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Psychopathological symptoms in fibromyalgia and their associations with resistance to pharmacotherapy with SNRI

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Summary

Aim. Fibromyalgia (FM) is often comorbid with psychiatric disorders. Moreover, several studies show that psychiatric disorders may be linked to the severity and impact of FM. Therefore, the study described in the article had two main goals: (1) to explore various psychopathological symptom dimensions in patients with fibromyalgia and secondly, (2) to examine the links between psychopathology and response to treatment with serotonin and norepinephrine reuptake inhibitors (SNRI).

Method. This cross-sectional study was performed between December 2020 and November 2022. The definition of resistance to SNRI was <30% reduction of pain after ≥8 weeks of treatment. 30 FM subjects responsive to SNRI (FM T[+]), 32 patients non-responsive to SNRI (FM T[–]) and 30 healthy controls were enrolled. Participants were examined by physicians and completed self-report tools to evaluate levels of depression (*Quick Inventory of Depressive Symptomatology*, *Hospital Anxiety and Depression Scale*), anxiety (*State and Trait Anxiety Inventory*), anhedonia (*Snaith-Hamilton Pleasure Scale*), bipolar symptoms (*Mood Disorder Questionnaire*, *Hypomania Checklist*), and dissociation (*Dissociative Experiences Scale – Revised*). ANOVA analysis and a series of simple logistic regressions were used to examine the associations between psychopathological variables and response to SNRI.

Results. FM T[–] vs. FM T[+] showed higher levels of: depression, state and trait anxiety and anhedonia as well as higher proportion of scores indicating the presence of anxiety disorder. Increased severity of depression, anxiety and anhedonia were predictors of resistance to SNRI.

Conclusions. Modifiable psychopathological symptoms vary in FM T[+] vs. FM T[–] and are predictors of resistance to SNRI. Psychological assessment should be integrated into standard care for FM patients.

Key words: antidepressants, psychopathology, fibromyalgia

Introduction

Fibromyalgia (FM) is characterized by widespread pain, fatigue, stiffness as well as depressed mood, anxiety and sleep disturbances. Indeed, some psychopathological symptoms are part of the FM syndrome [1]; however, in many FM patients their severity warrants a separate diagnosis and as a consequence should be addressed with an appropriate treatment. A recent systematic review noted that among FM patients the current prevalence of psychiatric comorbidities is: 9-27% for anxiety disorders, 2-44% for post-traumatic stress disorder (PTSD), 5-76% for depression, 1-9% for bipolar disorder and 19.3% for personality disorder, while their lifetime occurrence reaches: 9.1% for generalized anxiety disorder, 33% for panic disorder, 16.1% for PTSD, 63% for depression and 26.2% for bipolar disorder [2]. It was reported that depression and anxiety are linked to the severity of pain and other FM symptoms assessed with the Fibromyalgia Impact Questionnaire (FIQ) as well as worse functional status in FM [3–5]. While the studies assessing bipolar features in FM are sparse, there is some evidence supporting the relationships between the bipolar spectrum and FM severity [6], patients' quality of life [7], FM clinical presentation and socioeconomic status [8].

It is known that pain may significantly impair reward processing and that the higher levels anhedonia in chronic pain patients vs. healthy controls (HC) are not fully explained by the severity of depression [9]. Yet, there is a dearth of evidence on prevalence, severity and impact of anhedonia in FM. Our preliminary data showed that compared to HC, FM subjects more often suffered from anhedonia (10% vs. 29.21%) [10]. Moreover, Boehme et al. [11] observed that compared to HC, FM patients reported lower levels of pleasantness to tactile stimuli. What is more, a study performed by Duatre et al. [12] revealed that patients with FM present higher rates of dissociative symptoms than HC and participants with rheumatic diseases (rheumatoid arthritis, osteoarthritis, Sjögren´s syndrome or systemic erythematosus lupus). Also, Berkol et al. [13] reported that dissociative symptoms are more common in FM than in HC and that their levels are associated with the severity of pain and other FM symptoms.

The literature on the epidemiology of psychopathological symptoms in FM is fragmentary with the majority of research focusing solely on clinical diagnoses. Due to the relationships between severity of psychiatric and FM symptoms, it is vital to explore the prevalence and role of different dimensions of psychiatric symptoms in FM. Despite the burning issue of dissatisfying level of treatment effectiveness in FM, the data on the links between psychopathology and response to pharmacological therapy in FM are scarce [14]. Kim et al. [15] reported that higher levels of FM severity and trait anxiety were predictive of improvement after a year of pharmacological treatment. Our previous works showed that the severity of psychological variables such as depression, anxiety, depressive, irritable and anxious affective temperaments, personality traits such

as introversion or neuroticism and schizotypy are associated with resistance to SNRI treatment [16,17] and that diagnoses of depression, anxiety and personality disorder are predictors of lack of response to treatment with SNRI [18]. The aim of this work was to assess the severity of depression, anxiety, bipolar spectrum symptoms, anhedonia and dissociation in FM. Furthermore, our goal was to examine the associations between different dimensions of psychopathology and response to SNRI in FM.

