Investigation of alexithymia levels in fibromyalgia before and after treatment

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Abstract

Objective

The aim of the study was to investigate changes in alexithymia scores upon fibromyalgia (FM) treatment.

Methods

This prospective observational cohort study was conducted at the Istanbul Physical Medicine and Rehabilitation Training and Research Hospital. Patients diagnosed with fibromyalgia syndrome (FM) according to American College of Rheumatology criteria were included. All participants received duloxetine treatment, combined aerobic exercise. FM symptoms were assessed using Visual Analog Scale (VAS) at baseline and at 6 months, while alexithymia was evaluated using Toronto Alexithymia Scale-20 (TAS-20) at baseline, 3, and 6 months. Statistical analysis included repeated measures ANOVA with Greenhouse-Geisser correction, paired t-tests, and correlation analyses, with adjustments for age, BMI, and daily medication count.

Results

A total of 100 patients completed the study. VAS scores significantly decreased from the baseline (mean ± SD: 7.4±1.2) to 6 months (4.1±1.3; $p<0.001$). TAS-20 total scores also showed significant reductions at 3 months (57.8±7.6) and 6 months (54.2±7.1) compared to the baseline (61.5±7.9; $p<0.001$). Improvements in TAS-20 scores was correlated with reductions in VAS scores ($r=0.41$, $p=0.002$).

Conclusion

Combined duloxetine treatment and aerobic exercise could significantly improve both alexithymia symptoms and pain levels in FMS patients over a six-month period. Higher baseline alexithymia scores were associated with greater improvements in both alexithymia and pain symptoms, suggesting that patients with more severe initial alexithymia may benefit more from this treatment.

Key words

fibromyalgia, alexithymia, duloxetine

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Introduction

Fibromyalgia (FM) is a chronic pain condition that is characterised by widespread musculoskeletal pain, fatigue, sleep disturbances, and cognitive difficulties (1). FM affects approximately 0.2–6.6% of the world's population and is more commonly seen in women (2). FM is frequently characterised by the co-occurrence of both physical and psychological comorbidities. Among the latter, depression, bipolar disorder, panic disorder, and post-traumatic stress disorder (PTSD) are commonly observed (3). Psychological variables were shown to play an important role in determining the daily functioning as well as physical and mental health status of FM patients along with a greater impact than the intensity of pain (4). Alexithymia is a personality construct that is marked by deficits in the identification and description of feelings, differentiation between emotional and somatic experiences, and a predominantly externally oriented cognitive style coupled with diminished emotional awareness and imagination (5-7). Alexithymia is known to be prevalent among the FM patient population. Recent studies have confirmed that FM patients have significantly higher levels of alexithymia compared to both healthy individuals and those with other rheumatological conditions (8-11). Alexithymia in FM is also associated with a lower quality of life and heightened psychological distress, encompassing both anxiety and depressive symptoms (12, 13).

Many agents are used in the pharmacological treatment of FM (14), one of which is duloxetine, a serotonin and noradrenaline reuptake inhibitor (SNRI) (15). Duloxetine increases the availability of these neurotransmitters, particularly within the descending pain modulatory pathways of the brain and spinal cord. This enhanced neurotransmission strengthens the body's natural pain inhibition systems, which are often disrupted in FM patients (16, 17). As a widely used and effective treatment for FM, duloxetine has been shown to improve pain scores, quality of life, and mental health status in patients with FM (18).

Neuroanatomical and neurofunctional imaging studies provide compelling evidence for a link between alexithymia and FM in specific brain regions and the potential therapeutic effects of duloxetine. For example, the insula and cingulate cortex are known to play a crucial role in the pathophysiology of alexithymia and may serve as a key integration hub for interoceptive, emotional, and cognitive processes. Neuroimaging studies have demonstrated altered insular activity in patients with alexithymia (19-22). Research on patients with major depression has shown increased activity in the limbic areas of the brain, notably the amygdala, insula, and subcallosal cingulate cortex (23). SNRIs like duloxetine are of particular relevance for pharmacological interventions in major depression as they can modulate neuronal activity in these precise brain regions (24). The European League Against Rheumatism suggests a multimodal approach for managing FM, which suggests pharmacological along with non-pharmacological interventions like exercise instead of monotherapy (25). Aerobic exercise, in particular, has been shown to promote neuroplasticity in the brain regions associated with emotional regulation and cognitive function. Indeed, studies have shown that 12 weeks of regular exercise training may contribute to neural network plasticity by increasing the functional connectivity of the anterior insula with other cortical regions, along with improvements in subjective well-being (26).

