Cumhuriyet Tıp Derg 2009; 31: 22-30
Cumhuriyet Med J 2009; 31: 22-30

The effect of tegaserod on quality of life in patients having co-existence of irritable bowel syndrome and fibromyalgia

İrritabl barsak sendromu ve fibromiyaljinin birlikte görüldüğü hastalarda tegaserodun yaşam kalitesi üzerine etkisi

İlkay Çakır, Yüksel Seçkin, Özlem Yönem, Fatih Kılıçlı

Department of Endocrinology (İ. Çakır, MD, Specialist in Internal Medicine), Erciyes University School of Medicine, Kayseri; Department of Gastroenterology (Assist. Prof. Y. Seçkin, MD), İnönü University School of Medicine , Malatya; Departments of Gastroenterology (Assoc. Prof. Ö. Yönem, MD) and Internal Medicine (F. Kılıçlı, MD, Specialist in Internal Medicine), Cumhuriyet University School of Medicine, TR-58140 Sivas

Abstract

Aim. The aim of this study is to investigate the effect of tegaserod on symptoms and quality of life in patients who have irritable bowel syndrome and fibromyalgia co-existence. **Methods.** The study was performed between the time March 2005 and September 2005. Two groups were formed; constipation predominant irritable bowel syndrome (IBS-C) patients having co-existence of fibromyalgia (IBS-C plus FMS group, 28 female patients) and IBS-C patients without fibromyalgia (IBS-C group, 28 female patients). Turkish brief version of WHOQOL (World Health Organization Quality of Life) named as WHOQOL-BREF-TR scale was used to determine the QoL of patients. Visual anolog scale was used to determine the severity of pain. Tegaserod 6 mg tablet was given to the study groups administered ½ hours before breakfast and dinner. They were called for control visits at the first and second months of therapy. WHOQOL-BREF-TR scale was answered by patients during these visits. **Results.** When the total QoL scores of the study groups were compared, there was no difference between the pretreatment values of study groups. But we found a significant difference when the first and second month values of the study groups were compared. ($p<0.05$). **Conclusions.** QoL increased in only IBS-C patients but not in patients with a co-existence of fibromyalgia and IBS-C. The reason for this result can be explained by scale related problems as it only determines psychological, environmental and social areas and social and psychological additional support therapies could be required for IBS-C and FMS patients. Although there was no cardiovascular side effects of tegaserod in our study subjects, the drug was withdrawn from market in 2007.

Keywords: Irritable bowel syndrome, fibromyalgia, quality of life

Özet

Amaç. Bu çalışmanın amacı irritabl barsak sendromu ile birlikte fibromyaljisi olan hastalarda tegaserodun semptomlar ile yaşam kalitesine etkisini araştırmaktır. **Yöntem.** Çalışma Mart 2005 ve Eylül 2005 tarihleri arasında yapıldı. Konstipasyon-baskın irritabl barsak sendromu ile birlikte fibromyaljili hasta grubu (28 bayan) ve yalnızca konstipasyon-baskın irritabl barsak sendromulu hasta grubu (28 bayan) oluşturuldu. Yaşam kalitesinin değerlendirilmesinde WHOQOL (Dünya Sağlık Örgütü yaşam kalitesi ölçeği)'nin Türkçe kısa versiyonu olan WHOQOL-BREF-TR kullanıldı. Ağrının şiddetinin değerlendirilmesinde ise görsel analog ölçek kullanıldı. Her iki gruba da tegaserod 6 mg tablet kahvaltı ve akşam yemeğinden yarım saat önce almaları tavsiye edilerek verildi. Hastalar tedavinin 1. ve 3. aylarında kontrole çağırıldılar. Kontrole geldiklerinde WHOQOL-BREF-TR'deki soruları cevaplamaları istendi. **Bulgular.** Toplam yaşam kalitesi puanları değerlendirildiğinde her iki grubun tedavi öncesi değerleri arasında anlamlı bir farklılık saptanmadı. Ancak her iki grubun birinci ve ikinci aylarındaki değerleri arasındaki fark anlamlı bulundu ($p<0,05$). **Sonuçlar.** WHOQOL-BREF-TR yaşam kalitesi toplam puanları tedavi ile