Material and methods

The data for this cross-sectional study were collected between December 2020 and November 2022. Participants were recruited from the psychiatry as well as rheumatology and immunology departments. The following inclusion criteria were applied for the FM patients group: a) age 18-65 years old; b) rheumatologist-confirmed diagnosis of fibromyalgia according to the 2016 American College of Rheumatology criteria [1]; c) history of SNRI pharmacotherapy: duloxetine (60-120 mg/d), venlafaxine (150-225 mg/d) or milnacipran (100-200 mg/d). The exclusion criteria for this group were: a) any severe, acute, or chronic pain (other than FM), rheumatological or other somatic disorders; b) substance use disorder (other than smoking); c) any severe mental illnesses (psychoses, bipolar disorder) or severe personality disorder (according to the classification suggested by Tyrer et al. [19]; d) no history of SNRI pharmacotherapy or history of taking subtherapeutic SNRI doses or history of SNRI pharmacotherapy continued for <8 weeks. The choice of a specific SNRI was at the discretion of the attending physician, who took the clinical presentation, comorbidities and possible interactions into consideration.

A group of HC was recruited from family and acquaintances of the researchers. The inclusion criterion was: a) age 18-65 years old. The exclusion criteria for HC group were: a) severe, acute, or chronic psychiatric disorders; b) severe, acute, or chronic somatic disorders; c) substance use disorder (other than smoking). A physician examined every participant, collected the demographic and clinical data. We allowed for the inclusion of subjects with comorbidities (asthma, allergies, dermatoses, thyroid insufficiency, hyperlipidemia and hypertension) on condition that these were appropriately treated and well controlled (to assure this, subjects provided certificates from their attending physicians or laboratory test results).

Patients were split into subgroups of responsive to SNRI (FM T[+]) or resistant to SNRI (FM T[-]). In order to do so, subjects reported the level of pain relief after ≥8 weeks of SNRI treatment on the scale from 0 (no change in the level of pain) to 10 (complete resolution of pain). Based on the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT), which defines at least 30% pain relief as moderate and at least 50% pain relief as substantial clinical outcome [20], we defined the treatment response to SNRI as at least 30% pain relief (that is, no less than: 3 points for initial NRS scores 7–10; no less than: 2 points for initial NRS scores 4–6) because our goal was to distinguish participants who significantly benefited from the SNRI treatment from those who did not. Each participant filled self-report questionnaires which examined the symptoms of:

a) depression: The 16-item Quick Inventory of Depressive Symptomatology – Self-report version (QIDS) which scores sad mood, concentration, self-criticism, suicidal ideation, general interest, energy/fatigue, sleep disturbance (initial, middle, and late insomnia or hypersomnia), decrease/increase in appetite/weight, psychomotor agitation/retardation in the 7 days before the assessment. The scores between 0 to 5 are considered normal (QIDS [-]) while higher scores suggest the presence of depression (QIDS [+]): 6-10 mild, 11-15 moderate, 16-20 – severe, 21-27 very severe [21];
b) depression and anxiety: The Hospital Anxiety and Depression Scale (HADS) which is a self-assessment scale designed to detect states of depression and anxiety that is broadly used to explore this symptomatology in a general medical setting; it consists of 7-item depression (HADS-D) and anxiety (HADS-A) subscales. The scores between 0-7 are classified as normal (HADS-A [-]; HADS-D [-]) and higher scores indicate increased levels of depression and/or anxiety: 8-10 borderline abnormal, 11-14 abnormal [22, 23];
c) anxiety: State and Trait Anxiety Inventory (STAI) which measures the levels of anxiety in two 20-item subscales of state anxiety (how subject feels at the moment; STAI-X) and trait anxiety (how subject feels in general; STAI-Y) [24];
d) anhedonia: Snaith-Hamilton Pleasure Scale (SHAPS) which measures the hedonic tone on a scale consisting of 14 items. In this work to detect subjects with anhedonia we set the cut-off score of >2 which indicates significantly lower hedonic tone than observed in the general population. Patients were allocated to subgroups scoring >2 (SHAPS [+]) or ≤2 (SHAPS [-]) [25, 26];
e) bipolar spectrum features: 1) the Mood Disorder Questionnaire (MDQ): MDQ was constructed by Hirshfeld et al. [27] in order to monitor for bipolar spectrum; for this study we used the validated Polish version of this brief 13-item inventory [28]. The cut-off score for positive screening for the presence of bipolar spectrum features was ≥7 and patients were divided into subgroups scoring ≥7 (MDQ [+]) or <7 (MDQ [-]), and 2) the Hypomania Checklist (HCL): HCL was constructed by Angst et al. [29] to assess the occurrence of hypo/manic symptoms across the lifespan. We used the validated Polish version of the 32-item inventory [30]. The cut-off score for positive screening for the presence of bipolar spectrum features was ≥14 and patients were divided into subgroups scoring ≥14 (HCL [+]) or <14 (HCL [-]) [29–31];
f) dissociation: Dissociative Experiences Scale – Revised (DES-R) which was developed to screen for dissociative disorders. It consists of 28 items assessing the frequency of dissociative experiences on the scale from “never” to “once or more a day”. The cut-off for allowing for identification of clinical cases of dissociative disorders is 71.5. Subjects were therefore split into subgroups scoring >71.5 (DES-R [+]) or ≤71.5 (DES-R [-]). We used the Polish version which has shown good psychometric properties [32].

