A Comparison of Reboxetine and Amitriptylline in the Treatment of Fibromyalgia Syndrome with Co-morbid Depressive Symptoms: An Open-label Preliminary Study

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ÖZET:
Komorbid depresif semptomları olan fibromialjijalı hastalarda reboksetin ve amitriptilinin tedavilerinin karşılaştırılması: Aşık ön çalışma


Yöntem: Depresif semptomlar da olan 21 FM hastası 25-75mg/gün amitriptilinin ya da 8 mg/gün reboksetine rando- mize edildi. Hastalar başlangıç, 2,4 ve 8. haftalarda Fibrom- yaljije Etki Anketi (FEA), Beck Anksiyete ve Depresyon Ölçekleri (BAI, BDI), Hamilton Anksiyete ve Depresyon Ölçekleri (HAM-A, HAM-D) ile değerlendirildi.Ịği âyetli Görsel Analog Skala (GAS) ile değerlendirildi.


Anahat sözcükler: Antidepressanlar, fibromyaljijalı, amitriptil- lin, reboksetin.

Klinik Psikofarmakoloji Bülteni 2010;20:29-37

ABSTRACT:
A comparison of reboxetine and amitriptylline in the treatment of fibromyalgia syndrome with co-morbid depressive symptoms: an open-label preliminary study

Objective: Fibromyalgia (FM) is a chronic debilitating disorder that results in millions of dollars of healthcare costs and lost wages each year worldwide. It is a significant public health concern and new treatments are needed. In this study, we aimed to compare the effectiveness of a widely used tricyclic antidepressant for FM (amitriptylline) and one that has not yet been widely used (reboxetine) for FM in a within-subject pre-posttreatment design. Additionally, since noradrenaline (NA) is thought to play a relevant role in the antinoceptive mechanisms, we also aimed to examine the effectiveness of reboxetine as a selective NA reuptake inhibitor (NARI) in patients with fibromyalgia.

Methods: Twenty-one patients with fibromyalgia were randomized to receive amitriptylline (25-75 mg/day) or reboxetine (8 mg/day). Patients were administered the Fibromyalgia Impact Questionnaire (FIQ), the Beck Depression and Anxiety Inventories (BDI, BAI), and the Hamilton Rating Scales for Depression and Anxiety (HAM- D, HAM-A) at the treatment weeks 2, 4, and 8. The intensity of the pain was recorded using a Visual Analog Scale (VAS).

Results: We found both medications to be associated with improvement in pain (decreased VAS scores), FIQ scores, and depressive symptomatology. General linear model repeated measures analysis on the VAS and FIQ scores showed a significant decrease over time in both treatment groups without significant group difference or time x group interaction effect. There were no serious adverse events in both groups.

Conclusions: This open trial demonstrated that either reboxetine or amitriptylline would be effective for the treatment of pain symptoms in patients with FM. Since open-label clinical effectiveness studies do not provide definitive conclusions about causality or efficacy, double blind, placebo-controlled studies in larger clinical groups are needed to reach a definitive conclusion. Our findings provide clinical researchers important information about the novel treatment options for FM.

Key words: Antidepressants, fibromyalgia, amitriptylline, reboxetine.

Bulletin of Clinical Psychopharmacology 2010;20:29-37

INTRODUCTION

Fibromyalgia (FM) is a chronic disorder characterized by chronic widespread pain and tenderness and is often accompanied by fatigue, sleep disturbances, and morning stiffness (1). FM affects 2-4% of the general population in developed countries and constitutes a significant public health problem (2). Although the pathophysiology of FM
is unknown, it has been hypothesized that dysfunction of pain processing within the central nervous system specifically central monoaminergic neurotransmission may play a role in its etiology (1).

Although they have attracted criticism, the diagnostic criteria issued in 1990 are useful for recruiting homogeneous patient populations in clinical studies among FM patients (1). In addition to neurobiological mechanisms, behavioral and psychological factors play a role in the expression of symptoms in many FM patients (3). However, contribution of psychological factors to FM is also controversial. Although depression is common, it is difficult to determine whether it is a cause of the condition or a consequence of the chronic pain (4,5). One study showed that fifty percent of patients report a history of depression but only 30% have depression at the time of the diagnosis of FM (6).