yalnızca konstipasyon baskın irritabl barsak sendromu olan hastalarda arttı. Konstipasyon ve fibromyalji sendromunun birlikte olduğu hastalarda ise artmadı. Bunun nedeni ölçekle ilgili problemler olabilir. Çünkü ölçek psikolojik, çevresel ve sosyal alanları içermektedir ve irritabl barsak sendromuna fibromyalji de eklenince bu tür hastalara tedavide ek psikolojik ve sosyal destek tedavisi verilmesi gerekebilir. Çalışmamızda ilaç ile ilişkili herhangi bir kardiyovasküler yan etkiye rastlanmamakla birlikte kardiyovasküler yan etkileri nedeniyle çalışmanın tamamlanmasından sonra 2007 yılında tegaserodun kullanımı yasaklandı.

Anahtar sözcükler: İrritabl barsak sendromu, fibromyalji, yaşam kalitesi

Geliş tarihi/Received: March 16, 2009; **Kabul tarihi/Accepted:** April 11, 2009

Corresponding author:

Fatih Kılıçlı, İç Hastalıkları Anabilim Dalı, Cumhuriyet Üniversitesi Tıp Fakültesi, TR-58140 Sivas. Email: fkilicli@yahoo.com

Introduction

The mechanisms of symptoms in functional gastrointestinal diseases are complex and as yet no net organic cause for IBS has been defined. Various hypotheses have been proposed such as dysmotility, visceral hypersensitivity, inflammation, infection, imbalance in neurotransmitters and psychosocial factors like stress [1].

There is an overlap of IBS with other chronic episodic disorders such as fibromyalgia, irritable urinary bladder, premenstrual dysphoric disorder and chronic fatigue syndrome [2]. Fibromyalgia syndrome is a common and chronic syndrome of widespread pain that usually affects middle-aged woman [3]. The disease is characterized by widespread musculoskeletal pain, along with depression, sleep disturbance, decreased pain threshold, significant fatigue and multiple tender points [4].

Irritable bowel syndrome reduces the life quality of patients. In various studies it has been shown that quality of life (QoL) of patients with IBS is worse than other patients with chronic diseases and similar to some important medical conditions such as depression [5-7].

Tegaserod which is used in constipation-dominant IBS is a selective partial agonist of 5-HT4 receptor. It induces peristaltism and increases the motility of gastrointestinal channel by releasing calcitonin gene related peptide, substance P and vasoactive intestinal peptide [8, 9]. It can play a direct role in initiating peristaltic reflex by its serotonin-like effect [10]. Additionally tegaserod stimulates chlor and water secretion in large bowel and this loosens the consistency of gaita [11].

The purpose of this study is to investigate the effect of Tegaserod on symptoms and QoL in patients who have IBS plus FMS.

Material and methods

Our study was approved by the local ethical committee and carried out in the Physical Rehabilitation, Internal Medicine, and Gastroenterology Clinics of Cumhuriyet University Hospital between March 2005 and September 2005. Laboratory investigations were performed in the Biochemistry, Hematology and Nuclear Medicine Laboratories of the same hospital. Female patients with constipation-predominant irritable bowel

syndrome and symptoms of fibromyalgia were included in the study. All of the patients were informed about the study, and a written informed consent form was obtained from all the patients.

Female patients with an age range of 18-55 were included in the study. Patients with an additional disease, and using medications, and pregnant or nursing women were excluded from the study. Patients having alarming characteristics and red dot signs notified by American Gastroenterological Association were also excluded and these were separated for further investigations.

IBS-C (Constipation dominant IBS) was diagnosed by using the latest Rome II criteria. FMS (Fibromyalgia syndrome) was investigated in these IBS-C patients according to 1990 ACR criteria. Two groups were formed; IBS-C patients having co-existence of FMS (IBS-C plus FMS group, 28 female patients) and IBS-C patients without FMS (IBS-C group, 28 female patients). The mean age of the patients in the study groups were 37.7±4.9 (min 37, max 42) years and 34.6±6.7 (min 34, max 41) years, respectively.

All of the patients included in the study were evaluated by clinical history and physical examination, their body weights were noted. Tender points were determined by digital palpation. The patients were inquired for their alarm symptoms and measurements of complete blood count, erythrocyte sedimentation rate, liver and renal function tests, serum electrolytes, thyroidal function tests, fecal occult blood tests, abdominal plain films, urinary tests were performed to exclude any organic disease. Their electrocardiograms were obtained in the follow-up period. Turkish brief version of WHOQOL (World Health Organization Quality of Life) named as WHOQOL-BREF-TR scale was used to determine the QoL of patients [12]. Visual analog scale was used to determine the severity of pain.