All psychopathological assessments were analyzed as a continuous measure. Furthermore, regarding the instruments in which the cut-off scores are mentioned above

we also performed an analysis comparing subjects with positive screens to those with negative screens for possible presence of specific disorders. Next, patients with FM were asked to fill the FIQ. The FIQ was created with the aim to assess all the symptomatology related to FM. It consists of 20 questions measuring the level of impairment in physical tasks, work and well-being, severity of pain, fatigue, sleep, stiffness, anxiety and depression experienced by the patient in the week prior to examination [33]. In addition, the severity of FM was assessed by several components of the diagnostic criteria, that is, the Widespread Pain Index (WPI), Symptom Severity Scale (SSI) and Fibromyalgia Severity (FS) [1].

All participants signed an informed written consent. The study was approved by the Bioethics Committee of the Jagiellonian University in Krakow (approval no. 1072.6120.172.2021) and conducted in congruence with the Declaration of Helsinki [34].

Statistical analysis

The Student's *t*-test was used for the comparison of the quantitative variables and the Chi-squared test was used to compare the qualitative variables between studied groups. In order to assess the homogeneity of variances the Levene's test was performed. To assess the levels of psychopathological symptoms and the severity of FM in the patient groups one-way ANOVA was carried out. Also, post-hoc tests (Tukey or Games-Howell) and effect size calculation (eta-squared or Hedges' g) were performed. The relationships between the psychopathological variables and the lack of response to SNRI treatment were examined with a series of simple logistic regression analyses. Given the high correlations between psychopathological factors, it was not possible to build a regression model with >1 independent variable. Statistical analyses were conducted with the use of R software [35]. The *t*-test (with Welch correction when appropriate), Chi-squared test, ANOVA, effect size and post-hoc comparisons were carried out using rstatix package. For other analyses, functions from stats package were used.

Study sample

A total of 101 patients were recruited for this study, yet 39 were not enrolled because the diagnostic process indicated the presence of serious comorbidities ($n = 21$; 17 non-responsive and 4 responsive to SNRI) or they did not agree to participate in the study ($n = 18$; 10 non-responsive and 8 responsive to SNRI). In sum, 92 subjects were enrolled: 30 FM T[+] patients, 32 FM T[-] patients and 30 HC.

Results

General group characteristics

All groups were comparable with regard to sex, employment, marital status, and presence of somatic comorbidities. FM T[-] showed higher BMI than HC ($p = 0.004$),

while no significant differences in BMI were found between FM T[+] vs. FM T[-] and FM T[+] vs. HC. The proportion of smoking subjects was higher in FM T[-] vs. HC and FM T[-] vs. FM T[+], while the proportions of smoking participants were similar in FM T[+] vs. HC (Table 1).

Table 1. **General group characteristics**

Variable	HC n = 30	FM n = 62	FM T[+] n = 30	FM T[-] n = 32	HC vs. FM *	HC vs. FM T[+] vs. FM T[-] **	HC vs. FM T[+]	HC vs. FM T[-]	FM T[+] vs. FM T[-]
Age (mean years ± *SD*)	42.93 ± 12.75	44.53 ± 11.11	43.53 ± 10.81	45.47 ± 11.48	$t(90) = -0.62$ $p = 0.54$	$F(2, 89) = 0.4$ $p = 0.67$	$p = 0.98$	$p = 0.67$	$p = 0.79$
BMI (mean kg/m^2 ± SD)	23.99 ± 3.77	27.11 ± 5.74	25.78 ± 5.87	28.35 ± 5.42	$t(90) = -2.7$ **$p = 0.008$**	$F(2, 89) = 5.72$ **$p = 0.005$**	$p = 0.37$	**$p = 0.004$**	$p = 0.12$
Sex (female)	27	52	25	27	$\chi^2(92, 1) = 0.22$ $p = 0.64$	$\chi^2(92, 2) = 0.64$ $p = 0.73$	$p = 1$	$p = 1$	$p = 1$
Relationship (married)***	26	47	24	23	$\chi^2(92, 4) = 4.06$ $p = 0.4$	$\chi^2(92, 8) = 11.6$ $p = 0.17$	NA	$p = 0.34$	$p = 0.14$
Employed (yes)****	26	40	22	18	$\chi^2(92, 5) = 8.31$ $p = 0.14$	$\chi^2(92, 10) = 15$ $p = 0.13$	$p = 1$	$p = 0.4$	$p = 1$
Hyperlipidemia (yes)	4	2	1	1	$\chi^2(92, 1) = 1.93$ $p = 0.16$	$\chi^2(92, 2) = 3.39$ $p = 0.18$	$p = 1$	$p = 0.55$	$p = 1$
Hypertension (yes)	4	9	2	7	$\chi^2(92, 1) < 0.001$ $p > 0.99$	$\chi^2(92, 2) = 2.97$ $p = 0.23$	$p = 1$	$p = 0.68$	$p = 0.54$
Hypothyroidism (yes)	4	11	8	3	$\chi^2(92, 1) = 0.06$ $p = 0.81$	$\chi^2(92, 2) = 3.68$ $p = 0.16$	$p > 0.99$	$p = 0.48$	$p = 0.44$
Smoking (yes)	3	14	2	12	$\chi^2(92, 1) = 2.19$ $p = 0.14$	$\chi^2(92, 2) = 16.1$ **$p < 0.001$**	$p = 1$	**$p = 0.001$**	**$p = 0.007$**