Patients with FM are difficult to treat. A number of pharmacological treatments have been studied with varying degrees of success including anticonvulsants, antispasticity agents, anxiolytics, sedatives, antidepressant, antipsychotics and opioids (7–9). Antidepressants have an antinociceptive effect on various forms of pain but none of the antidepressant drugs, have yet been approved by the FDA for the treatment of FM (10–14). The recent meta-analyses of antidepressant trials have shown that tricyclic antidepressants to be moderately effective in the treatment of patients with FM (7,15). Although the studies evaluating the effects of selective serotonin reuptake inhibitors (SSRIs) in the treatment of FM yielded inconsistent results, these medications are better tolerated than the tricyclic antidepressants (16,17).

The effect mechanism of tricyclic antidepressants on the fibromyalgia remains unclear. Recent clinical reports have suggested that analgesic effects of tricyclic antidepressants (TCAs) such as amitryptilline appear to be mediated partly via active metabolites, which act to selectively increase NA reuptake (10). Consequently, this has focused attention upon drugs which act to selectively increase 5-HT and NA levels for the treatment of chronic pain (18,19).

Reboxetine is a specific NA reuptake inhibitor used for treating patients with depression without a specific action on serotonin (20). Reboxetine may have analgesic properties similar to TCAs without many of the associated side effects. There are few recent studies on the use of reboxetine for FM or other chronic pains (21,22). In their case series, Krell et al. (2005) reported that depressed patients with FM experienced significant relief of pain before any significant improvement in actual mood symptoms using noradrenergic antidepressant, reboxetine. In this current study, we examined the effectiveness and safety of reboxetine in comparison with amitryptilline in the treatment of FM.

METHODS

Subjects

The study was conducted between June 2005 and April 2006 at the outpatient clinics of Zonguldak Karaelmas University (ZKU) Medical School. The Local Ethic Commitee at the Karaelmas University Hospital, Zonguldak approved the protocol, and all subjects provided written informed consent. All consecutive patients diagnosed as having FM with depressive symptoms according to American College of Rheumatology (ACR) criteria in the outpatient clinics of the Department of Physical Therapy and Rehabilitation were included. Patients were excluded if they had evidence of traumatic injury, inflammatory rheumatic disease, or infectious or endocrine-related arthropathy; clinically unstable medical illness such as hepatic or renal impairment; a history of seizure, head trauma, or stroke. Patients with lifetime history of hypomania, mania, psychosis, or dementia; alcohol or substance dependence during the past 6 months; a substantial risk of suicide; were also excluded. Patients using psychotropic agents (antidepressants, anxiolytics, and antipsychotics) and/ or analgesics (including nonsteroidal antiinflammatory drugs) within the last month before the randomization visit were not included in the study. All patients provided informed consent and none refused to participate.

At the initial assessment, the study group was evaluated by using the Structured Clinical Interview for Axis I Disorders (SCID-I) for the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (23,24).

Study Instruments

The subjects were given the following scales in
addition to the sociodemographic data form:

**The Fibromyalgia Impact Questionnaire (FIQ):**

The FIQ is a self-report instrument composed of 19 items. (25). First 10 items comprise a physical functioning scale; each item is rated on a 4-point Likert-type scale. On items 11 and 12, subjects indicated the number of days that they felt well or missed work because of FM symptoms. Items 13 through 19 are 10-cm visual analog scales along which subjects rated the difficulty in performing their job responsibilities, pain, fatigue, morning tiredness, stiffness, anxiety, and depression. All subscores, with the exception of the 2 work-related scores, were summed to yield the total score of FM impact, which ranges from 0 (no impact) to 80 (maximum impact). The FIQ is widely used in patients with FM to evaluate both the clinical severity of the disease and the efficacy of different interventions. It has been found to be valid and reliable in Turkish FM patients (26).