Increased norepinephrine levels have also been associated with alexithymia, and increased serotonin reuptake was reported to increase alexithymia levels (27, 28). Alexithymic patients with major depression were shown to respond more favourably to treatment with paroxetine, a selective serotonin reuptake inhibitor (SSRI), compared to patients without alexithymic, suggesting that the presence of alexithymia may be a potential predictor of treatment response (29). In light of these findings, the combination of multifaceted interventions such as duloxetine and aerobic exercise may offer combinatorial effects in improving emotional awareness in FM patients. These interventions can simultaneously target multiple neurobiological underpinnings of alexithymia, primarily by

optimising the balance between different neurotransmitters and promoting structural adaptations in the emotional processing networks.

The aim of the current study was to explore how alexithymia levels influence treatment outcomes in FM patients treated with duloxetine. Despite its well-established association with FM outcomes, alexithymia levels have not been thoroughly investigated in clinical follow-up studies in FM patients. Based on several converging lines of evidence, we hypothesised a decrease in alexithymia levels in FM syndrome patients receiving duloxetine treatment. With the current approach, we provide insights into the optimisation of therapeutic strategies tailored to individual needs based on emotional processing capabilities.

Methods

The current prospective observational cohort study was conducted between January 2024 and December 2024 at the Istanbul Physical Medicine and Rehabilitation Training and Research Hospital. Patients diagnosed with FM according to the American College of Rheumatology criteria were eligible for inclusion. Additional inclusion criteria were age between 18 and 65 years, pain severity ≥4 on the Visual Analog Scale (VAS) over the previous two weeks, stable treatment regimen with no significant modifications within the past three months, and a literacy level that was sufficient for the completion of the questionnaire. Exclusion criteria included pregnancy, breastfeeding, or planned pregnancy during the study period, presence of chronic pain syndromes other than FM (*e.g.* myofascial pain syndrome), concomitant autoimmune or inflammatory diseases such as rheumatoid arthritis or systemic lupus erythematosus, uncontrolled chronic medical conditions (*e.g.* diabetes, severe cardiovascular, hepatic, renal, or pulmonary disease), serious psychiatric conditions such as schizophrenia, bipolar disorder, or substance use disorders within the past two years, and recent changes (within two months) in pharmacological treatments targeting pain or FM symptoms.

Demographic and clinical data, including age, body mass index (BMI), and number of medications used daily were collected from all patients at the baseline during the initial study enrolment. These variables were later incorporated as covariates in our correlation analyses to control for potential confounding effects when examining the relationship between pre-treatment values and post-treatment changes in the Toronto Alexithymia Scale-20 (TAS-20) and VAS scores. VAS was adopted as the primary pain measure in the current study due to its high accuracy in assessing pain intensity in FM, practicality of usage in clinical practice, and its sensitivity to treatment-related changes (30, 31). Patients meeting these criteria were initiated on a combined intervention consisting of duloxetine treatment and a structured aerobic exercise program (power walking at least three times per week, approximately half an hour per session). Treatment adherence was rigorously monitored throughout the study period. All patients attended monthly follow-up appointments at the Istanbul Physical Medicine and Rehabilitation Training and Research Hospital, during which both medication adherence and exercise compliance were assessed. Exercise adherence was verified through structured patient interviews, exercise logbooks provided to the patients at the baseline, and physical activity questionnaires. Patients who failed to complete at least 70% of their prescribed exercise sessions or who discontinued duloxetine treatment were classified as non-adherent and were excluded from the final analysis. Pain was assessed using the VAS at baseline and at 6 months, while alexithymia was evaluated using the TAS-20 at the baseline, 3 months, and 6 months. Statistical analyses were conducted using repeated measures ANOVA, paired t-tests, and correlation analyses adjusted for age, BMI, and daily medication count.

