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Efficacy of Paroxetine and Amitriptyline in Posttraumatic Stress Disorder: An Open-label Comparative Study

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ÖZET:

Travma sonrası stres bozukluğunda amitriptilin ve paroksetinin etkinliği: Açık etiketli karşılaştırmalı çalışma

Amaç: Bu çalışmanın amacı çatışma ile ilişkili Travma Sonrası Stres Bozukluğu (TSSB) olan askerlerde amitriptilin ve paroksetinin etkinliğini değerlendirmektir.
Yöntem: Çalışmaya Gülhane Askeri Tıp Akademisi Psikiyatri Servisinde yatan, kronik nitelik kazanmış TSSB tanısı konulan 50 hasta alındı. Primer ölçümler "Clinician Administered Post Traumatic Stress Disorder Scale" (CAPS), Klinik Genel İzlenim-Şiddet Ölçeği (CGI-S) ve Klinik Genel İzlenim-İyileşme Ölçeği (CGI-I) ile yapıldı. Hastalar tedavi gruplarına (25 hasta paroksetin, 25 hasta amitiriptilin) rasgele seçildi ve 12 haftalık tedavi protokolüne alındılar. Paroksetin grubundan 22, amitriptilin grubundan 20 hasta çalışma protokolünü tamamladı.
Bulgular: Paroksetin ve amitriptilin tedavisi yanıt oranları sırasıyla % 31.8 ve% 55 idi. Gruplar arasında CAPS toplam puanı değişimlerinde anlamlı bir fark var iken, anksiyete ve depresyon puanlarındaki değişim, CGI-şiddet ve CGI-ilerleme için fark bulunmadı.
Sonuç: Çatışma ile ilişkili TSSB olgularının tedavisinde hem paroksetin hem de amitriptilinin etkili olduğu söylenebilir. İki grup arasında istatistiksel bir fark olmamakla birlikte amitriptilin ile tedavi cevabı daha yüksek olma eğilimindedir. CAPS 2 belirti kümeleri açısından bakıldığında amitriptilinin intruziv belirtiler ve aşırı uyarılma belirtilerini daha fazla azalttığı görülmektedir.

Anahtar sözcükler: TSSB, amitriptilin, paroksetin

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ABSTRACT:

Efficacy of paroxetine and amitriptyline in posttraumatic stress disorder: an open-label comparative study

Objective: To evaluate the efficacy of amitriptyline and paroxetine in soldiers with combat-related post traumatic stress disorder (PTSD).
Method: Fifty patients who were admitted to Gülhane Military Medical Academy Psychiatry Inpatient Clinic and who were diagnosed as chronic PTSD were enrolled. The primary outcome measures for the study was 17-item total severity score of the Clinician-Administered PTSD Scale (CAPS), Investigator-rated Clinical Global Impression (CGI-S) and CGI–Improvement Scales (CGI-I). Patients were randomized to 12 weeks of treatment with either paroxetine (25 patients) or amitriptyline (25 patients). Twenty-two patients from paroxetine group and 20 patients from amitriptyline group completed the study protocol.
Results: Treatment response rates for paroxetine and amitriptyline was 31.8% and 55%, respectively. While there was a significant difference for CAPS-2 total score changes between the groups, no statistically significant difference was found for CGI severity, CGI progress, change in depression and anxiety scores.
Conclusions: Both amitriptyline and paroxetine seem to be effective in the treatment of combat related PTSD cases. Despite no statistically significant difference between both groups, treatment response with amitriptyline seems to be higher. When we look at the changes in symptom patterns in terms of CAPS 2 scores, it was found that amitriptyline have decreased intrusive and increased arousal symptoms more than paroxetine.

Key words: PTSD, amitriptyline, paroxetine

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INTRODUCTION

Exposure to extreme traumatic events is the reason of posttraumatic stress disorder (PTSD). People suffering from this disorder are characterized by persistent re-experiencing of the traumatic event and they avoid from stimuli that are associated with trauma. Numbing of general responsiveness and persistent symptoms of increased arousal are other clinical characteristics (1).

