue collar	19	7	2		
Unemployed	8	0	4		
Smoking status					
Current	22	3	4	χ^2=2.89 NS	χ^2= 2.8 NS
Past	8	1	1		
Never	27	9	9		
Alcohol use					
Daily	6	2	3	χ^2= 3.96 NS	χ^2= 3.75 NS
Occasional	6	0	0		
Never	45	11	11		

BIP-II: Bipolar II disorder; MinBP: Minor bipolar disorder; PureHyp: Minor bipolar disorder.

Table III. HCL-32 total and factor 1 and 2 scores in patients with fibromyalgia and bipolar II disorder, minor bipolar disorder and pure hypomania.

HCL-32	BIP-II n=63	MinBP n=14	PureHyp n=18	ANOVA or χ^2	*p*-value
Sum score	19.04 ± 3.83	17.36 ± 4.83	16.7 ± 3.33	F= 2.81	P=0.065 NS
Factor 1 (Active-elated)	12.3 ± 1.9	11.07 ± 2.9	11.06 ± 2.08	F=3.48	P=0.035
Factor 2 (risk-taking/irritable)	3.23 ± 2.3	2.54 ± 2.8	2.5 ± 1.9	F = 0.90	NS
Sum score 14+	53 (84.1%)	12 (85.7%)	14 (77.7%)	χ^2= 1.91	NS

HCL-32: Hypomania symptom checklist; BIP-II: Bipolar II disorder; MinBP: Minor bipolar disorder; PureHyp: Minor bipolar disorder.

Overall, 79 of the 95 patients (83%) scored equal to or above the cut-off point of 14 for bipolar disorder, suggested by Angst *et al*. (16) in their original validation of the HCL-32. Patients with BIP-II scored highest on the HCL-32 active/elated subscale, which includes overactivity, mood elation and faster thinking. *Post hoc* analyses demonstrated that the difference was due to the subgroup with pure hypomania. This result is not surprising, as this group included several individuals with a subsyndromal hypomanic episode (limited hypomanic symptoms). The factor 2 score did not distinguish the three diagnostic subgroups (Table III).

Sixty (63%) of the 95 subjects with bipolar spectrum disorders reported current or past use of antidepressants prescribed for a depressive episode or for the treatment of diffuse pain. In all cases the hypomanic symptoms rated on the HCL-32 were present before the medication was taken.

We found no statistically significant differences between the proportion of patients with major bipolar spectrum and minor bipolar spectrum disorders in their endorsement of the individual items of the HCL-32 (Fig. 1).

HCL-32 items relating to overactivity were rated as present by the vast majority of subjects, more specifically "I feel more energetic and more active" (93.5%), "I am physically more active" (89%), "I do things more quickly and/or more easily" (89%), with no significant differences between major and minor bipolar spectrum disorders. Positive responses to items reflecting the mental aspect of overactivity such as "I plan more activities or projects", "I have more ideas, I am more creative" were also highly represented (95.5% and 90%, respectively), demonstrating that overactivity is not merely a "physical" behaviour but has a psychological counterpart according to the classic descriptions of hypomania based on three basic domains: elation of mood, thinking, and behaviour (31).

As shown in Table IV, several fibromyalgia-related aspects, such as age at onset, duration of illness, time to diagnosis, presence of headache, are not significantly different in the various di-

