Effects of antidepressant mirtazapine on fibromyalgia symptoms

Samborski W[1], Leżańska-Szpera M[2], Rybakowski JK[2]

[1] Department of Physiotherapy and Rheumatology, University of Medical Sciences, Poznań, Poland
[2] Department of Adult Psychiatry, University of Medical Sciences, Poznań, Poland

Abstract

Purpose: **Fibromyalgia syndrome (FS) is a form of non-articular rheumatism. The main criteria are the widespread musculoskeletal pain and tender points at multiple characteristic sites which are associated with several vegetative and functional symptoms. Depression is the most frequent psychiatric concomitant of FS. Etiology is unknown, connection between disturbances of serotonin metabolism and pathogenesis is postulated. Pharmacological therapy with analgetic and nonsteroidal antiinflammatory drugs is not very effective. Positive effects were reported in some patients treated with antidepressant drugs, especially serotonergic agents.**

Material and methods: **In the study a novel antidepressant drug mirtazapine was used characterized by selective blockade of 5-HT2 and 5-HT3 receptors. In an open trial participated 29 patients with FS, who met 1990 ACR criteria for fibromyalgia. All were treated with mirtazapine for 6 weeks. Intensity of pain, sleep disturbances, fatigue and other symptoms were measured using visuale analogue scale, severity of depression was evaluated with HDRS and BDI.**

Results: **An open trial completed 26 patients, the majority of them experienced a clinical improvement at the end of the study as a consequence of ≥40% reduced intensity of fibromyalgia symptoms as well as reduced severity of depression. The significant correlation between reduction in depression after 6 weeks of mirtazapine treatment with the reduction on all four main symptoms of FS suggests a common pathophysiology of depression and symptoms of fibromyalgia. The data thus far obtained indicate the blockade of 5-HT2 and 5-HT3 receptors with mirtazapine as an effective and promising method in FS.**

Conclusions: **Further double-blind placebo-controlled study are required to confirm our results.**

Key words: fibromyalgia, blockade of 5-HT2 and 5-HT3 receptors, mirtazapine.

Introduction

Fibromyalgia syndrome (FS) is a form of non-articular rheumatism. Widespread musculoskeletal pain is the dominant symptom, and tender points at multiple characteristic sites can be demonstrated in most instances [1,2]. FS is frequently associated with chronic fatigue, poor sleep, irritable bowel, headaches, dysmenorrhea and other vegetative symptoms [3-5]. All studies confirm the female preponderance as well as the chronicity of symptoms in this syndrome [6,7]. Muscle biopses reveal no inflammatory processes and basic laboratory tests are normal [8,9]. Depression is the most frequent psychiatric concomitant of FS and observed association between FS and depression has been considered in several ways: is FS a variant of depression (somatized depression) or are the symptoms of depression secondary to disturbances in the process of coping with chronic and painful disease? Another possibility is that depression and FS share common aspects of their pathophysiology [10,11].

Several studies have shown that central serotonin abnormality may be connected with an increased pain sensitivity, sleep disturbance and depression [12]. Because these symptoms are prominent in FS, an association between FS and disturbed serotonin (5-HT) metabolism has been postulated [13]. There is some evidence supporting this hypothesis such as showing a decrease in both serum concentration of 5-HT and

ADDRESS FOR CORRESPONDENCE:
Samborski W
Department of Physiotherapy and Rheumatology
University of Medical Sciences
ul. 28 czerwca 1956 r 135/147
61-545 Poznań, Poland
Tel: +061-8-310-244

Received 1.07.2003 8.06.2004

plasma concentration of tryptophan (5-HT precursor) in FS. A relationship exists between the 5-HT serum concentration and the intensity of pain as well as the number of specific "tender points" [14-16]. A presence of antibodies against 5-HT in patients with FS has been also demonstrated [17,18].