Tegaserod 6-mg tablet was given to the study groups as administered 30 min before breakfast and dinner. They were called for control visits at the first and second months of therapy. WHOQOL-BREF-TR scale was answered by patients during these visits. This scale includes a total of 27 questions; 26 from the original scale and 1 question directed towards social and cultural constraints in the Turkish society. There were also questions in the scale related to physical, social relations, environmental and mental areas. Questions 3, 4,10, 15, 16, 17, 18, 19 and 21 are related to the physical area, questions 5, 6, 7, 8, 20, 22 and 26 are related to the social area, questions 12, 13, 14, 24 and 25 are related to environmental area and the questions 9, 11, 23 and 27 are related to the mental area. Each question was scored from 1 to 5, 5 being the worst and 1 being the best. Questions 3, 4, 26 and 27 are negative and calculated by subtracting the score given by the patient from 6. The QoL of the patients were calculated according to the total scores of patients. By this calculation, $\leq$ 27 scores yielded very bad, 28-54 scores yielded mild bad, 55-81 scores neither good nor bad, and 82-108 scores fairly good, and patients getting 100-135 scores were categorized as very good. The calculated scores were compared separately for each area and as totally.

One of the patients in the IBS-C group quitted the study because of the development of severe diarrhea. Two patients in the IBS-C plus FMS group did not attend their follow-up visits and they were excluded from the study.

Statistical analysis

Data were given as mean±SD. ANOVA with Tukey test and t test were used for statistical analyses. In all comparisons, a significance level of 0.05 was applied.

Results

The mean ages (37.8 ± 4.9 and 34.6 ± 6.7) of IBS-C plus FMS and IBS-C groups, respectively, were comparable (t=1.96, p=0.056; p>0.05).

Physical area scores

The physical area scores of the study groups before treatment and at the first and second months of treatment were comparable (p>0.05). The physical area score of the patients in FMS plus IBS-C group before treatment and at their first and second months of treatment were similar (p>0.05). The physical area score of the patients in IBS-C group before treatment and at their first and second months of treatment were different. (p<0.05).When the values are compared in two separate groups, the difference between the first month and pretreatment values were found to be significant while there were no differences between either the pretreatment–second month or first month-second month values (p>0.05) (Table 1).

Table 1. Physical area score of patients before and at the first and second months of treatment

	Physical area score before treatment	Physical area score at the month 1	Physical area score at the month 2	
FMS plus IBS-C group	27.8±5.3	28.5±4.7	28.5±4.5	F=1.27 p=0.287 p>0.05
IBS-C group	28.6±5.5	30.7±4.6	30.4±4.6	F=3.71 p=0.031 p<0.05
Result	t=0.55 P=0.584 p>0.05	t=1.68 P=0.098 p>0.05	t=1.48 P=0.145 p>0.05	

Social area scores

While there was no difference between the two groups in their pre-treatment score of social area (p>0.05), significant differences were found between the study groups at the end of the first and second months (p<0.05), with scores higher in the IBS-C group at all periods of treatment. The social area score of IBS-C group concerning the first and second months of treatment were increased when compared with the other group (Table 2).

Environmental area scores

Significant differences were found between the two groups in their environmental area scores before treatment and at the end of the first and second months (p<0.05), with scores higher in the IBS-C group at all periods of treatment (Table 2).

We also found no difference between the within group values of social scores at the first and second months of treatment in the FMS plus IBS-C and IBS-C groups (p>0.05) (Table 3).

Table 2. Social area score of patients before treatment and at the first and second months of treatment

	Social area score before treatment	Social area score at the month 1	Social area score at the month 2	Results
FMS plus IBS-C group	21.3±4.1	21.6±2.8	22.0±3.3	F=1.05 p=0.356 p>0.05
IBS-C group	23.3±4.9	24.3±3.9	24.1±4.4	F=1.47 p=0.289 p>0.05
Results	t=1.59 p=0.117 p>0.05	t=2.85 p=0.006 p<0.05	t=2.02 p=0.049 p<0.05	

Psychological area scores

The psychological area scores of the two groups before treatment and at the first and second months of treatment were similar (p>0.05) (Table 4). We also found no difference between the within group values of psychological area points at the first and second months of treatment in the FMS plus IBS-C and IBS-C groups (p>0.05).