FM – fibromyalgia patients as a whole group; FM T[+] – patients responsive to SNRI treatment; FM T[-] – patients resistant to SNRI treatment; HC – healthy controls; SD – standard deviation

$\chi 2$ test was used to compare the qualitative data; *T-test was used to assess the differences in quantitative data; ** – ANOVA was used to assess the differences in quantitative data; *** – comparison of married, informal relationship, single, divorced, widowed subgroups; **** – comparison of

employed, unemployed, retired, on pension or student subgroups. P values resulting from pairwise $\chi 2$ tests were adjusted using the Bonferroni correction.

Fibromyalgia clinical presentation

Significant differences were observed in the clinical presentation of fibromyalgia in FM T[+] vs. FM T[-]. The latter were characterized by longer duration of illness ($p = 0.017$), higher total score of FIQ ($p < 0.001$) and higher subscale scores of physical functioning ($p < 0.001$), well-being ($p = 0.009$), work-related ($p < 0.001$), pain ($p = 0.003$), fatigue/sleep ($p = 0.033$) and stiffness ($p = 0.018$) compared to FM T[+]. Additionally, higher scores of symptom severity ($p < 0.001$) and general severity of FM ($p = 0.004$) were noted in FM T[-] vs. FM T[+] (Table 2).

Table 2. **Fibromyalgia clinical presentation**

Variable	FM	FM T[+]	FM T[-]	T-Test	FM T[+] vs. FM T[-]	Effect size
Duration of illness (mean years ± *SD*)	12.35 ± 10.63	9.10 ± 7.27	15.41 ± 12.37	$t(50.7) = -2.47$	**$p = 0.017$**	$g = 0.622$ medium
Time from onset to diagnosis (mean years ± *SD*)	7.10 ± 7.11	6.08 ± 6.88	8.06 ± 7.29	$t(60) = -1.1$	$p = 0.275$	$g = 0.28$ small
FIQ sum (mean ± *SD*)	50.86 ± 19.97	40.18 ± 19.59	60.88 ± 14.54	$t(53.4) = -4.7$	**$p < 0.001$**	$g = 1.2$ large
FIQ physical functioning (mean ± *SD*)	2.79 ± 2.40	1.76 ± 1.91	3.75 ± 2.45	$t(60) = -3.57$	**$p < 0.001$**	$g = 0.911$ large
FIQ well-being (mean ± *SD*)	6.20 ± 3.01	5.18 ± 3.19	7.15 ± 2.51	$t(60) = -2.7$	**$p = 0.009$**	$g = 0.685$ medium
FIQ work-related (mean ± *SD*)	9.09 ± 5.03	6.47 ± 4.20	11.54 ± 4.53	$t(60) = -4.56$	**$p < 0.001$**	$g = 1.16$ large
FIQ pain (mean ± *SD*)	5.66 ± 2.10	4.87 ± 1.94	6.41 ± 2.00	$t(60) = -3.07$	**$p = 0.003$**	$g = 0.781$ medium
FIQ fatigue/ sleep (mean ± *SD*)	12.85 ± 5.72	11.27 ± 6.09	14.34 ± 5.00	$t(60) = -2.18$	**$p = 0.033$**	$g = 0.552$ medium
FIQ stiffness (mean ± *SD*)	5.76 ± 3.19	4.77 ± 3.51	6.69 ± 2.58	$t(53.1) = -2.44$	**$p = 0.018$**	$g = 0.623$ medium
FIQ psychological symptoms (mean ± *SD*)	8.60 ± 5.42	7.73 ± 4.87	9.41 ± 5.84	$t(60) = -1.22$	$p = 0.227$	$g = 0.311$ small