Pharmacological therapy of FS is mostly unsatisfactory. Analgetic agents and nonsteroidal antiinflammatory drugs are not very effective. On the other hand, a favorable therapeutic response was observed to antidepressant drugs. Positive effects were reported in some FS patients treated with tricyclic antidepressants – imipramine and amitriptyline [19,20], with selective serotonin reuptake inhibitors – citalopram and fluoxetine [21,22], and also with the novel antidepressant venlafaxine [23]. Influencing serotonergic system makes an important element of mechanism of each of these drugs. A recent meta-analysis of fibromyalgia treatment with antidepressant drugs suggests a significant effect of such treatment on sleep, fatigue, pain and well-being of patients. However, it is not clear whether this effect is related to antidepressant action [24,25].

Apart from antidepressant drugs, some effect in FS was also observed with serotonergic agents, e.g. selective blockers of serotonergic receptors. In the study with ketanserine, the drug blocking serotonin 5-HT2 receptors, it was found that quality of sleep in FS was improved [26]. Also, a therapy with tropisetron or ondansetron, the selective 5-HT3 receptor antagonists reduced pain intensity in about half of FS patients whereas no change in pain level was seen in the other half. The lack of uniform pattern of responsiveness to these agents may suggest a heterogeneity of pathogenic background in relation to serotonergic system in FS patients [27-29].

Mirtazapine is a novel antidepressant drug characterized, among others, by selective blockade of both 5-HT2 and 5-HT3 receptors. In view of previous moderately promising studies with selective serotonin receptor antagonists, we hypothesized that this drug may be useful in the treatment of fibromyalgia. In this study we present the results of an open trial of mirtazapine in FS patients.

Materials and methods

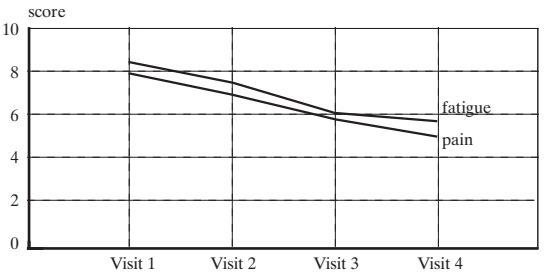
Subjects

The study group consisted of 29 patients with FS (25 female and 4 male) with mean age 45.6 years (range 20-64). All patients met the 1990 American College of Rheumatology diagnostic criteria for FS [30]. Each patient underwent routine clinical examination, radiographic and laboratory investigation to establish the diagnosis (excluding other inflammatory, rheumatic, metabolic, endocrine disease associated with muscle pain). They all gave written consent to the study which was also approved by the Ethics Committee, University of Medical Sciences, Poznań.

Procedure

The patients were free from all antidepressant medication for at least 7 days before the administration of mirtazapine. Throughout the study, no other drugs were permitted with the exception of paracetamol, if required by the patient, but not exceeding 2 g/day. The patients were treated with mirtazapine for 6 weeks (42 days), the first week with 15 mg in the evening, the next 5 weeks the dose could be increased to 30 mg in the evening. All patients were examined by the rheumatologist and psychiatrist before enrolling into the study (visit 1), after 7 days (visit 2), after 21 days (visit 3) and after 42 days (visit 4).

Figure 1. **Intensity of pain and fatigue in the courses of mirtazapine treatment. (VAS score)**



Assessment

Intensity of pain, sleep disturbances, fatigue and other symptoms: cold extremities, dryness of mouth, perfuse sweating, dizziness, gastric problems, headache or migraine, irregular breathing, arrhythmia, paresthesia and urinary urgency was measured using visual analogue scale (VAS) where 0=no symptom and 10=extreme intensity of symptoms [31]. The duration of morning stiffness was measured in minutes.

The severity of depression was measured using the Hamilton Depression Rating Scale (HDRS) – 17 item version [32] and Beck Depression Inventory [33].

Patient was considered improved, if he/she obtained the reduction of ≥40% of the following main symptoms: pain, fatigue, sleep disturbances and depression.

Statistics

For the statistical analysis, the Wilcoxon-Test, the Mann-Whithney U Test and ANOVA procedure were used.