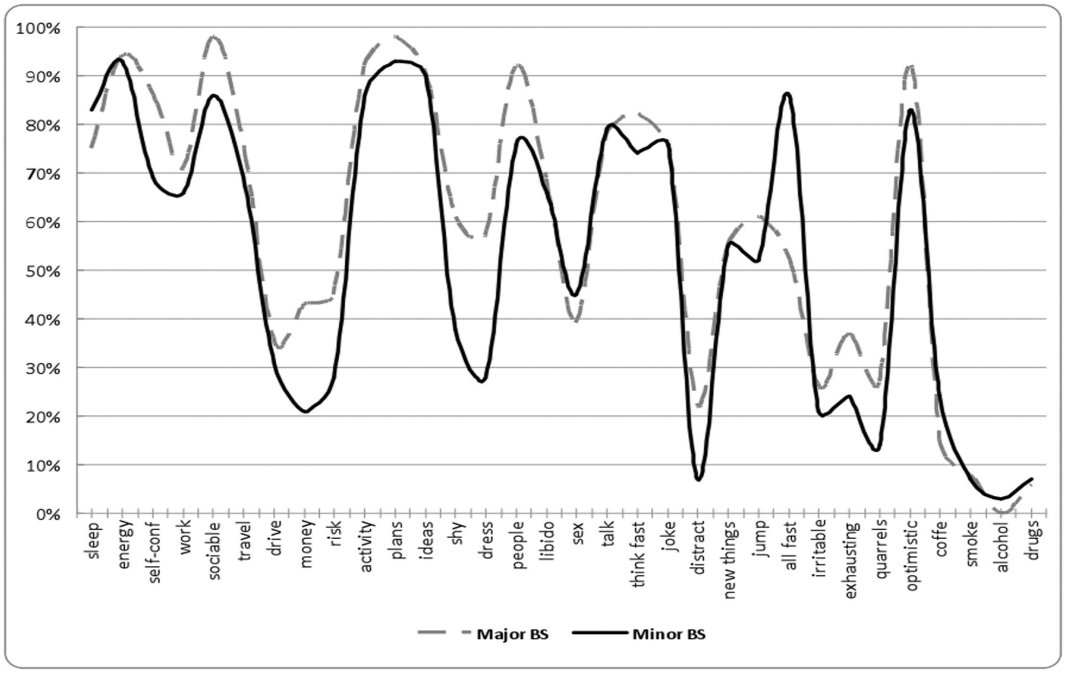

Fig. 1. Hypomania symptom checklist (HCL-32) items rated positive by fibromyalgia patients with major and minor bipolar spectrum disorders.

agnostic subgroups of bipolar spectrum disorders, suggesting that the severity of mood disorder is not related to the clinical characteristics of fibromyalgia.

Discussion

Our study shows a higher-than-expected comorbidity between fibromyalgia and bipolar spectrum disorders among patients with fibromyalgia as compared to the general population. The rate found in the present study (86%) is higher than the top prevalence rate of bipolar spectrum disorders reported in the literature from community studies. The Zurich Cohort Study (17), from which we derive the diagnostic criteria, has shown that bipolar spectrum disorders affect up to 11% of the general population, while other community studies applying DSM diagnoses have reported lifetime prevalence rates ranging from 5.1% (32) to 8.3% (33). Applying DSM-IV criteria, we found 30 patients with bipolar II disorder (27%), a further 47 patients with bipolar disorder NOS (43%), and not a single case with MDD. Thus, in our sample the DSM rates of bipolar disorders, too, are much higher than in the community studies.

Our findings are consistent with those from the few studies on fibromyalgia in the literature, two of which were carried out in Italian populations. The first Italian study showed the frequency of manic symptoms (59%) in a sample of patients with fibromyalgia to be approximately double that in the control population (34). In the most recent investigation a high rate of lifetime manic symptoms was related to the severity of pain and a worse quality of life (35).

The data from the hypomania symptom checklist are in agreement with the diagnostic evaluation based on the SCID-CV. Overall, 79 of the 95 patients (83%) with fibromyalgia diagnosed as having a bipolar spectrum disorder had a score equal to or above the cut-off point of 14, considered the screening threshold for hypomania.

Our findings support the hypothesis that the overactivity described in previous studies of patients with fibromyalgia and chronic fatigue is an element of bipolarity. The HCL-32 items relating to overactivity were endorsed by the vast majority of subjects, as were the HCL-32 items reflecting the other two basic domains of hypomania, elation of mood and faster thinking (31).

High total HCL-32 scores and overactivity were found both in major and in minor bipolar spectrum fibromyalgia patients, confirming that overactivity is a core characteristic in fibromyalgia patients independently of the severity of the associated mood disorder

In our study a lifetime major depressive episode was diagnosed, in the context of bipolar spectrum disorders, in 63 of 110 patients with fibromyalgia (57%). This value is consistent with the literature, which reported rates of lifetime major depressive disorder comorbidity ranging from 20% to 86% (36-38) with a median of 58%.

Moreover, we found that 14 of the 110 patients (12.7%) had both subthreshold depressive and hypomanic symptoms (minor bipolar disorders). This result is compatible with a recent study showing that subthreshold depressive symptoms are more represented in fibromyalgia than in rheumatoid arthritis patients (39).