Ethics committee approval for the study was obtained from the Istanbul Bakırköy Dr Sadi Konuk Research and Training Hospital with decision number 2024-01-02. Detailed informed consent was obtained from all patients. This study was conducted in accordance with the Declaration of Helsinki.

All statistical analyses were conducted using IBM SPSS Statistics 26.0. Descriptive statistics were used to summarise demographic and clinical characteristics, with the results presented as mean ± standard deviation (SD) for continuous variables and percentages for categorical variables. To evaluate changes in the TAS-20 scores and its subscales as a function of time during treatment with duloxetine, repeated measures analysis of variance (ANOVA) was carried out. When the assumption of sphericity was violated, as assessed by Mauchly's Test of Sphericity, the Greenhouse-Geisser correction was applied. Effect sizes were calculated using the partial eta squared (η^2) to assess the magnitude of the observed effects. Changes in VAS scores between the baseline and 6 months were analysed using paired t-test. Correlation analyses were conducted to examine the relationship between pre-treatment TAS-20 and VAS values and post-treatment changes in these measures. Pearson correlation coefficients were calculated, and the analyses were adjusted for age, body mass index (BMI), and daily medication count as control variables to account for potential confounding factors. A *p*-value of less than 0.05 was considered statistically significant for all statistical tests. Pairwise comparisons for repeated measures were adjusted using Bonferroni corrections to control for multiple comparisons. A *post-hoc* power analysis was conducted using G*Power 3.1 for the primary outcomes. For the repeated measures ANOVA of TAS-20 scores across three time points (baseline, 3 and 6 months) with our sample of 100 participants, we obtained α=0.05, and the observed effect size was f=0.962 (converted from η^2=0.480). For this, the achieved power was >99%. For the paired t-test that compared baseline and the 6-month VAS scores (t=10.124), the achieved power was also >99%. These analyses confirm that the current study was adequately powered to detect the observed changes in both alexithymia and pain outcomes. This comprehensive statistical approach ensured the accurate evaluation of treatment effects and the relationship between key variables.

Results

The demographic and clinical characteristics of the participants are summarised in Table I. The mean age of the participants was 48.33±10.20 years (range 29.00-69.00). The mean body mass index was 27.48±4.87 kg/m^2. Among the participants, 75% were married, while 25% were single. Educational levels varied, with 2% being illiterate, 26% having completed primary school, 19% middle school, 34% high school, and 19% university level education. Occupation distribution showed that 51% were housewives, 34% were employed, 8% were unemployed, and 7% were retired. Most of the participants (39%) reported no daily medication use, while 36% used 1-3 medications, 20% used 4-7, and 5% used more than 7 medications. Half of the participants (50%) reported no additional diseases, whereas 21% had only one comorbidity, and 29% reported multiple comorbidities. Based on the TAS-20 cut-off score, 53% of participants were classified as non-alexithymic (<61), while 47% were classified as alexithymic (≥61).

Changes in the scores obtained from TAS-20 and its subscales over the duration of treatment with duloxetine are presented in Table II. Significant reductions in the TAS-20 total scores were observed during the treatment period. The mean TAS-20 total score decreased from 55.00±12.77 at the baseline to 51.95±12.42 at the 3rd month and 49.07±2.50 at the 6th month. This change was statistically significant with a main effect of time ($F=91.35$, $p<0.001$, $\eta^2=0.480$). Pairwise comparisons revealed significant differences between all three time points ($p<0.001$).

Subscales of the TAS-20 also showed significant improvements during the treatment. Difficulty Identifying Feelings (DIF) scores decreased from 19.53±7.26 at the baseline to 18.49±7.04 at the 3rd month and 17.36±6.77 at the 6th month. This change was statistically significant, with a main effect of time ($F=47.36$, $p<0.001$, $\eta^2=0.324$). Pairwise comparisons between all three time points were statistically significant ($p<0.001$). Difficulty Describing Feelings (DDF) scores decreased from 13.32±4.28 at the baseline to 12.60±4.05 at the 3rd month and 11.97±4.05 at the 6th month, showing a statistically significant effect of time ($F=29.58$, $p<0.001$, $\eta^2=0.230$). Externally Oriented Thinking (EOT) scores also declined significantly, from 22.15±4.03 at the baseline to 20.86±4.01 at the 3rd month and 19.74±4.27 at the 6th month. This decrease was statistically significant with a main effect of time ($F=52.96$, $p<0.001$, $\eta^2=0.349$). The mean VAS score significantly decreased from 6.48±1.26 at the baseline to 5.38±1.05 at the 6th month ($t=10.124$ and $p<0.001$, paired t-test).