Table 3. Environmental area score of patients before treatment and at the first and second months of treatment

	Environmental area score before treatment	Environmental area score at the month 1	Environmental area score at the month 2	Result
FMS plus IBS-C group	15.7±3.1	15.9±2.7	16.3±2.2	F=0.88 p=0.421 p>0.05
IBS-C group	17.6±3.2	18.0±3.0	18.2±3.4	F=0.92 p=0.401 p>0.05
Result	t=2.13 p=0.037 p<0.05	t=2.65 p=0.011 p<0.05	t=2.41 p=0.020 p<0.05	

Table 4. Psychological area score of patients before treatment and at the first and second months of treatment

	Pretreatment psychological area score	Psychological area score at the month 1	Psychological area score at the month 2	Result
FMS plus IBS-C group	13.2±2.5	13.1±2.2	13.2±2.5	F=0.07 p=0.928 p>0.05
IBS-C group	13.9±2.5	14.2±2.3	14.5±2.8	F=1.27 p=0.287 p>0.05
Result	t=0.90 p=0.368 p>0.05	t=1.78 p=0.081 p>0.05	t=1.92 p=0.060 p>0.05	

Total scores of QoL

Total scores of the patients in the FMS plus IBS-C group before treatment and at the first and second months of treatment were comparable (p>0.05). The points of the patients belonging to IBS-C group were categorized as neither good nor bad.

The difference in the total points of the patients in the IBS-C group before treatment and at the first and second months of treatment were statistically significant ($p<0.05$). When the total points of patients in the IBS-C group were compared in pairs according to their time periods of treatment, the difference between the pretreatment and first-month values and also the difference between pretreatment and second month values were found to be significant ($p<0.05$) while the difference between the first and second month values were not significant ($p>0.05$). The score of IBS-C group was categorized as fairly good (Table 5).

Table 5. Total QoL scores of patients before treatment and at the first and second months of treatment

	Pretreatment TQoL score	TQoL score at the month 1	TQoL score at the month 2	Result
FMS plus IBS-C group	77.7±10.6	79.1±9.8	80.1±9.7	F=2.45 p=0.096 p>0.05
IBS-C group	80.0±14.0	87.11±10.8	88.11±12.0	F=4.99 p=0.010 p<0.05
SONUÇ	t=1.54 p=0.128 p>0.05	t=2.81 p=0.007 p<0.05	t=2.66 p=0.010 p<0.05	

TPLQ, total quality of life score.

When the life quality points of the study groups were compared, there was no difference between the pretreatment values of the study groups but we found a significant difference between their first and second month values ($p<0.05$) (Table 5).

Discussion

World Health Organization (WHO) has defined life quality depending on perceiving the place of individuals within the cultural values, purposes, expectations and acceptances of the population they live in. A scale is developed including various countries and cultures by preserving the similar psychometric characteristics and forms. Short form of this scale including 26 questions (WHOQOL-BREF) was developed for pragmatic reasons (12).

IBS is a distressing condition disturbing the QoL and, therefore it should be treated [13]. In a US householder survey of functional gastrointestinal disorders, work absenteeism was found to be 13 days per year for patients with IBS while this period was 4 days in the control group [14]. General health status of IBS patients in the UK and US was found worse than the control group [15]. QoL scores of patients with IBS were even found to be lower than the scores of the patients with gastroesophageal reflux disease, diabetes mellitus, or end-stage renal disease [16].

Drossman et al. [17] have compared QoL of the patients with various hepatic and gastrointestinal disorders by using the Functional Bowel Disorder Severity Index, and patients with IBS had the worst scores of life quality when compared with the scores of patients with peptic ulcer disease, ulcerative colitis, liver diseases or other hepato-biliary disorders.

In the present study, WHOQOL-BREF scale was used to determine the QoL of patients with IBS-C, and their pretreatment score yielded 80.0±14.0 points which corresponded to a neither good nor a bad category. Thus the actual QoL of these patients were lower than

that reported in the literature. This could be due to insufficient self-expression of our patients as a result of the fatalist and consentful behaviors acquired by the religion or tradition.