Results

Among 26 patients who completed an open trial with mirtazapine, the majority experienced a clinical improvement at the end of the study as a consequence of ≥40% reduced intensity of fibromyalgia symptoms. In 13 patients (50%), the reduction of pain and fatigue level was observed. The decrease of intensity of these symptoms in whole group of patients with subsequent visits is depicted in *Fig. 1*.

The improvement of the sleep quality with significant reduction on VAS was noted in 19 patients (73%), what was also supported by the decrease of intensity on HDRS sleep subscale (items 4-6). This is shown in *Fig. 2*.

The reduced severity of depressive symptoms ≥40% on HDRS scale was observed in 18 patients (69%) and on BDI scale in 16 subjects (61%). The mean intensity of depressive symptoms during subsequent visits in shown in *Fig. 3*.

Figure 2. **Sleep disturbances in the course of mirtazapine treatment (VAS score and HDRS sleep subscale)**

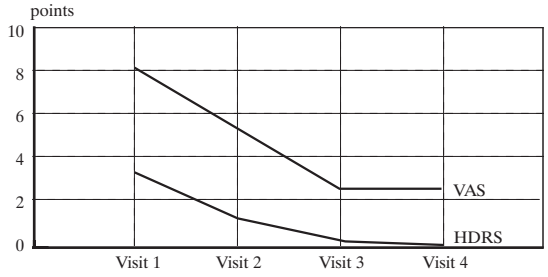


Figure 3. **Intensity of depression (HDRS and BDI scores) in the course of mirtazapine treatment**

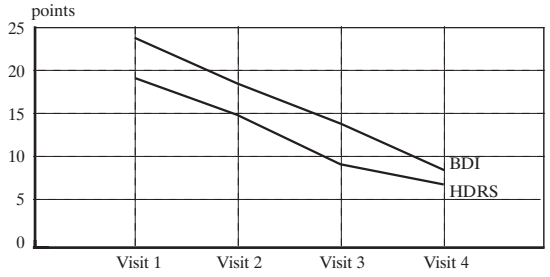


Table 1. **Intensity of fibromyalgia symptoms before and after therapy with mirtazapine in patients with fibromyalgia (n=26)**

Symptoms VAS	n=26		
	I	II	p<
Pain	7.92	5.0	0.0005
Morning stiff. (min)	67.9	48.7	0.0005
Fatigue	8.4	5.7	0.0005
Sleep disturbances	8.2	2.7	0.0001
Cold extremities	7.3	4.7	0.0005
Dryness of mouth	6.0	4.9	0.005
Perfuse sweating	6.4	4.2	0.001
Dizziness	5.6	2.7	0.0005
Headache	6.5	3.3	0.0001
Gastric problems	5.5	2.7	0.0005
Arrhythmia	7.4	4.3	0.0005
Irregular breathing	4.9	3.5	0.005
Paresthesia	8.0	4.2	0.0005
Urinary urgency	5.4	2.9	0.001

I – before enrolling into the study;
II–after 6 weeks treatment with mirtazapine

Table 2. **Correlation between reduction of depression (HDRS and BDI scales) and reduction of main fibromyalgia symptoms after 6 weeks of mirtazapine treatment**

	Reduction in HDRS	Reduction in BDI
Pain	0.72**	0.63**
Sleep disturbances	0.46*	0.42*
Fatigue	0.77**	0.69**
Morning stiffness	0.64**	0.53*

* p<0.05; ** p<0.005

The improvement expressed as ≥40% reduced intensity on all mentioned above parameters was observed in 10 patients (38%).

A significant amelioration after mirtazapine treatment was also noted in such somatic symptoms as cold extremities, dryness of mouth, perfuse sweating, dizziness, headache, gastrointestinal symptoms, arrhythmia, irregular breathing, paresthesia and urinary urgency what was shown in *Tab. 1*.

The mean weekly dosage of paracetamol in whole group of patients was reduced from 4.5 g taken during the week before treatment to 1.5 g during the last week (p<0.0005).

Eight patients complained of sleepiness and hypotension in the first days of therapy. In 5 cases the dose of mirtazapine was reduced to 15 mg daily and treatment was continued. Three female patients dropped out from the study after second visit on account of this side effect. Other side effects were not observed during mirtazapine treatment.