**The Beck Depression Inventory (BDI):**

The BDI is a 21-item self-report questionnaire that assesses severity of depression (27). Individuals are asked to rate themselves on a 0–3 spectrum (0 = least, 3 = most) with a score range of 0 to 63. The total score is a sum of all items. It was shown to be valid and reliable in a Turkish sample (28).

**The Beck Anxiety Inventory (BAI):**

The BAI is a 21-item self-report questionnaire (29). Each item is rated on a 4-point Likert scale ranging from 0 (not at all) to 3 (severely, I could barely stand it). The total score ranges from 0 to 63. It was shown to be valid and reliable in a Turkish sample (30).

**The Hamilton Rating Scale for Depression (HAM-D) and Anxiety (HAM-A):**

The levels of depression and anxiety were also assessed by the psychiatrists using the Hamilton Anxiety (31) and 17 item Depression (32) Scales. These scales have been demonstrated to be valid and reliable in Turkish population studies (33, 34).

**The 100-mm Visual Analog Scale (VAS):**

The intensity of the pain was recorded with a visual analog scale (VAS) of 100-mm length by patients (35). The 100-mm VAS was used with anchors of “no pain” and of “pain as bad as it could be.” Most studies that compare VAS with numerical and verbal ratings conclude that the VAS or numerical ratings are statistically preferable to the verbal rating scales (35).

**UKU Side Effect Rating Scale**

UKU has been developed to provide a comprehensive side effect rating scale with well-defined and operationalized items to assess the side effects of psychopharmacological medications (36).

**Procedure**

All patients were able to complete the questionnaires independently. With the FIQ and VAS pain being the primary outcome measures, 4 other scales were also given to patients to investigate the association between psychological distress and symptom severity. Self-report scales (e.g., Beck Depression and Anxiety) were administered to patients, as well as the Hamilton rating scales for depression and anxiety, which were rated by clinicians. After the initial assessment, study subjects were randomly assigned to treatment with reboxetine 4-8 mg/day (Group I) or 25-75 mg/day amitryptylline (Group II). Therapeutic effects were assessed at weeks 2, 4, and 8 of treatment. No change was made in the dose of the medication from the beginning to the end of the study.

**Statistical Analysis**

Our data were registered and analyzed using the SPSS for Windows (37). The primary efficacy measures were total VAS and FIQ scores from baseline to endpoint. Differences in test score change rates between treatment groups were tested using Mann-Whitney U analyses as well. In addition differences over time between groups were measured using Friedman and Bonferroni corrected Wilcoxon sign rank test analyses of nonparametric
distributed data. All tests were performed 2-tailed. P values less than 0.05 were considered statistically significant.

**RESULTS**

Thirty-one patients enrolled for the study; six subjects were excluded (recent antidepressant usage (n=3) and major depression with suicidal ideation (n=3) and remaining twenty-five patients that were eligible included in the study. Three patients (one patient randomized to reboxetine and two patient randomized to amitryptilline) withdrew from the study because of adverse effects and one patient randomized to reboxetine did not return for any of the follow-up assessments. Twenty-one subjects were included in the efficacy analysis. Mean age was 41.9 years (SD=11.5, range 24–69 years), 85% were married, 70% completed at least 8 years of education. All the eligible patients were women. There were no significant differences in any baseline measures between subjects randomized to amitryptilline (n=11) or reboxetine (n=10).

The clinical features of the subjects throughout the study are summarized listed in Table 1.

### Pain symptoms (VAS)

During treatment with reboxetine and amitryptilline groups, the pain ratings on a visual analogue scale (VAS) decreased significantly (Figure 1). The differences between the patients treated with reboxetine and amitryptilline did not reach statistical significance at the end of the trial. Although, at the second weeks of the treatment there was a significant decrease in both groups, decreases in VAS scores were significantly higher in reboxetine group compared to the amitryptilline group. There was a significant overall effect of time in total VAS score from baseline to endpoint (F=8.2, df=3, p<0.0001). VAS mean scores of the groups for each assessment week are presented in Table 1. When amitryptilline and reboxetine groups’ mean scores are compared by Mann Whitney U test, there were no significant differences at any week between groups (p>0.05).