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WPI (mean ± *SD*)	14.19 ± 4.31	13.20 ± 4.84	15.13 ± 3.57	$t(53.2) = -1.77$	$p = 0.082$	$g = 0.453$ small
SSS (mean ± *SD*)	8.05 ± 2.72	6.83 ± 2.55	9.19 ± 2.39	$t(60) = -3.76$	**$p < 0.001$**	$g = 0.953$ large
FS (mean ± *SD*)	22.23 ± 6.00	20.00 ± 6.23	24.31 ± 5.03	$t(60) = -3.01$	**$p = 0.004$**	$g = 0.762$ medium

FIQ – Fibromyalgia Impact Questionnaire; FM – fibromyalgia patients as a whole group; FM T[+] – patients responsive to SNRI treatment; FM T[-] – patients resistant to SNRI treatment; FS – Fibromyalgia Severity; g – Hedges' g; HC – healthy controls; SD – standard deviation; SSS – Symptom Severity Scale; WPI – Widespread Pain Index

Hedges' g is the measure of effect size. Effect size lower than 0.2 was considered negligible, 0.2-0.5 – small, 0.5-0.8 – medium and > 0.8 – large.

Psychopathological variables

Depression

As indicated by QIDS and HADS-D, FM as a whole, FM T[+] and FM T[-] presented higher levels of depression than HC ($p < 0.001$). Also, FM T[-] showed more pronounced symptoms of depression vs. FM T[+] ($p < 0.001$; $p < 0.01$) (Table 3). Both QIDS[+] and HADS-D[+] above cut-off scores suggested the presence of depression more often in FM T[-] vs. HC ($p < 0.001$; $p = 0.0002$) while no significant differences were noted between FM T[+] and HC. QIDS[+] scores suggested the presence of depression more commonly in FM T[-] vs. HC, while the same comparison of HADS-D[+] scores did not reach the level of significance (Table 4).

Anxiety

As measured by HADS-A as well as both state and trait STAI subscales, the levels of anxiety were higher in FM as a whole and FM T[-] vs. HC ($p < 0.001$). While the anxious symptomatology was more severe in FM T[-] vs. FM T[+] ($p < 0.001$; $p = 0.001$), the differences in anxiety assessments between HC and FM T[+] were not significant (Table 3). Above cut-off HADS-A[+] scores suggested the occurrence of anxiety above normal levels was higher in FM vs. HC ($p < 0.001$) and in FM T[-] vs. FM T[+] ($p = 0.012$) (Table 4).

Anhedonia

The severity of anhedonia as measured by SHAPS was higher in the whole FM group ($p = 0.005$) and FM T[-] vs. HC ($p = 0.001$). Moreover, the levels of anhedonia were more pronounced in FM T[-] vs. FM T[+] ($p = 0.008$) but comparable in FM T[+] vs. HC (Table 3). Also, SHAPS[+] scores exceeded the cut-off more often in FM ($p = 0.003$) and FM T[-] vs. HC ($p = 0.01$) but the proportions of above cut-off anhedonia scores were comparable between FM T[+] vs. HC and FM T[-] (Table 4).

Bipolarity

As evaluated by MDQ, FM as a whole ($p < 0.001$), FM T[+] ($p = 0.027$) and FM T[-] ($p < 0.001$) presented higher levels of bipolar spectrum symptoms vs. HC, and FM T[-] showed more bipolar spectrum symptoms vs. FM [+] ($p = 0.014$). The assessment with HCL also showed a higher level of bipolar features in FM ($p = 0.003$) and FM T[-] ($p = 0.007$) vs. HC; however, it did not indicate significant differences between HC and FM T[+] ($p = 0.093$) or FM T[-] vs. FM T[+] ($p = 0.592$) (Table 3). Moreover, the proportion of MDQ[+] and HCL[+] indicating possible presence of bipolar features was higher in FM vs. HC ($p = 0.02$) and in FM T[-] vs. FM T[+] ($p = 0.005$; $p = 0.048$). MDQ[+] suggested a higher proportion of positive screens for bipolar features in FM T[-] vs. FM T[+] ($p = 0.044$) but HCL[+] did not (Table 4).

Dissociative symptomatology

The severity of dissociative symptoms rated by DES-R score was higher in FM as a whole ($p < 0.001$), FM T[+] ($p = 0.02$) and FM T[-] vs. HC ($p < 0.001$). On the other hand, the levels of dissociative symptoms were comparable in FM T[+] vs. FM T[-] (Table 3). No significant differences in the occurrence of dissociative symptoms DES[+] exceeding the cut-off score between studied groups were observed (Table 4).