In the whole group of patients before treatment, there was a significant correlation between the intensity of depression, measured both with HDRS and BDI, and the intensity of pain and morning stiffness but not with the intensity of fatigue and sleep disturbances. The magnitude of reduction in depression after 6 weeks of mirtazapine treatment significantly correlated with the magnitude of reduction on all four main symptoms of FS, what was shown in *Tab. 2*.

Among 26 patients who completed the study, 18 of them (group A) had at least a moderately severe level of depression before mirtazapine treatment (HDRS score ≥18, mean 22.7) and 8 patients (group B) presented mild depressive symptoms (HDRS score <18, mean 13.1). *Tab. 3* shows the results of pain intensity, morning stiffness, fatigue and all other fibromyalgia symptoms before and after 6 weeks of treatment with mirtazapine in both groups of patients. Before treatment in patients from group A more intensity of fibromyalgia symptoms was observed in comparison with group B (range 7 to 47%) but the differences were not significant. Improvement after the therapy was statistically significant in both groups although in group A the mirtazapine seemed to be more effective (*Tab. 3*).

Discussion

The results obtained suggest that mirtazapine, 15-30 mg daily, is effective in reducing pain intensity, sleep disturbances, fatigue, intensity of vegetative and functional symptoms as well as the severity of depression in the majority of fibromyalgia patients.

The most robust effect of mirtazapine was observed on sleep quality. The sleep disturbances in FS are well known phenomenon, resembling those of depressive patients [34,35]. The beneficial effect of mirtazapine may be attributed to the action of this drug on 5-HT2 receptors. The analysis of 4, 5 and 6 HDRS items indicate, that treatment with mirtazapine leads

Table 3. **Intensity of fibromyalgia symptoms before and after therapy with mirtazapine (Group A: patients with ≥18 pts in HDRS; group B: patients with <18 pts in HDRS)**

Symptoms VAS	Group A n=18			Group B n=8			Difference IA and IB (%)
	I	II	p<	I	II	p<	
Pain	8.3	5.6	0.005	7.0	3.9	0.05	16
Morning stiff. (min)	79.2	61.2	0.005	42.5	23.7	0.05	47
Fatigue	8.4	6.1	0.005	8.4	5.0	0.05	0
Sleep disturbances	8.1	3.4	0.001	8.4	1.2	0.01	-4
Cold extremities	7.5	4.9	0.005	6.7	4.2	0.05	11
Dryness of mouth	6.5	5.6	0.05	4.9	3.5	0.05	25
Perfuse sweating	7.2	5.0	0.005	4.5	2.7	NS	38
Dizziness	5.9	3.2	0.005	4.9	1.7	0.05	18
Headache	6.9	3.6	0.005	5.6	2.6	0.05	19
Gastric problems	6.2	3.1	0.005	4.0	2.0	0.05	36
Arrhythmia	7.6	3.8	0.005	7.1	5.4	0.05	7
Irregular breathing	5.2	3.6	0.01	4.2	3.2	NS	20
Paresthesia	8.0	4.4	0.01	7.9	3.9	0.05	2
Urinary urgency	5.5	2.8	0.005	5.2	3.0	0.05	6

I – before enrolling into the study
II – after 6 weeks treatment with mirtazapine
NS – not significant

to improvement of sleep quality, especially problems with too early awakening.

We observed relatively high prevalence of depression symptoms among examined patients, 18 of them (69%) represented at least moderately severe level of depression (score ≥18). Depression was the second phenomenon in fibromyalgia patients, after sleep, which was influenced most favorably during mirtazapine treatment.

Important observation of our study is also significant improvement in other vegetative and functional symptoms, like pain, fatigue, headache, gastrointestinal complaints, paresthesia and urinary urgency. These disturbances are the reason of many complaints, significantly restricting life activity of patients. Another advantage of mirtazapine treatment is a possibility of significantly reducing the use of analgetic agents. Apart from hypotension in the initial period of therapy, there were no serious adverse effects during the treatment with mirtazapine in our study.