Tegaserod has been found to be superior to placebo in studies investigating this drug's effectivity against IBS-C [18-20]. Therapeutic effect has often been observed within the first week of treatment and response rates increased during the treatment period of 12 weeks. In one study, 881 patients with irritable bowel syndrome, characterized by abdominal pain, bloating and constipation, received tegaserod, 2 mg b. d. or 6 mg b. d., or placebo for 12 weeks. Tegaserod, 2 mg b. d. and 6 mg b. d., showed a statistically significant relief of overall irritable bowel syndrome symptoms, measured by a weekly, self-administered questionnaire. At the end-point, treatment differences from placebo were 12.7% and 11.8% for 2 mg bid and 6 mg bid, respectively. The number of bowel movements increased significantly more than the placebo in both of these studies [18, 21]. Stool consistency was found to be looser than placebo in three of these cases [18, 21, 22].

The effect of tegaserod on general recovery has been investigated in a placebo-controlled 3 months lasting study and the therapeutic gain has been reported to decrease to 5% at the end of the study while it was 13% at the first month due to the increase in placebo effect. There has been a recurrence in symptoms when the drug was withdrawn [18].

Layer et al. [23] have determined the efficacy and tolerability of tegaserod. The patients have received tegaserod for 1 month, and have been randomized at the end of that treatment period to receive either placebo or tegaserod in case of the recurrence of symptoms. Tegaserod was found to improve symptoms when compared with the placebo after the initial treatment period of 1 month and also after the randomization period given in case of recurrence. Tegasarod has also been found to increase the effectivity in work and increase the QoL.

In our study QoL scores of the patients after the first and second month of treatment showed an increase when compared with the basal values only in the IBS-C group and their category improved to the fairly good from neither good nor bad. This difference was statistically significant. These results are similar to the results of other studies in the literature showing tegaserod 6 mg bid is effective in ameliorating the symptoms of IBS-C.

The effect of tegaserod on productivity and daily activity in IBS-C patients was determined in a placebo-controlled study. Compared with placebo, tegaserod significantly reduced work and daily activity impairment at weeks 2 and 4 in this study [24].

The points regarding the social and environmental areas of the life quality scale at the first and second months were only higher in the IBS-C when compared with the IBS-FMS group in our study. Gur et al. [25] have assessed the QoL of patients with fibromyalgia by using Nottingham Health Profile (NHP), Health Assessment Questionnaire (HAQ), and Fibromyalgia Impact Questionnaire (FIQ). They have indicated that there was an important relationship between pain, depression and QoL scales in young fibromyalgia patients. Buchardt et al. [26] have also shown in their study that QoL in patients with fibromyalgia is low. Bernardt et al. [27] have also reported similar results.

Although there was no healthy control group, we found that the QoL in patients with IBS plus FMS was lower compared with patients with IBS.

We did not observe any statistically significant increase in the WHOQOL-BREF total scores of IBS-C plus FMS patients after the first and second month of treatment. WHOQOL-BREF life quality points only increased in the IBS-C patients. That can be explained by scale related problems as it only determines psychological, environmental, and social areas, and social and psychological support therapies are also required for IBS-C and FMS patients.

Conflicts of interest

The authors have no conflicts of interest to declare.