Table 3. **Comparisons of psychopathological variables in assessed groups**

Variable	HC mean score ± *SD*	FM mean score ± *SD*	T-Test HC vs. FM effect size*	FM T[+] mean score ± *SD*	FM T[-] mean score ± *SD*	ANOVA and effect size**	HC vs. FM T[+]	HC vs. FM T[-]	FM T[+] vs. FM T[-]
QIDS sum	3.63 ± 2.86	11.15 ± 5.21	$t(88.5) = -8.91$ **$p < 0.001$** $g = 1.79$	8.40 ± 3.48	13.72 ± 5.29	$F(2, 89) = 47.4$ **$p < 0.001$** $\eta^2 = 0.52$	**$p < 0.001$**	**$p < 0.001$**	**$p < 0.001$**
HADS-D sum	3.17 ± 2.31	8.24 ± 4.23	$t(88.6) = -7.43$ **$p < 0.001$** $g = 1.49$	6.67 ± 3.62	9.72 ± 4.28	$F(2, 89) = 30.91$ **$p < 0.001$** $\eta^2 = 0.376$	**$p < 0.001$**	**$p < 0.001$**	**$p = 0.01$**
HADS-A sum	6.43 ± 2.66	9.90 ± 4.42	$t(85.6) = -4.67$ **$p < 0.001$** $g = 0.951$	7.93 ± 3.53	11.75 ± 4.41	$F(2, 89) = 16.195$ **$p < 0.001$** $\eta^2 = 0.286$	$p = 0.16$	**$p < 0.001$**	**$p = 0.001$**
STAI-X sum	34.77 ± 8.14	45.61 ± 12.97	$t(83.9) = -4.89$ **$p < 0.001$** $g = 1$	39.60 ± 9.35	51.25 ± 13.48	$F(2, 89) = 16.684$ **$p < 0.001$** $\eta^2 = 0.307$	$p = 0.091$	**$p < 0.001$**	**$p < 0.001$**
STAI-Y sum	42.77 ± 6.92	52.58 ± 10.05	$t(90) = -4.82$ **$p < 0.001$** $g = 1.14$	47.40 ± 7.79	57.44 ± 9.57	$F(2, 89) = 26.062$ **$p < 0.001$** $\eta^2 = 0.369$	$p = 0.078$	**$p < 0.001$**	**$p < 0.001$**
SHAPS sum	20.53 ± 5.51	24.82 ± 7.13	$t(90) = -2.9$ **$p = 0.005$** $g = 0.673$	22.27 ± 6.45	27.22 ± 6.99	$F(2, 89) = 9.289$ **$p < 0.001$** $\eta^2 = 0.173$	$p = 0.544$	**$p < 0.001$**	**$p = 0.008$**
MDQ sum	2.33 ± 2.50	5.60 ± 3.51	$t(90) = -4.56$ **$p < 0.001$** $g = 1.07$	4.43 ± 3.45	6.69 ± 3.25	$F(2, 89) = 15.339$ **$p < 0.001$** $\eta^2 = 0.256$	**$p = 0.027$**	**$p < 0.001$**	**$p = 0.014$**
HCL sum	10.73 ± 6.01	15.02 ± 6.51	$t(90) = -3.03$ **$p = 0.003$** $g = 0.684$	14.20 ± 6.42	15.78 ± 6.59	$F(2, 89) = 5.076$ **$p = 0.008$** $\eta^2 = 0.111$	$p = 0.093$	**$p = 0.007$**	$p = 0.592$
DES-R sum	14.97 ± 12.40	35.71 ± 26.36	$t(73.1) = -4.72$ **$p < 0.001$** $g = -1.01$	30.20 ± 24.39	41.46 ± 27.61	$F(2, 89) = 11.413$ **$p < 0.001$** $\eta^2 = 0.209$	**$p = 0.02$**	**$p < 0.001$**	$p = 0.296$

DES-R – Dissociative Experiences Scale– Revised; HADS-A – Hospital Anxiety and Depression Scale – anxiety subscale; HADS-D – Hospital Anxiety and Depression Scale– depression subscale; FM – fibromyalgia patients as a whole group; FM T[+] – patients responsive to SNRI treatment;

FM T[-] – patients resistant to SNRI treatment; HC – healthy controls; HCL – hypomania checklist; MDQ – Mood Disorder Questionnaire; SHAPS – Snaith-Hamilton Pleasure Scale; STAI-X – State and Trait Anxiety Inventory – state subscale; STAI-Y – State and Trait Anxiety Inventory – trait subscale; QIDS – Quick Inventory of Depressive Symptomatology

Hedges' g is the measure of effect size. Effect size lower than 0.2 was considered negligible, 0.2-0.5 – small, 0.5-0.8 – medium and > 0.8 – large.

η^2 – (eta squared) is the measure of effect size. Effect size lower than 0.01 was counted as negligible, 0.01-0.06 as small, 0.06-0.14 as medium and higher than 0.14 as large.