It should also be noted that no patient in our sample received a diagnosis of unipolar major depression. This striking result is partly supported by the studies reporting that more than half the patients with "unipolar" major depression were found to have bipolar disorder when the patient assessment was made by trained clinicians by means of a semi-structured systematic interview of past hypomania (22, 40)

Beyond the diagnostic issue, we could hypothesise that bipolar spectrum disorders, but not unipolar depressive disorders, may represent a risk factor for the clinical expression of fibromyalgia symptoms. Indeed our results strongly suggest that fibromyalgia is related not specifically to depression but rather to

Table IV. Fibromyalgia-related aspects in patients with fibromyalgia and bipolar II disorder (major bipolar spectrum), minor bipolar disorder and pure hypomania (minor bipolar spectrum).

Fibromyalgia: clinical features	Major bipolar spectrum	Minor bipolar spectrum		*p*-value BIP-II/MinBip/ PureHyp	*p*-value Major/Minor BipSpectrum
	BIP-II	MinBIP	PureHYP		
	63 (66.3%)	14 (14.7%)	18 (18.9%)		
Age at onset	35.5± 12.2	33.14± 14.5	38.4 ± 13.3	F=0.686 NS	t=.0207 NS
Duration of illness (months)	134.9± 116.5	160.3± 165.5	87.8 ± 76.5	F=1.64 NS	t=-0.59 NS
Time to diagnosis (months)	110.7± 109.3	86.85± 122	54.3 ± 74.2	F=1.8 NS	t=1.76
Headache (yes/no)	47/11	14/0	16/2	χ^2=3.48 NS	χ^2= 2.69 NS

BIP-II: Bipolar II disorder; MinBP: Minor bipolar disorder; PureHyp: Minor bipolar disorder.

bipolar spectrum disorders and in particular to the hypomania/overactivity component. Threshold and subthreshold hypomanic features, especially overactivity, rather than full-blown and subthreshold depressive manifestations, were found in our population of patients with fibromyalgia.

The majority (63%) of patients with fibromyalgia in our study had taken antidepressants drugs for a depressive episode or pain; none had taken stimulants, such as modafinil, methylphenidate or amphetamines. Within the limits of a cross-sectional assessment, we established that the onset of hypomania/symptoms of overactivity was always prior to the drug use, so that these features cannot be considered as induced by the antidepressants.

It should be noted, however, that there is an extensive literature supporting the inclusion of hypomania that initially manifests after pharmacological antidepressant treatment as characteristic of bipolarity. This position is based on prospective observations that the vast majority of adult (14) and adolescent (41) patients with antidepressant-associated hypomanic episodes progress to bipolar states with spontaneous hypomania or mania. Moreover such patients often have a family history of bipolar disorders and a high susceptibility to rapid cycling (26).

Another main finding of this study is that fibromyalgia patients, despite the very different levels of severity of the comorbid bipolar spectrum disorder (subgroups from subthreshold hypomania via minor bipolar to bipolar II disorder) were indistinguishable with regard to demographic characteristics, health habits and clinical features of fibromyalgia.

These results are in agreement with the growing number of studies showing the levels of clinical severity, role impairment and comorbidity of subthreshold bipolar spectrum syndromes to be quite high and comparable to those found in non-bipolar major depression (42, 43).

These findings have treatment implications, since both a missed diagnosis of bipolar spectrum disorders and pain treatment may lead to the overuse of antidepressants, which may in turn worsen the course of the illness, inducing rapid cycling and mixed states (44, 40).

Our results have also to be considered in the context of brain research. Evidence from experimental pain studies (45) supports the hypothesis of an up-regulation of nociceptive activity in the Central Nervous System of fibromyalgia patients, as demonstrated by functional brain-imaging studies showing that the increased perception of pain in fibromyalgia is related to an augmentation of sensory processing in pain-related brain regions (46). Moreover, the role of a dysfunctions in pain modulation, as well as in pain perception, is suggested by the finding of a decreased grey matter in the brain areas (prefrontal, cingulate, and insular cortices) involved in inhibitory pain modulation in fibromyalgia patients (47).

The accumulating evidence that bipolar disorder is associated with early and persisting neuroanatomic, neurophysiologic and neurocognitive abnormalities raises the possibility that some alterations in brain structure and function are central to the pathophysiology of both bipolar disorder and fibromyalgia (48).