A separate analysis was conducted for FM patients with alexithymia (TAS-20≥61) at the baseline (Table III). The mean TAS-20 total score decreased significantly from 65.68±5.26 to 58.25±8.78 at the 6th month ($t=7.493$, $p<0.001$), indicating a remarkable decrease in alexithymia symptoms. Each TAS-20 subscale also showed improvement including DIF (decreased from 25.32±4.36 to 22.36±4.94, $t=6.512$, $p<0.001$), DDF (decreased from 16.59±2.55 to 15.53±2.67, $t=3.423$, $p=0.001$), and EOT (decreased from 23.76±3.19 to 21.14±4.09, $t=6.091$, $p<0.001$). The proportion of patients with symptoms of alexithymia decreased from 100% to 42.6% at the 6th month, suggesting a clinically meaningful improvement with treatment. Additionally, pain severity, measured by the VAS, showed a statistically significant reduction (7.00±1.08 to 5.65±1.10, $t=8.438$, $p<0.001$).

Correlations between pre-treatment values and post-treatment changes, controlled for age, BMI, and daily medication count, are presented in Table IV. Pre-treatment TAS-20 scores were positively correlated with changes in TAS-20 scores ($r=0.256$, $p=0.011$) and VAS scores ($r=0.444$, $p<0.001$). Pre-treatment VAS scores were significantly correlated with changes in TAS-20 scores ($r=0.138$, $p=0.178$) and VAS scores ($r=0.599$, $p<0.001$). These results suggest that higher pre-treatment alexithymia and pain levels were associated with greater improvements in these measures following the treatment.

Table I. Characteristics of the study participants.

Variables	n (%)
Age	
Mean	48.33
Standard deviation	10.20
min-max	29.00–69.00
Body mass index	
Mean	27.48
Standard deviation	4.87
Marital status	
Married	75 (75.0)
Single	25 (25.0)
Education	
Illiterate	2 (2.0)
Primary school	26 (26.0)
Middle school	19 (19.0)
High school	34 (34.0)
University	19 (19.0)
Occupation	
Working	34 (34.0)
Retired	7 (7.0)
Unemployed	8 (8.0)
Housewife	51 (51.0)
Daily medication count	
None	39 (39.0)
1–3	36 (36.0)
4–7	20 (20.0)
>7	5 (5.0)
Additional diseases	
None	50 (50.0)
One disease	21 (21.0)
Multiple diseases	29 (29.0)
Cut-off (Toronto Alexithymia Scale-20)	
<61 (No alexithymia)	53 (53.0)
≥61 (Alexithymia)	47 (47.0)

Discussion

To our knowledge, the current study is the first to explore the impact of duloxetine treatment on alexithymia in patients with FM. The results suggest that duloxetine may offer therapeutic benefits that extend beyond pain relief and mood regulation, reaching into the realm of emotional processing difficulties, which is a frequently overlooked aspect of FM. Notably, patients with higher levels of alexithymia at the baseline showed greater clinical improvement, pointing to a potential role for alexithymia as a predictor of treatment response. These findings open the door to more personalised treatment strategies that take emotional functioning into account, rather than focusing solely on somatic symptoms.

The prevalence of alexithymia in FM patients is reported to be around 48%; however, the range is very wide (19% to 92%) (8). Corroborating this, the proportion of patients with a TAS-20 score

Table II. Changes in Toronto alexithymia scale and subscales over time during duloxetine treatment.

