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TIANEPTINE IN THE COMBINED TREATMENT OF COMBAT RELATED POSTTRAUMATIC STRESS DISORDER

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SUMMARY

Background: *The aim of this study was to evaluate the efficacy of tianeptine, an antidepressant that acts by increasing serotonin reuptake, in the treatment of posttraumatic stress disorder and to compare the effects of tianeptine and fluoxetine, an antidepressant from the selective serotonin reuptake inhibitors class.*

Subjects and methods: *43 war veterans suffering from posttraumatic stress disorder were included in the study. During the 5.5 months of treatment 21 patients were receiving tianeptine and 22 were receiving fluoxetine. In addition, all patients took part in intensive trauma specific group psychotherapy. The effects of the two antidepressants on symptoms of PTSD, depression and anxiety after 5.5 months of treatment were assessed using the Harvard Trauma Questionnaire, Beck Depression Inventory, STAI and the List of Drug Use and Side Effects.*

Results: *There was no significant difference between the two treatment groups regarding their effect on symptoms and severity of depression. The level of anxiety was the same in the first measurement but the difference became significant in other three measurements in favor of tianeptine. The anxiolytics and other co-prescribed drugs remain the same in both groups, the use of analgesics significantly increase in fluoxetine group during the course of treatment.*

Conclusion: *The study demonstrated that tianeptine is as effective as fluoxetine in the treatment of PTSD, with even stronger effect on anxiety and equal tolerance.*

Key words: *tianeptine - fluoxetine - PTSD - treatment - war veterans*

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INTRODUCTION

Posttraumatic stress disorder (PTSD) is historically strongly associated with war-related situations (Martenyi & Soldatenkova 2006). Many studies have shown that a large percentage of war veterans feel the symptoms of PTSD even decades after the combat experience (Solomon & Mikulincer 2006). During the war in Croatia (1991-1995), an estimated million people were exposed to war trauma and about 10 000 of the Homeland War veterans (15% prevalence) have developed PTSD, with an alarmingly high suicide rate (Kozaric-Kovacic et al. 2002).

Apart from the group of symptoms that characterize PTSD (reexperiencing, avoidance and exaggerated startle response), anxiety and depression is what is commonly observed in patients with this disorder (Hoge et al. 2004, Ikin et al. 2010) as well as somatization and psychosomatic problems (Schnurr & Green 2004, Benyamini & Solomon 2005).

Due to the long-lasting and resistant symptoms, management of chronic combat PTSD is complex and may involve the use of various treatment modalities, involving both pharmacotherapy and various types of psychotherapy, as reported in the mayority of studies (Christopher et al. 2009).

Psychotherapy in combat trauma-induced disorders tries to act on several different levels: on working through and integrating the traumatic event, on processing the "retraumatization" that appears on return to the peacetime lifestyle and on overcoming the communication difficulties in the family and social environment (Moro & Franciskovic 1998). In an attempt to include all these levels, therapy programs are often developed in order to approach different segments of PTSD patient's dysfunction in various therapeutic settings (Davidson & Van der Kolk 1995, Rosenheck et al. 1997, Foa 2000).

Increasing recognition that PTSD is characterised by specific psychobiological dysfunctions (Mellman 2002, Bonne et al. 2004, Charney 2004), provide a rationale for the use of medication treatments. There is growing evidence for rather specific dysregulations of neurotransmitter systems (including the serotonin, noradrenaline, and dopamine systems) and neuroendocrine systems (including the hypothalamus-pituitary-adrenal axis), as well as for structural and functional neuranatomical abnormalities in PTSD (Hull 2002, Bremner & Vermetten 2004, Friedman & Davison 2007).

Pharmacotherapy proved to be partially effective in reduction of symptoms of increased irritability and

reexperiencing, but most often it had no effect on symptoms of avoidance (Maxmen & Ward 2002). Along with new developments in neurophysiology of stress response antidepresants, anxiolytics, anti-adrenergic agents, anticonvulsants, benzodiazepines, atipycal antipsychotics and novel agents came to be used for drug treatment, but the results were only partially satisfactory (Friedman & Davidson 2007, Ravindran & Stein 2009, Stein et al. 2009). Also, most studies in this area suffer from serious limitations due to small sample sizes, relative shortness, and lack of including patients in other forms of therapy.

Antidepressants are currently the preferred medication for PTSD, with the most substantial evidence available to support the use of the selective serotonin reuptake inhibitors (SSRI) (Foa 2000, Ursano et al. 2004). Among the SSRIs fluoxetine has been found effective in the pharmacological treatment of PTSD in at least four pozitive double-blind, placebo-controlled studies, (Van Der Kolk et al. 1994, Connor et al. 1999, Martenyi et al. 2002a, Martenyi et al. 2002b). However, in general, most studies showed that medical therapy of trauma-induced states was less effective when the patients were war veterans and the trauma was combat-related.