Neuroimaging studies have shown a significant overlap in brain areas that are functionally and/or structurally abnormal in bipolar disorder and fibromyalgia, including dorsolateral prefrontal cortex (DLPFC), orbitofrontal cortical (OFC), insula, anterior cingulate cortex (ACC), amygdala, hippocampus and thalamus (49, 50).

We may speculate that both hypomanic symptoms and pain sensitivity are related to a "hyperadrenergic state". Patients with mania were found to have significantly higher CSF levels of norepinephrine and its main metabolite MHPG (3-methoxy-4 hydroxyphenylglycol) (51), consistent with an enhanced central noradrenergic activity, and a high pain sensitivity has been detected in individuals with hyperadrenergic condition due to defective catecholamine-degrading enzymes (52).

Limitations: our study may suffer from referral bias; the population is from a tertiary care facility, which may have resulted in an overestimation of the prevalence of mood disorders.

The strengths of the study should also be noted; these include the use of a semi-structured diagnostic and investigator-based clinical psychiatric interview and of an innovative but well-validated measure of hypomanic symptoms, which enabled us to address the difficulties of some respondents in recalling hypomanic symptoms that were only present for a few days, especially if the symptoms were not impairing.

References

1. MEASE P, BUSKILA D, SARZI-PUTTINI P: The fibromyalgia conundrum. *Clin Exp Rheumatol*. 2009; 27 (Suppl. 56): S2-4.
2. BAZZICHI L, SERNISSI F, CONSENSI A, GIACOMELLI C, SARZI-PUTTINI P: Fibromyalgia: a critical digest of the recent literature. *Clin Exp Rheumatol* 2011; 29 (Suppl. 69): S1-11.
3. DI FRANCO M, IANNUCCELLI C, ATZENI F *et al*.: Pharmacological treatment of fibromyalgia. *Clin Exp Rheumatol* 2010; 28 (Suppl. 63): S110-6.
4. HAVILAND MG, BANTA JE, PRZEKOP P: Fibromyalgia: prevalence, course, and comorbidities in hospitalized patients in the United States, 1999-2007. *Clin Exp Rheumatol* 2011; (Suppl. 69): S79-87.
5. DI FRANCO M, IANNUCCELLI C, BAZZICHI L *et al*.: Misdiagnosis in fibromyalgia: a mul-