References

1. Drossman DA, Camilleri M, Mayer EA,Whitehead WE. AGA technical review on irritable bowel syndrome. Gastroenterology 2002; 123: 2108–31.
2. Mayer EA, Fass R, Fullerton S. Intestinal and extraintestinal symptoms in functional gastrointestinal disorders. Eur J Surg 1998 Supp; 583: 29-31.
3. Bennett RM. The rational management of fibromyalgia patients. Rheumatic Diseases Clinics of North America 2002; 28: 181–99.
4. Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL, Tugwell P, Campbell SM, Abeles M, Clark P. The American College of Rheumatology 1990 criteria for the classification of fibromyalgia: report of the multicenter criteria committee. Arthritis and Rheumatism; 1990; 30: 160–72.
5. El-Serag HB, Olden K, Bjorkman D, Health-related quality of life among persons with irritable bowel syndrome: a systematic review. Aliment Pharmacol Ther 2002; 16: 1171–85.
6. Frank L, Kleinman L, Rentz A, Ciesla G, Kim J J, Zacker, C. Health-related quality of life associated with irritable bowel syndrome: Comparison with other chronic diseases. Clinical Therapeutics 2002; 24: 675–89.
7. Koloski NA, Talley NJ, Boyce PM. The impact of functional gastrointestinal disorders on quality of life. American Journal of Gastroenterology 2000; 95: 67–71.
8. Grider JR, Foxx-Orenstein AE, Jin JG. 5-Hydroxy-tryptamine4 receptor agonists initiate the peristalic reflex in human, rat, and guinea pig intestine. Gastroenterology 1998; 115: 370-80.
9. Fioramonti J, Million M, Bueno L. Investigations on a 5-HT4 agonist (SDZ HTF 919) and its main metabolite in conscious dogs: effects of gastrointestinal motility and impaired gastric emptying. Gastroenterology 1998; 114 (4 Suppl. Pt 2): A752.
10. Zimmerman AE. Tegaserod: a 5-HT4 agonist for women with constipation-predominant irritable bowel syndrome. Formulary 2002; 37: 449-61.
11. Stoner M, Arcuni J Lee J. A selective 5-HT4 receptor agonist induces cAMP mediated Cl-efflux from rat colonocytes. Gastroenterology 1999; 116 Pt 2: A648.
12. Harper H, Power M, Group TW. Development of the World Health Organization WHOQOL-BREF quality of life assessment. Psychol Med 1998; 28: 551-8.
13. Camilleri M, Heading RC, Thompson WG. Consensus report: clinical perspectives, mechanisms, diagnosis and management of irritable bowel syndrome. Aliment Pharmacol Ther; 2002; 16: 1407–30.
14. Drossman DA, Li Z, Andruzzi E. US householder survey of functional GI disorders: prevalence, sociodemography, and health impact. Dig Dis Sci 1993; 38: 1569– 80.
15. Hahn BA, Yan S, Strassels S. Impact of irritable bowel syndrome on quality of life and resource use in the United States and United Kingdom. Digestion 1999; 60: 77–81.
16. Gralnek IM, Hays RD, Kilbourne A. The impact of irritable bowel syndrome on health-related quality of life. Gastroenterology 2000; 119: 654-660.

17. Drossman DA, Whitehead WE, Toner BB. What determines severity among patients with painful functional bowel disorders? Am J Gastroenterol 2000; 95: 974–80.
18. Novick J, Miner P, Krause R. A randomized, double-blind, placebo-controlled trial of tegaserod in female patients suffering from irritable bowel syndrome with constipation. Aliment Pharmacol Ther 2002; 16: 1877–88.
19. Mueller-Lissner S, Fumagalli I, Bardhan KD. Tegaserod, a 5-HT4 receptor partial agonist, relieves symptoms in irritable bowel syndrome patients with abdominal pain, bloating and constipation. Am J Gastroenterol 2001; 15: 1655–66.
20. Yunus MB. Aldag JC, Pumphrey LJ. A study of association between current smoking and fibromyalgia symptoms. Arthritis Rheum 2000; 43: 332.
21. Lea R, Whorwell PJ. Benefit-risk assessment of tegaserod in irritable bowel syndrome. Drug Saf 2004; 27: 229-42.
22. Kellow J, Lee OY, Chang FY. An Asia-Pacific, double blind, placebo controlled, randomised study to evaluate the efficacy, safety, and tolerability of tegaserod in patients with irritable bowel syndrome. Gut 2003; 52: 671-6.
23. Layer P, KellerJ, Mueller-Lissner S. Tegaserod: Long-term treatment for irritable bowel syndrome patients with constipation in primary care. Digestion 2005; 71:238-44.
24. Reilly MC, Barghout V, Mcburney CR, Niecko TE.. Effect of tegaserod on work and daily activity in irritable bowel syndrome with constipation. Aliment Pharmacol Ther 2005; 22: 373–80.
25. Gur A, Cevık R, Nas K, Sarac AJ,Ozen S. Quality of life in young fibromyalgia patients and effect of depression. APLAR Journal of Rheumatology 2006; 9: 70–8.
26. Burckhardt CS, Clark SR, Bennett RM, Fibromyalgia and quality of life: A comperative analysis. J Rheumatol 1993; 20: 475-9.
27. Bernard AL, Prince A, Edsall P. Quality of life issues for in fibromyalgia patients. Arthritis Care Res 2000; 13:42-50.