PTSD's lifetime prevalence changes from 7% to 12%, significantly higher among military veterans who have been exposed to combat (2-4). Combat related PTSD is associated with more chronicity, comorbidity, and disability; therefore the effective treatment of this kind of PTSD is especially important.

Studies on pharmacotherapy for combat-related PTSD

have shown inconsistent results (5-15). Although some studies have been shown that tricyclic antidepressants (TCA) and monoamine oxidase inhibitor (MAOI) antidepressants are more effective than placebo (5,6); others have reported the contrary (7-9). Despite the small number of published controlled studies on selective serotonin reuptake inhibitors (SSRIs) among PTSD patients, SSRIs are commonly used as first line treatment for PTSD. In fact, there are less consistent results on the efficacy of SSRI treatments for combat-related PTSD (10-14).

In the literature, there is no study that have compared the efficacy of amitriptyline and paroxetine in the treatment of combat-related PTSD. Accordingly, in this study, we aimed to compare the efficacy of amitriptyline and paroxetine in Turkish soldiers with combat-related PTSD.

METHODS

Patients

Fifty patients who were admitted to the Gülhane Military Medical Academy Psychiatry Inpatient Clinic and who were diagnosed as chronic PTSD with Structured Clinical Interview for the DSM-IV Axis I Disorders (SCID-I) were enrolled. SCID-I was administered by two trained psychiatrists. Concurrent affective and anxiety disorders were allowed when PTSD was considered as the principal diagnosis (i.e. the main focus of attention or need for treatment) and that the onset of PTSD preceded that of concurrent disorders. Furthermore, patients were not allowed to have another axis I disorder as a principal diagnosis within 6 months of screening.

Subject Inclusion/Exclusion Criteria

Patients were excluded if they had previously been treated with an SSRI at antidepressant doses for at least 4 weeks; if they have had manifested psychotic symptoms or serious suicidal ideation or met criteria for schizophrenia, schizoaffective, organic or bipolar disorders; or exhibited behavior strongly suggestive of inability to comply with a research protocol. Subjects with a substance abuse diagnosis during last 6 months, unstable medical illness or abnormal laboratory or electrocardiographic examinations were also excluded. Before entering the trial, patients were ensured to be medication-free for 4 weeks if they were previously taking antipsychotics, lithium, anxiolytics, MAOI or SSRIs; or medication-free for 2 weeks if they were previously taking any other antidepressant. Concomitant pharmacotherapy or psychotherapy was not allowed during the study period. Supportive clinical management was provided by a treating physician.

Measurements

Sociodemographic (age, gender, level of education, and marital status) and clinical features of the subjects were examined by using a data query form. PTSD was diagnosed with the Turkish version of the SCID-I form (15-16). The primary outcome measures for the study consisted of the 17-item total severity score of the CAPS (17); the investigator-rated CGI-S and Clinical Global Impression–Improvement Scale (CGI-I) (18). The validity and reliability studies of CAPS Turkish form were conducted by Aker et al (19). The Clinician Administered PTSD Scale is a validated clinical interview designed to assess the frequency and severity of each of the 17 DSM-IV defined PTSD symptoms as well as criterion F (social and occupational impairment). CAPS part 1, is used to assess a patient's current and lifetime DSM-IV diagnosis of PTSD, while CAPS part 2 is used to evaluate symptom severity and change. Primary outcome assessments were performed at baseline and at study treatment weeks 1, 2, 3, 4, 6, 8, 10, and 12. CAPS-2 was not administered at weeks 1 and 3, and the CGI-I was not administered at baseline. Symptoms of depression and anxiety (secondary outcome assessments) were evaluated by the Beck Depression Inventory [20] and the Beck Anxiety Inventory [21], respectively. Secondary outcome assessments were performed at baseline and at study treatment weeks 2, 4, 6, 8, 10, and 12.