ticentre study. *Clin Exp Rheumatol* 2011; 29 (Suppl. 69): S104-8.
6. ULUS Y, AKYOL Y, TANDER B, DURMUS D, BILGICI A, KURU O: Sleep quality in fibromyalgia and rheumatoid arthritis: associations with pain, fatigue, depression, and disease activity. *Clin Exp Rheumatol* 2011; 29 (Suppl. 69): S92-6.
7. HUDSON JI, GOLDENBERG DL, POPE HGJ, KECK PEJ, SCHLESINGER L: Comorbidity of fibromyalgia with medical and psychiatric disorders. *Am J Med* 1992; 92: 363-7.
8. GOLDENBERG DL: Fibromyalgia syndrome a decade later. What have we learned? *Arch Intern Med* 199; 159: 777-5.
9. AHLES TA, KHAN SA, YUNUS MB, SPIEGEL DA, MASI AT: Psychiatric status of patients with primary fibromyalgia, patients with rheumatoid arthritis and subjects without pain: a blind comparison of DSM-III diagnoses. *Am J Psychiatry* 1991; 148: 1721-6.
10. WALKER EA, KEEGAN D, GARDNER G, SULLIVAN M, KATON WJ, BERNSTEIN D: Psychosocial factors in fibromyalgia compared with rheumatoid arthritis: psychiatric diagnoses and functional disability. *Psychosom Med* 1997; 59: 565-71.
11. WARE NC: Society, mind and body in chronic fatigue syndrome: an anthropological view. *In*: BOCK G, WHELAN J (Eds.), *Chronic Fatigue Syndrome*. *Wiley, Chichester,* 1993; pp. 62-82.
12. VAN HOUDENHOVE B, ONGHENA P, NEERINCKX E, HELLIN J: Does high 'action-proneness' make people more vulnerable to chronic fatigue syndrome? A controlled psychometric study. *J Psychosom Res* 1995; 39: 633-40.
13. VAN HOUDENHOVE B, NEERINCKX E, ONGHENA P, LYSENS R, VERTOMMEN H: Premorbid 'overactivity' lifestyle in chronic fatigue syndrome and fibromyalgia. An etiological factor or proof of good citizenship? *J Psychosom Res* 2001; 51: 571-6.
14. AKISKAL HS: The bipolar spectrum: new concepts in classification and diagnosis. *In*: GRINSPOON L. (Ed.), *Psychiatry update: The American Psychiatric Association Annual Review*. *American Psychiatric Press, Washington D.C.,* 1983: pp. 271-92.
15. CASSANO GB, FRANK E, MINIATI M *et al*.: Conceptual underpinnings and empirical support for the mood spectrum. *Psychiatr Clin N Am* 2002; 25: 699-712.
16. ANGST J, ADOLFSSON R, BENAZZI F *et al*.: The HCL-32: towards a self-assessment tool for hypomanic symptoms in outpatients. *J Affect Disord* 2005; 88: 217-33.
17. ANGST J, GAMMA A, BENAZZI F, AJDACIC V. EICH D. RÖSSLER W: Toward a re-definition of subthreshold bipolarity: epidemiology and proposed criteria for bipolar-II, minor bipolar disorders and hypomania. *J Affect Disord* 2003; 73: 133-46.
18. BENAZZI F: Challenging DSM-IV criteria for hypomania: diagnosing based on number of no-priority symptoms. *Eur Psychiatry* 2007; 22: 99-103.
19. BENAZZI F: Is overactivity the core feature of hypomania in bipolar II disorder? *Psychopathology* 2007; 40: 54-60.
20. 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.
21. FIRST MB, SPITZER RL, GIBBON M, WILLIAMS JBW: Structured clinical interview for DSM-IV Axis I Disorders - clinician version (SCID-CV). *American Psychiatric Press, Washington DC* 1997.
22. BENAZZI F, AKISKAL H: Refining the evaluation of bipolar II: beyond the strict SCID-CV guidelines for hypomania. *J Affect Disord* 2003; 73: 33-8.
23. 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.
24. 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 Ment Health* 2006.
25. MEYER TD, HAMMELSTEIN P, NILSSON LG, SKEPPAR,P. ADOLFSSON R, ANGST J: The Hypomania Checklist (HCL-32): its factorial structure and association to indices of impairment in German and Swedish nonclinical samples. *Compr Psychiatry* 2007; 48: 79-87.
26. AKISKAL H: Validating 'hard' and 'soft' phenotypes within the bipolar spectrum: continuity or discontinuity? *J Affect Disord* 2003; 73: 1-5.
27. BENAZZI F, AKISKAL HS: The dual factor structure of self-rated MDQ hypomania: energized-activity versus irritable-thought racing. *J Affect Disord* 2003; 73: 59-64.
28. VIETA E, SANCHEZ-MORENO J, BULBENA A *et al*.: Cross validation with the mood disorder questionnaire (MDQ) of an instrument for the detection of hypomania in Spanish: the 32 item hypomania symptom check list (HCL-32). J *Affect Disord* 2007; 101: 43-55.
29. MARCUS DA, BERNSTEIN C, RUDY TE: Fibromyalgia and headache: an epidemiological study supporting migraine as part of the fibromyalgia syndrome. *Clin Rheumatol* 2005; 24: 595-601.