Table 4. **Presence of psychopathology in studied subjects**

Variable		HC *n* = 30	FM *n* = 62	FM T[+] *n* = 30	FM T[-] *n* = 32	HC vs. FM	HC vs. FM T[+] vs. FM T[-]	HC vs. FM T[+]	HC vs. FM T[-]	FM T[+] vs. FM T[-]
QIDS [+]	mild	5	20	14	6	$\chi^2(92, 4) = 37.3$ ***p* < 0.001**	$\chi^2(92, 8) = 54.4$ ***p* < 0.001**	NA	***p* < 0.001**	***p* = 0.02**
	moderate	1	21	8	13					
	severe	0	6	1	5					
	very severe	0	5	0	15					
HADS-D [+]	borderline abnormal	0	14	7	7	$\chi^2(92, 2) = 20.6$ ***p* < 0.001**	$\chi(92, 4) = 29.6$ ***p* < 0.001**	$p = 0.13$	***p* = 0.00002**	$p = 0.07$
	abnormal	1	18	4	14					
HADS-A [+]	borderline abnormal	8	13	7	6	$\chi^2(92, 2) = 18.4$ ***p* < 0.001**	$\chi^2(92, 4) = 29.9$ ***p* < 0.001**	$p = 0.12$	***p* < 0.001**	***p* = 0.012**
	abnormal	1	29	8	21					
SHAPS [+]		2	24	10	14	$\chi^2(92, 1) = 8.72$ ***p* = 0.003**	$\chi^2(92, 2) = 11.1$ ***p* = 0.004**	$p = 0.07$	***p* = 0.01**	$p = 1$
MDQ [+]		2	19	5	14	$\chi^2(92, 1) = 5.31$ ***p* = 0.02**	$\chi^2(92, 2) = 13$ ***p* = 0.001**	$p = 1$	***p* = 0.005**	***p* = 0.044**
HCL [+]		7	32	13	19	$\chi^2(92, 1) = 5.51$ ***p* = 0.02**	$\chi^2(92, 2) = 8.25$ ***p* = 0.02**	$p = 0.51$	***p* = 0.048**	$p = 0.94$
DES-R [+]		0	4	1	3	$\chi^2(79, 1) = 2.58$ $p = 0.292$	$\chi^2(79, 2) = 4.42$ $p = 0.067$	$p = 1$	$p = 0.33$	$p = 1$

DES-R – Dissociative Experiences Scale – Revised; HADS-A – Hospital Anxiety and Depression Scale – anxiety subscale; HADS-D – Hospital Anxiety and Depression Scale – depression subscale;

HCL – hypomania checklist; MDQ – Mood Disorder Questionnaire; SHAPS – Snaith-Hamilton Pleasure Scale; STAI-X – State and Trait Anxiety Inventory – state subscale; STAI-Y – State and Trait Anxiety Inventory – trait subscale; QIDS – Quick Inventory of Depressive Symptomatology; [+] – indicates levels of psychopathology above the cut-off score of a specific tool. P values resulting from pairwise $\chi 2$ tests were adjusted using the Bonferroni correction. NA – not available.

Relationships between psychopathological variables and non-response to SNRI

Logistic regression analysis results showed that some of the psychopathological features assessed as continuous measures were predictors of non-response to SNRI pharmacotherapy in FM, that is: a) depression measured by QIDS (OR = 1.31, 95% CI [1.13,1.51]; $p < 0.001$) and HADS-D (OR = 1.22, 95% CI [1.06,1.4]; $p = 0.007$), b) anxiety evaluated by HADS-A (OR = 1.26, 95% CI [1.09-1.46]; $p = 0.002$), STAI-X (OR = 1.09, 95% CI [1.03,1.14]; $p = 0.001$) and STAI-Y (OR = 1.14, 95% CI [1.06,1.24]; $p < 0.001$), c) anhedonia assessed by SHAPS (OR = 1.12, 95% CI [1.03,1.21]; $p = 0.009$) and d) bipolarity examined by MDQ (OR = 1.23, 95% CI [1.04,1.44]; $p = 0.002$) (but not HCL). No significant predictive value of the bipolarity assessed with HCL or dissociative symptoms measured with DES was shown regarding the resistance to SNRI (Table 5).

Table 5. **Relationships between psychopathological variables and non-response to SNRI – odds ratios and logistic regression results**

Variable	Intercept	Slope	AIC	OR	2.50%	97.50%	*p*
QIDS sum	-2.826	0.267	71.047	1.31	1.13	1.51	**<0.001**
HADS-D sum	-1.530	0.196	81.181	1.22	1.06	1.4	**0.007**
HADS-A sum	-2.220	0.232	77.222	1.26	1.09	1.46	**0.002**
STAI-X sum	-3.757	0.084	76.045	1.09	1.03	1.14	**0.001**
STAI-Y sum	-7.019	0.135	71.865	1.14	1.06	1.24	**<0.001**
SHAPS sum	-2.644	0.110	81.892	1.12	1.03	1.21	**0.009**
HCL sum	-0.051	0.038	88.951	1.04	0.96	1.12	0.334
MDQ sum	-1.058	0.203	83.099	1.23	1.04	1.44	**0.015**
DES-R sum	-0.673	0.018	69.538	1.02	0.99	1.04	0.147

AIC – Akaike information criterion; DES-R – Dissociative Experiences Scale – Revised; HADS-A – Hospital Anxiety and Depression Scale – anxiety subscale; HADS-D – Hospital Anxiety and Depression Scale – depression subscale; HCL – hypomania checklist; MDQ – Mood Disorder Questionnaire; OR – odds ratio; SHAPS – Snaith-Hamilton Pleasure Scale; STAI-X – State and Trait Anxiety Inventory – state subscale; STAI-Y – State and Trait Anxiety Inventory – trait subscale; QIDS – Quick Inventory of Depressive Symptomatology