Study Design

This study was a unicentral, open-label, comparative randomized trial. The study was conducted between October 2008 and December 2009. The study protocol was approved by the Local Ethics Committee and all patients gave written informed consent. A physical examination was performed. ECG was performed and medical/surgical, psychiatric histories and a record of prior/concomitant medication use were taken. Patients were randomized to

12 weeks of open trial treatment with either paroxetine (25 patients) or amitriptyline (25 patients). Paroxetine treatment was initiated at 10 mg for the 1st week and was then increased to 20 mg for weeks 2 and 3, 30 mg for weeks 4 and 5, 40 mg for weeks 6 and 7, and 60 mg for weeks 8 through 12 if tolerated and clinically indicated. During the treatment period three patients from the paroxetine group were excluded from the study due to side effects. For patients excluded from paroxetine group the most common side effects reported were nausea, sexual aversion, drowsiness and yawning. Amitriptyline treatment was administered at 75 mg/day for the first three weeks (with an initial dose titration of 25 mg/day for the first three days, followed by 50 mg/day on days 4–7, then 75 mg/day for the following two weeks). After the 3rd week of amitriptyline treatment, the daily dose could be increased to 100 mg/day, as necessary. At the end of week 5, the dose could be increased to a maximum of 200 mg/day (or titrated down to 75 mg/day), according to the response. During the treatment, five patients in the amitriptyline group were excluded from the study due to side effects. The most common side effects reported were dry mouth, constipation, nausea, drowsiness and sexual aversion. The treating physician conducted weekly evaluations, with more extensive ratings after 4, 8, and 12 weeks of active drug treatment. Clinical response to treatment was defined as ≥30% decrease in CAPS-2 scores and a CGI-I rating of 1 (very much improved) or 2 (much improved).

Statistical Analysis

Group comparisions for sociodemographic and clinical features were performed by either chi-square, student t test or Mann-Whitney U tests where appropriate. Response rates to treatment for two groups were compared with chi-square test. All statistical tests were 2-sided and performed at the .05 level of significance.

RESULTS

A total of 42 patients, 22 patients from paroxetine group and 20 patients from amitriptyline group completed the study. Clinical and sociodemographic features of the patients are summarized in Table-1. The groups were similar with respect to age, education level, marital status, physical injury, type of trauma and duration after trauma.

Treatment results concerning primary and secondary outcome measures are shown in Table-2. No difference was found between the two groups for pretreatment CAPS total and subscale scores, and for levels of depression and anxiety. While there were significant differences regarding changes in CAPS total scores (p=0.03) between the groups, anxiety scores (p=0.07), CGI severity (p=0.18), CGI progress (p=0.40) and change in depression scores (p=0.98) were similar between the groups.

The effects of treatment on CAPS-2 symptom clusters

Table 1: Demographic and clinical data

Variable	Paroxetine (n = 22)	Amitriptyline (n = 20)	Statistical Analysis	p
Age, mean (SD)	32.5 (4.7)	29.1 (7.4)	1.79[a]	0.08
Education (yrs)	11.0 (2.2)	9.7 (2.4)	1.84[a]	0.07
Marital status (%)			2.04[b]	0.36
Married	12 (54.5)	11 (55.0)		
Single	6 (27.3)	8 (40.0)		
Divorced	4 (18.2)	1(5.0)		
Physical injury,%			0.31[b]	0.58
Yes	6 (27.3)	4 (20.0)		
No	16 (72.7)	16 (80.0)		
Time from trau matic event			0.81[b]	0.67
0-6 month	5 (22.7)	6 (30.0)		
6 month-3 years	2 (9.1)	3 (15.0)		
Over 3 years	15 (68.2)	11(55.0)		
Type of traumatic event			3.02[b]	0.22
Mine	1 (4.6)	3 (15.0)		
Handgrenade	2 (9.2)	0 (0.0)		
Gun battle	19 (86.2)	17 (85.0)		