The issue of a possible relationship between therapeutic effect of mirtazapine in FS and antidepressant action of the drug can be answered positively. The magnitude of reduction in depression after 6 weeks of mirtazapine treatment in whole group of patients significantly correlated with the magnitude of reduction on all four main symptoms of FS. This would suggest a possibility of common pathophysiology of depression and symptoms of fibromyalgia.

In conclusion, our results indicate that mirtazapine can be an effective and promising method in the treatment of FS patients. These observations should be confirmed on the greater group of patients and in the double-blind placebo-controlled trial.

References

1. Baumgartner E, Finckh A, Cedraschi C, Vischer TL. A six year prospective study of a cohort of patients with fibromyalgia. Ann Rheum Dis, 2002; 61: 644-5.

2. Yunus M, Masi AT, Calabro JJ, Miller KA, Feingenbaum SL. Primary fibromyalgia (fibrositis): clinical study of 50 patients with matched normal controls. Sem Arthritis Rheum, 1981; 11: 151-61.

3. Bennett RM. Confounding features of the fibromyalgia syndrome: a current perspective of differential diagnosis. J Rheumatol, 1989; 16(19): 58-61.

4. Samborski W, Stratz T, Kretzmann, Mennet P, Müller W. Vergleichende Untersuchungen über das Vorkommen vegetativer und funktioneller Beschwerden bei Lumbalgien und generalisierten Tendomyopathien. Z Rheumatol, 1991; 50: 378-81.

5. Yunus M, Masi AT, Aldag JC. A controlled study of primary fibromyalgia syndrome: clinical features and association with other functional syndromes. J Rheumatol, 1989; 16(19): 62-71.

6. Goldenberg DL. Fibromyalgia syndrome: an emerging but controversial condition. JAMA, 1987; 257: 2782-7.

7. Wolfe F, Cathey MA. Prevalence of primary and secondary fibrositis. J Rheumatol, 1983; 10: 965-68.

8. Bennett RM, Clark SR, Campbell SM, Burchardt CS. Low levels of somatomedin C in patients with the fibromyalgia syndrome. Arthritis Rheum, 1992; 35; 10: 1113-6.

9. Kalyanraman UP, Kalyanraman K, Yunus MB, Masi AT. Muscle pathology in primary fibromyalgia syndrome (PFS): a light microscopic, histochemical and ultrastructural study. J Rheumatol, 1984; 11: 808-13.

10. Burckhardt CS, O'Reilly CO, Wiens AN, Clark SR, Campbell AM, Bennett RM. Assessing depression in fibromyalgia patients. Arthritis Care Res, 1994; 7: 35-9.

11. Meyer-Lindenberg A, Gallhofer B. Somatized depression as a subgroup of fibromyalgia syndrome. Z Rheumatol, 1998; 57(2): 92-3.

12. Meltzer HY, Lowy MT. The serotoninhypothesis of depression. In: Meltzer HY, ed. Psychopharmacology; The Third Generation of Progress. New York: Raven Press, 1987, 513-26.

13. Alnigenis MN, Barland P. Fibromyalgia syndrome andserotonim. Clin Exp Rheumatol, 2001; 19(2): 205-10.

14. Moldofsky H, Warsh JJ. Plasma tryptophan and musculoskeletal pain in nonarticular rheumatism ("fibrositis syndrome"). Pain, 1978; 5: 65-71.

15. Russell IJ, Michalek JE, Vipraio GA, Fletcher EM, Javors MA, Bowden CA. Serum serotonine and platelet ^{3}H-imipramine binding receptor density in patients with fibromyalgia/fibrositis syndrome. J Rheumatol 19: 104-9.

16. Samborski W, Stratz T, Schochat T, Mennet P, Müller W. Biochemische Veränderungen bei der Fibromyalgie. Z Rheumatol, 1996; 55: 168-73.

17. Anderberg UM, Marteinsdottir I, von Knorring L. Citalopram in patients with fibromyalgia – a randomized, double-blind, placebo-controlled study. Eur J Pain, 2000; 4(1): 27-35.