Discussion

There is already some data available on the prevalence of psychiatric disorders in FM and their links to the severity of FM. The novelty of this work lies in the exploration of links between multiple psychopathological variables and response to SNRI therapy. In general, previous studies focused on FM as a whole group. Based on our clinical experience and previous works [5,16–18], we divided patients into groups of either responsive or non-responsive to SNRI. Indeed, the results validate our hypothesis that FM patients differ in clinical presentation of FM and psychopathology. Precisely, compared to FM T[+], FM T[-] show: 1) higher levels of depression, 2) higher levels of state and trait anxiety and higher proportion of scores pointing to the presence of an anxiety disorder, 3) higher levels of anhedonia.

The scores suggesting the presence depression in the whole FM group reached 51.61-83.87% (29.03-67.74% if one excludes mild/borderline abnormal cases) while the presence of anxiety was 67.74% (46.77% if one excludes borderline abnormal cases), which is comparable to prevalence ranges reported by Kleykamp et al. [2]. What is more, the severity and occurrence of depression and anxiety in FM T[-] vs. FM T [+] were significantly higher, more often exceeded the threshold indicating the presence of clinical syndromes (regarding depression, QIDS showed statistically significant results and HADS-D a trend which did not reach significance) and were predictors of lack of response to SNRI therapy. As previously reported, we observed that patients with FM presented higher levels of state and trait anxiety than HC [36]; furthermore, our work showed that both state and trait anxiety were higher in FM T[-] vs. FM T[+] and both these variables were predictors of non-response to SNRI. The results uphold the observation we made in the preliminary report, suggesting that anhedonia is more pronounced and more often above the cut-off score indicating decreased hedonic tone in FM vs. HC [10]. The levels of anhedonia were higher in FM T[-] vs. FM T[+] and predictive of non-response to SNRI. However, the proportion of FM T[+] and FM T[-] presenting impaired hedonic tone was comparable. In the studied group, 38.71% of FM subjects presented impaired hedonic tone which is somewhat higher compared to the 25% noted in the mixed chronic pain patients group with low back pain, extremities pain, fibromyalgia, neck/head/shoulder, neuropathic/neurological and other pain disorders examined by Garland et al. [9]. The number of bipolar symptoms was significantly higher in FM vs. HC and occurrence of bipolar symptoms above the normal threshold was 30.56-51.61% which is in line with previous works by Kleykamp et al. [2] and Gota et al. [6].

Regarding the comparison of FM T[+] and FM T[-] in the aspects of: the number of bipolar spectrum symptoms, the proportion of positive screens for bipolar spectrum features and their predictive significance in non-response to SNRI, the results are inconclusive as in all these comparisons one tool implied a significant difference and a positive predictive value while the other did not. Indeed, higher levels of positive screens in the case of MDQ vs. HCL were also noted in earlier studies with the use of Polish versions of these tools implying the higher sensitivity of MDQ [37–39]. The issue of bipolar spectrum symptoms in FM is of particular importance: firstly, because there is data showing that use of SNRI is related to not only the risk of hypo/

manic switch in depression [40] but also to higher incidence of bipolar disorder in FM patients [41] and secondly, because in depression treatment the presence of bipolar features is associated with ineffectiveness [42] and our results imply that this is also the case in FM therapy. Perhaps patients with a significant number of bipolar symptoms should receive other drugs, e.g., pregabalin as first-line treatment or if treated with SNRI should be monitored for mood symptoms. Finally, the severity of dissociative symptomatology was significantly higher in FM, FM T[+], FM T[-] vs. HC which is in line with previous research by Berkol et al. [13] and Romeo et al. [43]. However, no significant differences between FM T[+] and FM T[-] were noted in the level of dissociation symptoms and the proportion of these exceeding scores of clinical thresholds, and the severity of dissociative symptoms was not associated with response to SNRI. These results need to be reexamined in future studies as the low number of positive cases of dissociative pathology limits our ability to evaluate the links between dissociation and pharmacological treatment of FM.

There are several limitations of our work, such as the relatively low number of subjects and the cross-sectional methodology. Nevertheless, these results are of substantial research and clinical value and may serve as the foundation for future studies and modifications in the management of patients.

Conclusions

To conclude, our work shows several noteworthy psychopathological differences between FM T[+] and FM T[-]. Additionally, the results indicate that some psychopathological features are predictors of non-response to SNRI. This is of crucial importance to clinical practice, since the majority of these psychopathological dimensions such as mood, anxiety, and anhedonia can be successfully treated with adjunctive medication and/or psychotherapy [44–46] even if some of them did not respond to SNRI [46–48] and potentially produce better treatment results in FM. Thus, we hold the view that assessment of psychopathology should be incorporated into standard care of FM patients.

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