[a]: t test value, [b]: chi square test

Table 2: Effect of study treatment on primary and secondary efficacy measures*

Efficacy Measures (Adjusted Scores)	Paroxetine Mean (n = 22)	Amitriptyline Mean (n = 20)	Z	p
CAPS-2 total scores				
Baseline	45.9 (10.2)	49.7 (12.7)	0.88	0.38
Change	−10.3 (12.8)	−20.2 (16.7)	2.19	0.03
End point	35.6 (9.6)	29.6 (11.9)	1.41	0.16
CGI-Severity				
Baseline	4.3 (0.63)	4.6 (0.82)	1.25	0.21
Change	−0.8 (0.13)	−1.4 (0.13)	1.36	0.18
End point	3.5 (0.80)	3.2 (0.91)	0.76	0.45
CGI-Improvement	3.2 (0.92)	3.0 (0.68)	0.84	0.40
Beck D total scores				
Baseline	32.7 (9.1)	31.8 (10.0)	0.24	0.81
Change	−10.9 (6.6)	−10.6 (6.9)	0.03	0.98
End point	21.8 (7.5)	21.3 (9.4)	0.44	0.66
Beck A total scores				
Baseline	23.0 (6.5)	25.6 (7.6)	1.49	0.14
Change	−8.4 (5.2)	−12.2 (7.0)	1.80	0.07
End point	14.6 (4.7)	13.4 (4.9)	0.57	0.57

*CAPS-2: Clinician Administered Posttraumatic Stress Disorder (PTSD) Scale Part 2; CGI, Clinical Global Impression; Beck A, Beck Anxiety Scale and Beck D, Beck Depression Scale
Z: Mann Whitney U test

Table 3: Effect of treatments on CAPS-2 symptom clusters*

PTSD Symptom Clusters (Adjusted Scores)	Paroxetine Mean (n = 22)	Amitriptyline Mean (n = 20)	Z	p
Reexperiencing/intrusion				
Baseline	11.9 (4.3)	14.1 (5.8)	1.32	0.19
Change	−1.8 (5.2)	−5.7 (6.8)	2.14	0.03
End point	10.1 (2.5)	8.4 (3.6)	1.47	0.14
Avoidance/numbing				
Baseline	18.1 (4.9)	18.3 (5.0)	0.40	0.69
Change	−4.2 (4.2)	−6.8 (6.9)	1.16	0.25
End point	13.9 (4.1)	11.5 (5.2)	1.68	0.09
Arousal				
Baseline	16. 0 (4.5)	17.4 (3.6)	0.87	0.38
Change	−4.4 (4.5)	−7.7 (4.8)	2.22	0.03
End point	11.6 (4.4)	9.7 (3.8)	1.46	0.15

*CAPS-2: Clinician Administered Posttraumatic Stress Disorder (PTSD) Scale Part 2; Baseline and end point scores are mean (SD)
Z: Mann Whitney U test

are shown in Table-3. Intrusive symptoms (p=0.03) and increased arousal symptoms (p=0.03) decreased more in amitriptyline group than paroxetine group, however there was no significant difference for decrease of avoidance symptoms between the groups (p=0.25).

The groups were similar with regard to treatment response rates (p = 0.21); while 7 out of 22 patients (31.8%) responded to paroxetine treatment, 11 out of 20 patients (55%) responded to amitriptyline medication. There was no statistically significant difference regarding to side effects between the groups.

DISCUSSION

The results of this study showed that the efficacy of paroxetine and amitriptyline were similar in the treatment of combat-related PTSD. CAPS, CGI, BDI and BAI scores showed steady improvements with time over the 12 weeks of the study for both agents.

Many studies showing the efficacy of SSRIs -especially sertraline, paroxetine and fluoxetine and other antidepressants- have been done in PTSD (22,23) Early reports for the efficacy of amitriptyline, imipramine and

the irreversible MAOIs in combat related PTSD exist in the literature (5-9). After the safety and efficiency of SSRIs have been shown, they were also been used for combat and non-combat related PTSD. Positive results were reported (9,11-13) and it was suggested that the serotonergic activity rather than the noradrenergic activity was playing an important role (24). Thereafter, SSRIs have been used as first line drugs, and especially sertraline and paroxetine have been approved in the United States and Europe (25). There are a few studies on sertraline use in combat-releated PTSD cases (26), but there is no study in the literature showing paroxetine efficiency in combat-related PTSD. Moreover, despite some studies comparing the efficacy of amitriptyline and paroxetine for other psychiatric disorders (25), we could not find a study for PTSD. In this regard, our study is important for being the first to compare amitriptyline (an agent efficiently used for combat-releated PTSD) with paroxetine (an agent approved for non-combat PTSD).