### Fibromyalgia Impact Questionnaire (FIQ)

During treatment with reboxetine and amitryptilline, significant improvements were seen mean scores of FIQ

![Figure 1: VAS Scores changes of the study groups.](image-url)
in all assessment weeks (Figure 2) There was a significant overall effect of time in total FIQ score from baseline to endpoint (F=4.24, df=3, p=0.009). The mean FIQ scores differed significantly between the reboxetine and amitryptilline treated patients only at week eight (p<0.05). Throughout the weeks the total number of trigger points was decreased in both groups, but only significant changes were observed in amitriptylline group between week 1 and 8 (p<0.05) (Figure 3).

### Depression and Anxiety (HAM-D, HAM-A, BDI, BAI)

The depressive symptomatology decreased significantly during treatment with both drugs regarding the HAM-D scores. The decrease in the total HAM-D scores was significant after only 1st week of treatment with amitryptilline and 2nd week of treatment with reboxetine. However, after 8 weeks of treatment, there was no statistically significant difference between the groups (Table 1).

The psychometric parameters regarding the BDI, BAI and HAM-A scores decreased significantly during treatment with both drugs. There was a statistically significant increase at the anxiety scores that assessed using HAM-A, only at the second week. After 8 weeks of treatment, groups did not differ in terms of the BDI, BAI and HAM-A scores.

### Side effects- UKU

Both reboxetine and amitryptiline were well tolerated at the doses used in the present study as shown in the UKU as well as in the smaller dropout rates (20% for reboxetine and 18% for amitryptiline) due to adverse effects. The most frequent adverse effects were predictable and these were headache (two subjects), constipation (five subjects), urinary retention (one subject), and dry mouth (six subjects) on reboxetine; sedation (eight subjects) constipation (five subject), and dry mouth (9 subjects) on amitryptiline. In addition to that, no serious side effect was observed in the patients and there were no significant differences between the treatment groups in terms of an incidence of adverse event. However; when the effects on patients’ daily performance of side effects were evaluated, reboxetine group was found advantageous over the amitryptilline group.
DISCUSSION

FM is a chronic debilitating disorder that results in millions of dollars of healthcare costs and lost wages each year in the world. It is significant public health concern and new treatments are needed. In this study, we compare the effectiveness of a widely used TCA for FM (amitriptyline) and one that has not yet been widely used (reboxetine) for FM using a within-subject pre-posttreatment design. We found both medications to be associated with improvement in pain (VAS scores), the FIQ scores, and depressive symptomatology.

To our knowledge, present study is the second report to evaluate the efficacy of the selective NA reuptake inhibitor reboxetine in FM patients. We found that both reboxetine and amitryptilline significantly improved the FIQ and VAS total scores; moreover, patients had a significantly decreased severity of depression and anxiety symptoms.

Given the high comorbidity of depression with FM, one might speculate that reboxetine and amitryptilline has exerted its effect by alleviating psychological distress (38). On the other hand, the effectiveness of antidepressants appears to be independent of their effect on comorbid depressive symptomatology. For instance, in their case series, Krell et al. reported that patient with FM experienced significant relief of pain before any significant improvement in actual mood symptoms using reboxetine (21).

In contrast, in a study comparing a serotonergic and noradrenergic drugs in treatment of pain disorder, Aragona et al. found that patients taking citalopram significantly reduced pain severity, whereas the reboxetine left pain symptoms almost unchanged (22), although their study groups differed our subjects that they all had the somatoform, DSM-IV-TR pain disorder.