30. FASMER OB: The prevalence of migraine in patients with bipolar and unipolar affective disorders. *Cephalalgia* 2001; 21: 894-9.
31. GOODWIN FK, JAMISON KR: Manic-depressive illness. *Oxford University Press, New York* Oxford 1990.
32. SZADOCZKY E, PAPP Z, VITRAI J, RIHMER Z, FÜREDI J: The prevalence of major depressive and bipolar disorders in Hungary. Results from a National Epidemiologic Survey. *J Affect Disord* 1998; 50: 153-62.
33. MORENO DH, ANDRADE LH: The lifetime prevalence, health service utilization and risk of suicide of bipolar spectrum subjects, including subthreshold categories in the São Paulo ECA study. J *Affect Disord* 2005; 87: 231-41.
34. CARTA MG, HARDOY MC, CADEDDU M *et al*.: The accuracy of the Italian version of the Hypomania Checklist (HCL-32) for the screening of bipolar disorders and comparison with the Mood Disorder Questionnaire (MDQ) in a clinical sample. *Clin Pract Epidemiol Ment Health* 2006; 2: 1-5.
35. DELL'OSSO L, BAZZICHI L, CONSOLI G *et al*.: Manic spectrum symptoms are correlated to the severity of pain and the health-related quality of life in patients with fibromyalgia. *Clin Exp Rheumatol* 2009; 27: 57-61.
36. ARNOLD LM, HUDSON JI, KECK PE, AUCHENBACH MB, JAVARAS KN, HESS EV: Comorbidity of fibromyalgia and psychiatric disorders. *J Clin Psychiatry* 2006; 67: 1219-25.
37. HUDSON JI, HUDSON MS, PLINER LE, GOLDENBERG DL, POPE HG JR.: Fibromyalgia and major affective disorder: a controlled phenomenology and family history study. *Am J Psychiatry* 1985; 142: 441-6.
38. WALKER EA, KEEGAN D, GARDNER G, SULLIVAN M, KATON WJ, BERNSTEIN D: Psychosocial factors in fibromyalgia compared with rheumatoid arthritis: psychiatric diagnoses and functional disability. *Psychosom Med* 1997; 59: 565-71.
39. PICCINNI A, BAZZICHI L, MARAZZITI D *et al*.: Subthreshold mood symptoms in patients with fibromyalgia and rheumatoid arthritis. *Clin Exp Rheumatol* 2011; 29 (Suppl. 69): S5-9.
40. GHAEMI SN, BOIMAN EE, GOODWIN FK: Diagnosting bipolar disorder and the effect of antidepressants: a naturalistic study. *J Clin Psychiatry* 200; 61: 804-8.
41. STROBER M, CARLSON G: Bipolar illness in adolescents with major depression. Clinical, genetic, and psychopharmacologic predictors in a three- to four-year prospective follow-up investigation. *Arch Gen Psychiatry* 198; 39: 549-55.
42. CALABRESE JR, HIRSCHFELD RMA, REED M *et al*.: Impact of bipolar disorder on a U.S. community sample. *J Clin Psychiatry* 2003; 64: 425-32.
43. DEAN BB, GERNER D, GERNER RH: A systematic review evaluating health-related quality of life, work impairment, and healthcare costs and utilization in bipolar disorder. *Curr Med Res Opin* 2004; 20: 139-54.
44. AKISKALHS, MALLYA G: Criteria for the 'soft' bipolar spectrum: treatment implications. *Psychopharmacol Bull* 1987; 23: 68-73.
45. LAUTENBACHER S, ROLLMAN GB, MCCAIN GA: Multi-method assessment of experimental and clinical pain in patients with fibromyalgia. *Pain* 1994; 59: 45-53.
46. BURGMER M, POGATZKI-ZAHN E, GAUBITZ M, WESSOLECK E, HEUFT G, PFLEIDERER B: Altered brain activity during pain processing in fibromyalgia. *Neuroimage* 2009; 44: 502-8.
47. ROBINSON ME, CRAGGS JG, PRICE DD, PERLSTEIN WM, STAUD R: Gray matter volumes of pain-related brain areas are decreased in fibromyalgia syndrome. *J Pain* 2011; 12: 436-43.
48. KEMPTON MJ, GEDDES JR, ETTINGER U, WILLIAMS SC, GRASBY PM: Meta-analysis, database, and meta-regression of 98 structural imaging studies in bipolar disorder. *Arch Gen Psychiat* 2008; 65: 1017-32.
49. STAUD R: Brain imaging in fibromyalgia syndrome. *Clin Exp Rheumatol* 2011; 29 (Suppl. 69): S109-17.
50. BROOKS BO, WANG PW, BONNER JC *et al*.: Decreased prefrontal, anterior cingulate, insula, and ventral striatal metabolism in medication-free depressed outpatients with bipolar disorder. *J Psychiatr Res* 2009; 43: 181-8.
51. SWANN AC, SECUNDA S, DAVIS JM *et al*.: CSF monoamine metabolites in mania. *Am J Psychiatry* 1983; 140: 396-400.
52. DIATCHENKO L, SLADE GD, NACKLEY AG *et al*.: Genetic basis for individual variation of pain perception and the development of a chronic pain condition. *Hum Mol Genet* 2005; 14: 135-43.