Scale	First day (mean ± SD)	3rd month (mean ± SD)	6th month (mean ± SD)	F/t	*p*	1↔2 (*p*)	1↔3 (*p*)	2↔3 (*p*)
Toronto Alexithymia Scale Total†	55.00 ± 12.77	51.95 ± 12.42	49.07 ± 12.50	91.35	<0.001	0.000	0.000	0.000
Difficulty identifying feelings†	19.53 ± 7.26	18.49 ± 7.04	17.36 ± 6.77	47.36	<0.001	0.000	0.000	0.000
Difficulty describing feelings†	13.32 ± 4.28	12.60 ± 4.05	11.97 ± 4.05	29.58	<0.001	0.000	0.000	0.000
Externally oriented thinking†	22.15 ± 4.03	20.86 ± 4.01	19.74 ± 4.27	52.96	<0.001	0.000	0.000	0.000
Visual analogue scale††	6.48 ± 1.26	--------	5.38 ± 1.05	10.124	<0.001	----------		

†Repeated measures ANOVA was used. ††Paired t-test was used. $p<0.05$ statistically significant.
Difficulty identifying feelings: The overall effect of time was significant (F=47.36, $p<0.001$, $\eta^2=0.324$). Pairwise comparisons showed differences between all three time points ($p<0.001$). Greenhouse-Geisser correction was applied ($\varepsilon=0.617$).
Difficulty describing feelings: Time effect was significant (F=29.58, $p<0.001$, $\eta^2=0.230$). Pairwise differences ranged from 0.720 to 1.350 ($p<0.001$). Greenhouse-Geisser correction was applied ($\varepsilon=0.842$).
Externally oriented thinking: Significant time effect observed (F=52.96, $p<0.001$, $\eta^2=0.349$). Differences between time points ranged from 1.290 to 2.410 ($p<0.001$). Greenhouse-Geisser correction was applied ($\varepsilon=0.781$).
Toronto Alexithymia Scale total: The strongest time effect observed (F=91.35, $p<0.001$, $\eta^2=0.480$). Pairwise differences ranged from 2.880 to 5.930 ($p<0.001$). Greenhouse-Geisser correction applied ($\varepsilon=0.584$).

Table III. Changes in Toronto alexithymia scale and its subscales over time during duloxetine treatment in fibromyalgia patients with alexithymia.

Scale	First day (mean ± SD)	6th month (mean ± SD)	t	*p*
Toronto Alexithymia Scale Total†	65.68 ± 5.26	58.25 ± 8.78	7.493	<0.001
Difficulty identifying feelings†	25.32 ± 4.36	22.36 ± 4.94	6.512	<0.001
Difficulty describing feelings†	16.59 ± 2.55	15.53 ± 2.67	3.423	0.001
Externally oriented thinking†	23.76 ± 3.19	21.14 ± 4.09	6.091	<0.001
Cut-off (Toronto Alexithymia Scale-20)	n (%)	n (%)		
≥61 (Alexithymia)	47 (100.0)	20 (42.6)		
Visual analogue scale†	7.00 ± 1.08	5.65 ± 1.10	8.438	<0.001

Note: Paired t-test was used. $p<0.05$ statistically significant.

exceeding 60 in the current study was found to be 47%. Since the symptoms of alexithymia can change depending on the situation, it is not considered to be a stable personality trait, but rather as a condition that emerges due to the presence of stress or disorders (32). In our study, the TAS-20 scores of FM patients showed significant decreases during the follow-up period. The changes in alexithymia symptoms in psychiatric diseases have been studied extensively; however, to our knowledge, no studies related to alexithymia during the treatment of FM have been reported to date. Antidepressants, psychotherapies and mindfulness-based interventions have been reported to reduce alexithymia levels in psychiatric disorders. For example, significant decreases in TAS-20 scores were reported upon treatment with the SSRI paroxetine in patients with major depression (29). In another study treatment of patients with post-stroke depression with the SNRI venlafaxine (similar to duloxetine) resulted a significantly greater decrease in alexithymia scores compared to fluoxetine, an SSRI, despite similar mitigatory effects on depression between the two drugs (33). Apart from pharmacotherapy, psychotherapeutic approaches such as short-term cognitive behavioural therapy (CBT) and hypnotherapy were reported to decrease alexithymia scores by increasing emotional awareness (34). Mindfulness-based interventions were associated with a moderate effect size in alexithymia in meta-analyses, and this effect was reported to last up to 3 months (35). In another study on major depression, a partial improvement in alexithymia levels was observed with psychotherapy; however, this change exhibited a more limited and selective profile compared to clinical improvement (36). However, some studies, albeit small, suggest that alexithymia may be a relatively stable trait, as higher levels after treatment were associated with increased disorder severity and a worse response to treatment (37-39). According to a systematic review, psychotherapy can significantly improve the quality of life of FM patients by reducing pain, depression, anxiety and other symptoms (40). In conclusion, in line with previous studies supporting that alexithymia is a treatment-sensitive phenomenon, our findings emphasise the role of SNRIs in this process. Therefore, a combination of pharmacotherapy and psychotherapy may show better clinical improvement and should be investigated in future studies.