The pathophysiology of FM remains unclear, and none of the available drugs are consistently effective in the long term. Recent theories of FM hypothesized that it was triggered in genetically predisposed individuals by unknown infectious, rheumatologic, psychoneuroendocrine, immunologic, or traumatic processes, or other causes of central nervous system irritability (1,3,4). Additionally, considering increased rates of comorbid psychiatric disorders, particularly depressive, anxiety, and somatoform disorders, among FM patients leads to a speculation whether fibromyalgia would be a distinct rheumatologic disease or an affective disorder variants (39). One of the strengths of clinical effectiveness studies is their potential for generalizability to real-world clinical cases. However, we excluded participants with Axis-I disorders other than depression (such as somatoform disorders, obsessive compulsive disorder and posttraumatic stress disorder) thus limiting the generalizability of these findings to patients with co-morbid FM and psychiatric disorders. This is a limitation of the current study as it has been estimated that 74.8% of FM patients have co-morbid Axis-I disorders (38).

Several researchers have shown evidence of serotonergic, noradrenergic, and substance P neurotransmitter dysregulation in FM (10). The present study findings are consistent with a recent review concluding that serotonergic-noradrenergic antidepressants have a stronger analgesic action than selective serotonergic antidepressants (40). A possible explanation for the decreased efficacy of the serotonin reuptake inhibitors (SSRI) compared to tricyclic antidepressants such as amitryptilline could reflect the absence of noradrenergic activity of SSRI’s (41). In concordance with findings that tricyclic antidepressants as typified by amitryptiline, act to non-selectively inhibit the reuptake of serotonin (5-HT) and noradrenaline (NA) that was found to be helpfull in alleviating the pain symptoms of our and other study samples (8,19).

In case it is confirmed in further and more specific studies, these results suggest that selective noradrenergic acting drugs might be used in pain symptoms of FM patients like TCAs (39). But one should consider that the selective action of an antidepressant on the central nervous system does not necessarily resulting a selective response (42). Similarly, several studies have suggested that mirtazapine, venlafaxine, duloxetine , milnacipran also act to enhance the activity of central NA and 5-HT neurones and might be useful in the treatment of pain in both humans and/ or animals (43-51,18,10).

Both reboxetine and amitryptilline were well tolerated in the doses used in the present study as shown in the UKU as well as in the smaller dropout rates (20% for reboxetine and 18 % for amitryptilline) due to adverse effects.

Our study sample comprises only women, this could be taking into account giving a better homogeneity of the
study group. This situation was almost unavoidable because it reflects the prevalence of FM in the population. Although fibromyalgia can occur in men and children, the most attended patients are middle-aged woman (1). This might confound our result due to sex-related differences in drug metabolism (52).

We should mention several limitations of our study. First, this was an open trial and it was neither controlled with placebo nor blinded. Three patients withdrew from the study because of adverse effects and one patient randomized to reboxetine did not return for any of follow-up assessments. Four of 21 patients (20%) withdrew from the study due to adverse effects of the drugs (two patient randomized to reboxetine and two patient randomized to amitryptilline), and this number is comparable to the reported in the literature. This drop-out rate may be due to well known initial side effects of antidepressants. Considering the fact that the antidepressants become more tolerable by the time, we might not have missed some of those patients if they had continued the treatment. Since FM patient had a higher family history of affective disorder, overlapping symptomatology of depression and therapeutic response to antidepressants it has often been considered to be a variant of depressive disorder (53). So, it should be considered as a limitation in this study that including FM patients with depressive symptoms instead of solely physician-diagnosed depressive disorders. Finally, study sample size is relatively small to draw a definitive conclusions regarding efficacy of medications.

In conclusion, this open trial clearly demonstrated that there was no statistical difference between amitryptilline and reboxetine in the treatment of fibromyalgia patients with depressive symptomatology. Both reboxetine and amitryptilline would be effective medications for management of FM and related mood symptoms. Reboxetine was quite promising as same as amitryptilline in alleviating the pain and disability associated with FM. Although reboxetine has more tolerable side effect profile than the amitryptilline, the evidence to support their use in the clinical treatment of FM, double blind, placebo-controlled studies in larger clinical groups are needed. While clinical effectiveness studies do not allow for definitive conclusions about causality or efficacy, we provide clinicians an option well-suited to yield information that might inform future controlled trials. Thus, our work appears to have the potential to provide clinical researchers with some important information about novel treatment options for FM.

References:


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