Several studies on the efficacy of the various drug treatments for combat-related PTSD have been made (5-14,26-34). In the studies that have investigated the efficiency of SSRIs in combat-related PTSD, it was found that these drugs had a moderate effect (25). In a placebo controlled study with 23 combat-related PTSD patients, Zohar et al (30) found the treatment response rate of sertraline as 41.1% (concerning CGI and CAPS score changes). Their results are similar to those of ours. It is noteworthy that efficiency of other SSRIs are lower at combat related PTSD (9-11,13,14,28,31-33). Suggested explanations include high symptom severity, male gender, the nature and severity of the inciting trauma, and possible combat specific signs and symptoms that may serve as negative predictors of response as well as other psychosocial variables such as receiving financial compensation for being ill and the high rates of chronicity and comorbidity observed in combat-related PTSD.

There are some studies that have shown efficiency of paroxetine in non-combat PTSD sample (34,35). In the 52 weeks follow-up study of Kim et al (34), they have found the response rate of paroxetine (20-40 mg) as 48.5%. In our study, paroxetine was effective at 31.8% of the patients. This difference could be due to the different trauma types of the two studies. Yet, in combat-related PTSD cases, SSRIs have been less effective than in other PTSD cases (4).

For combat-related PTSD, there are some studies showing the efficacy of amitriptyline and other TCAs (5-7,12,34). In the two combat related PTSD studies by Davidson et al (5,36), response rates to amitriptyline were found to be 34% and 48.3%, respectively. Treatment response rate is relatively higher in our study. This difference could be attributed to longer treatment duration, higher amitriptyline doses (200 mg/d) and shorter disease duration in our study. When we consider lower responce rates for combat related PTSD for SSRIs, we think that our response rate for amitriptyline is an important finding and puts forward an alternative for treatment of these cases.

In our study, it was shown that amitriptyline was effective in 11 out of 20 patients and that paroxetine was effective in 7 out of 22 patients. When we look at the changes in symptom patterns in terms of CAPS scores, it was found that amitriptyline have decreased intrusive and increased arousal symptoms more than paroxetine. Therefore, it seems to be more effective on intrusive and increased arousal symptoms. These effects of amitriptyline can be associated with its effects on the noradrenergic and other neurotransmitter systems, in addition to its serotonergic activity (37). It was indicated that SSRIs had a moderate effect on intrusive and increased arousal in combat related PTSD cases. In the study of Zohar and colleagues, sertraline was moderately effective on three symptom clusters and this effect was not different from placebo (31). In our study, it was also found that paroxetine had no effect on intrusive symptoms, with a lower effect than amitriptyline on increased arousal.

In the literature, we found no study on the effects of amitriptyline in non-combat PTSD sample. A few studies have been done in combat-related PTSD cases (5,36). It is supposed that studies are restricted due to high side effect risk of amitriptyline. In our study, although the number of excluded patients due to side effects in the amitriptyline group (5/25) were higher than the paroxetine group (3/25), the difference between the groups was not statistically significant.

The most important limitation of our study is being open ended and not including a placebo control group. Another important restriction is not excluding other anxiety and depressive disorders. Subsequent studies should be double-blinded and placebo controlled. In particular, because of the high treatment resistance and high chronicity risk of combat-related PTSD, studies on

psychotrop drugs that show their effects on other pathways and studies that are showing neurophysiological changes according to treatment results are necessary. Finally, we suggest that amitriptyline treatment should not be ruled out in the treatment of PTSD cases. Moreover it could be an important alternative.

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