Our overall findings indicate a decrease in the symptoms of alexithymia in FM patients upon therapeutic intervention. A more detailed analysis of the individual TAS-20 subscale scores and a comparison with the existing research provided a nuanced view of the treatment outcomes. We observed that FM patients with higher pre-treatment scores in the subscales DIF and DDF demonstrated greater improvements in both pain levels and alexithymia scores following treatment. However, individuals with a high EOT score only showed a reduction in pain levels after treatment. According to a meta-analysis that examined the relationship between FM and alexithymia, pain was positively correlated with anxiety and depression in general and especially in patients with DIF, while the relationship between EOT and pain was weaker. The association between alexithymia and pain was significantly weakened when controlled for anxiety, suggesting that the relationship may be largely due to anxiety. In other words, although alexithymia is associated with symptoms as seen in FM patients, anxiety appears to play an important role in the link with pain (8). DIF was shown to predict the

Table IV. Correlation between pre-treatment values and post-treatment changes controlled for age, daily medication count and body mass index.

Correlations								
Pre-treatment values			**Post-treatment changes**					
Control variables			Visual analogue scale	Toronto Alexithymia Scale	Difficulty identifying feelings	Difficulty describing feelings	Externally oriented thinking	Visual analogue scale
Age & Body Mass index & daily medication count	Toronto Alexithymia Scale	Correlation	0.444	0.256	0.261	0.224	0.097	0.343
		Significance (2-tailed)	<0.001	0.011	0.010	0.027	0.343	<0.001
	Difficulty identifying feelings	correlation	0.425	0.241	0.331	0.178	0.031	0.114
		Significance (2-tailed)	<0.001	0.017	<0.001	0.082	0.766	0.267
	Difficulty describing feelings	correlation	0.391	0.208	0.186	<0.346	0.010	0.180
		Significance (2-tailed)	<0.001	0.041	0.069	<0.001	0.919	0.077
	Externally oriented thinking	correlation	0.226	0.156	0.032	0.018	0.269	0.028
		Significance (2-tailed)	0.026	0.128	0.756	0.858	0.008	0.783
	Visual analogue scale	correlation	1.000	0.138	0.129	0.130	0.057	0.599
		Significance (2-tailed)		0.178	0.209	0.204	0.577	<0.001

$p<0.05$ statistically significant.

severity of residual depressive symptoms in unipolar depressed patients who responded positively to psychotherapy (41). In addition, a study investigating different types of therapy emphasised that DIF and EOT may have different effects on clinical outcomes. While DIF can negatively affect any association with favourable therapeutic outcomes, high EOT scores were found to play a positive role in the treatment of depression (42). However, in another study, patients with higher initial EOT scores were shown to exhibit greater symptom severity in depression at follow-up, indicating that EOT may have different effects depending on the context (43). Our results suggest that while the emotional awareness components of alexithymia (DIF, DDF) may be more amenable to comprehensive improvement through treatment, EOT appeared to be more resistant to change despite the associated improvements in pain perception.

Our data suggest that the presence of alexithymia may be able to predict treatment outcomes in FM, suggesting that further research could be beneficial to understand its impact. Our study found that patients with higher baseline alexithymia scores showed greater improvement after treatment, suggesting that alexithymia assessment may help identify patients most likely to benefit from treatment. A comprehensive systematic review of the effects of alexithymia in psychiatric disorders has shown that lower baseline and/or post-treatment alexithymia levels or improvements in alexithymia symptoms during treatment were associated with more favourable outcomes in the treatment of specific mental disorders. However, numerous conflicting findings have been noted, precluding any definitive conclusions on the true impact of alexithymia in the treatment of psychiatric disorders (44). The observed reduction in alexithymia levels in our sample is consistent with previous reports indicating that a decrease in the symptoms of alexithymia was associated with favourable treatment outcomes. However, our finding that higher baseline alexithymia levels may predict greater treatment benefit in the FM cohort evaluated in the current study supports the prevailing inconsistencies in the literature and strongly highlights the need for further research to understand the complex role of alexithymia in predicting treatment outcomes for FM.