18. Heymann RE, Helfenstein M, Feldman D. A double-blind, randomized, controlled study of amitriptyline, nortriptyline and placebo in patients with fibromyalgia. An analysis of outcome measures. Clin Exp Rheumatol, 2001; 19(6): 697-702.

19. Wysenbeek AJ, Mor F, Lurie I, Weinberger A. Imipramine for the treatment of fibrositis: a therapeutic trial. Ann Rheum Dis, 1985; 44: 752-3.

20. Samborski W, Służewska A, Łącki JK Hrycaj P, Rybakowski JK. Immunological disturbances in fibromyalgia and major depression. Proceedings of 14 European Immunology Meeting. Monduzzi Editore, 2001; 645-8.

21. Anderberg UM, Marteinsdottir I, von Knorring L. Citalopram in patients with fib Klein R, Bänsch M, Berg PA. Clinical relevance of antibodies against serotonin and gangliosides in patients with primary fibromyalgia syndrome. Psychoneuroendocrinology, 2000; 17; 6: 593-8.

22. Arnold LM, Hess EV, Hudson JI, Welge JA, Berno SEE, Keck PE Jr. A randomized, placebo-controlled, double-blind, flexible-dose study of fluoxetine in the treatment of women with fibromyalgia. Am J Med, 2002; 15; 112(3): 237-9.

23. Dwight MM, Arnold LM, O'Brien H, Metzger R, Morris-Park E, Keck PE. An open trial of venlafaxine treatment of fibromyalgia. Psychosomatics, 1998; 39(1): 14-7.

24. Arnold LM, Keck PE, Welge JA. Antidepressant treatment of fibromyalgia. A meta-analysis and review. Psychosomatics, 2000; 41(2): 104-13.

25. O'Malley PG, Balden E, Tomkins G, Santoro J, Kroenke K, Jackson JL. Treatment of fibromyalgia with antidepressants: a meta-analysis. J Gen Intern Med, 2000; 15: 659-66.

26. Stratz T, Mennet P, Benn HP, Mueller W. Blockierung der S2-Rezeptoren – Ein neues Behandlungsprinzip der generalisierten Tendomyopathie (Fibromyalgie)? Z Rheumatol, 1991; 50: 21-2.

27. Samborski W, Stratz T, Łącki JK, Klama K, Mennet P, Mueller W. The 5-HT3 blockers in the treatment of the primary fibromyalgia syndrome: a 10-day open study with Tropisetron at low dose. Mat Med Pol, 1996; 28: 17-9.

28. Burckhardt CS, O'Reilly CO, Wiens AN, Clark SR, Campbell AM, Bennett RM, Stratz T, Faerber L, Varga B, Baumgartner C, Haus U Mueller W. Fibromyalgia treatment with intravenous tropisetron administration. Drugs-Exp-Clin-Res, 2001; 27(3): 113-8.

29. Stratz T, Schochat T, Hrycaj P. Die Therapie der generalisierten Tendomyopathie (Fibromyalgie) durch Blockierung der 5-HT3 Rezeptoren. Z Rheumatol, 1994; 53: 335-8.

30. Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL, Tugwell P, Campbell SM, Abeles C, Clark P. The American College of Rheumatology 1990 criteria for the classification of fibromyalgia. Arthritis Rheum, 1990; 33: 160-72.

31. Huskisson EC. Measurement of pain. Lancet, 1974; 2: 1127-31.

32. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry, 1960; 23: 56-62.

33. Beck AT, Ward CH, Mendelsohn M. Assessing depression in fibromyalgia patients. Arthritis Care Res, 1961; 7: 35-9.

34. Dauvillierf Y, Touchon J. Sleep in fibromyalgia: review of clinical and polysomnographic data. Neurophysiol Clin, 2001; 31(1): 18-33.

35. Roizenblatt S, Moldofsky H, Benedito-Silva AA, Tufik S. Alpha sleep characteristic in fibromyalgia. Arthritis Rheum, 2001; 44(1): 222-30.