Given the known benefits of aerobic exercise on emotional processing, it is likely that this component of the combined treatment regimen employed in the current study contributed significantly to the decrease in alexithymia symptoms. A prospective randomised controlled trial in patients with chronic pain has shown that 8 weeks of aerobic exercise could effectively decrease in both pain and alexithymia levels (45). Similarly, a physical exercise program was found to significantly reduce alexithymia levels while improving social functioning in patients with bipolar disorder (46). These findings suggest that the aerobic exercise component of our treatment protocol very likely contributed significantly to the decrease in alexithymia scores. Aerobic exercise may reduce pain in FM by improving muscle oxygenation through exercise-induced hypoalgesia, which can trigger the release of endogenous opioids, calm the sympathetic system, and improve psy-

chosociological factors (47). The combinatorial effect of aerobic exercise and duloxetine in the current study on the amelioration of alexithymia may have relied on complementary pathways, *i.e.* pharmacological modulation of the serotonin and norepinephrine systems via duloxetine, alongside the neurobiological and psychological benefits of regular aerobic exercise. This combined approach likely explains the significant improvements observed in both alexithymia and pain symptoms observed in our patient population.

Nearly half of all FM patients report considerable dissatisfaction with the ineffective management of this chronic condition, highlighting the need for more effective and personalised treatment strategies (48). The quality of life of FM patients is already compromised, and the use of multiple medications often exacerbates this problem by introducing additional side effects and complications (49). Therefore, our study contributes towards the development of a more optimised treatment by highlighting the role of alexithymia in predicting treatment outcomes and the benefits of combining duloxetine with aerobic exercise. It demonstrates the potential to improve overall outcomes in FMS patients by identifying patients with higher baseline alexithymia levels as they are most likely to benefit from this intervention.

Our findings have several important clinical implications. First, routine alexithymia assessment using TAS-20 may supplement standard FM assessments that can be easily administered at the baseline and at follow-up appointments. Second, patients with higher baseline alexithymia scores may represent a subgroup that can particularly benefit from the combination of duloxetine and aerobic exercise, suggesting that alexithymia may serve as a treatment stratification tool. Third, monitoring changes in alexithymia over the course of treatment can provide clinicians with an outcome measure in addition to pain scales, and stable alexithymia scores may potentially indicate the need for treatment changes. Finally, our findings support the need for the development of integrated protocols that specifically address emotional processing difficulties in FM management, including targeted psychological components in addition to physical and pharmacological therapies.

While our study offers unique insights into the effects of a combination of duloxetine and aerobic exercise on alexithymia in FM patients, certain limitations need to be acknowledged. The absence of a control group precludes any conclusion on whether the two interventions affected alexithymia independently or in a combinatorial manner. Furthermore, given that FM is a complex disease encompassing multiple dimensions including widespread pain, fatigue, sleep disturbances, cognitive problems, and psychological distress, the use of a single measure of pain intensity (VAS) in our study can be considered as a limitation. Future studies should better elucidate the overall profile of FM by using more comprehensive instruments such as the FIQR or WPI/SS scales that assess all domains and the global status of FM. Although we excluded patients with diagnosed psychiatric disorders, unidentified anxiety conditions may have existed in the recruited patients, which is significant as anxiety was found to mediate the alexithymia-pain relationship in FM. The lack of a direct measurement of anxiety levels in the current study also limits our understanding of this interaction. Future research should address these limitations to better understand alexithymia modulation through different therapeutic approaches in FM.

Conclusion

The current study shows that a combination of duloxetine and aerobic exercise was associated with a decrease in alexithymia and pain symptoms in FM patients. Patients with higher baseline alexithymia scores showed greater improvement, suggesting that alexithymia may help identify the patients who will benefit the most. These findings underline the importance of considering emotional factors when planning any treatment for FM.

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