Tianeptine is an antidepressant whose mechanism of action is characterized by an increased serotonin reuptake. Tianeptine increases the spontaneous activity of hippocampal cells and accelerate their recovery after functional inhibition (Miller & McEwen 2006). It improves adaptation to stress, reduces excessive neuroendocrine stress response and have a notable anxiolityc effect (Delbende et al. 1991, Watanabe et al. 1992, Wagstaff et al. 2001). Tianeptine has a favorable effect on memory and learning and it is especially effective in alcoholics. The side effects reported are mild and relatively rare (Brink et al. 2006). The characteristics of tianeptine suggest that it can be effective in treating PTSD patients and some studies have already proven so (Crocq & Goujon 1994, Rumyantseva & Stepanov 2008).

However, studies comparing the efficacy of different antidepressants on the symptom clusters of PTSD are rare and most of them compare an active drug with placebo. Also, no studies have examined the effectiveness of tianeptine in the treatment of war veterans in Croatia, and according to the published literature, very few data exist on the efficiency of psychopharmacotherapy of combat related PTSD on Croatian war veterans in general.

Therefore, the aim of the study was to asses the efficacy of tianeptine and its mode of action in patients with PTSD, when used during trauma-specific psychotherapy, in comparison with fluoxetine, which is among the first-choice drugs in trauma-induced disorders.

SUBJECTS AND METHODS

Patients

The research was conducted among the patients in an intensive therapy program for psycho trauma-induced disorders that was organized during 6 months from January to May 2008 in the Regional Psycho-trauma Centre, Psychiatric Clinic, Clinical Hospital Center Rijeka, Croatia. The program is a combination of psychotherapy and pharmacotherapy. The psychotherapy program consist of work in a small group, an educational group and a skill training group and was conducted twice a week. Small group were trauma focused, dynamically oriented, intended for working through the traumatic events, while the educational and skill training groups focus on current difficulties in social communication. Group psychotherapy was conducted by three psychiatrists and one psychologist. All the therapist were trained in group psychotherapy, and had experience in working with veterans. Candidates were included in the program following a diagnostic screening, which consisted of a psychiatric interview and psychological assessment. The authors were not involved in the treatment of patients.

All 43 subjects were male, most of them had high school education (76%) and were married (71%), aged 37-60 (median 48 years), veterans who spent 6 months to 4 years in the battlefield (median 1,5 years), and were included in an intensive psychotherapy program for the first time. Prior to the inclusion in the study most of them were occasionally seeing a psychiatrist or a family phisision and they were receiving anxiolytics or antidepressants.

Inclusion criterion was combat related PTSD assessed with Harvard Trauma Questionnaire, Croatian version (Allden et al. 1998). Exclusion criterion for the treatment were addiction to alcohol or other psychoactive agents at the time of the interview and existence of psychotic or an organic mental disorder.

Traumatic experience of all patients consisted of various combat experience that took place from 1991 to 1995 during the Homelend War in Croatia. Four patients were victims of torture during imprisonment and three were refugees. None of the patients suffered from a severe cardiovascular, endocrine or neurological condition. Patients were asked to report any concomitant medication or disturbances of any kind that would appear during the research.

Drug Treatment

43 patients were randomized into two groups. The first group (n=22) received fluoxetine 40 mg a day and the second group (n=21) tianeptine 37.5 mg a day, in three separate doses, during the entire study period. The groups did not differ in mean age, traumatic experience, level of PTSD, education and marital status. None of the

patients was taking tianeptine or fluoxetine prior to inclusion in the study.

The dosage was maintained the same during the entire 5.5 months period, since the doses used were in literature described as effective. Results were checked by measurements before the start of the treatment and at the end, after 5,5 months. The severity of anxiety and depression was evaluated a month later (M1) and three months later (M3), as this would indicate the phase of the therapy program. Side effects, as reported by these patients, were monitored once a week, as well as the use of anxiolytics, hypnotics, analgesics and other drugs. All the drugs were prescribed by primary care physicians. All the patients were informed about the study prior to inclusion and gave their consent.

Evaluation

The following instruments were used to evaluate the patients immediately after inclusion and after 5.5 months of treatment:

- To measure the intensity of PTSD symptoms we used the Harvard Trauma Questionnaire (HTQ), Croatian version (Allden et al. 1998). The HTQ combines the measurement of trauma events (part I) and symptoms of PTSD (part II) as described in the DSM-IV (American Psychiatric Association). PTSD was defined according to a scoring algorithm previously described by the Harvard Refugee Trauma Group on the basis of DSM IV diagnostic criteria (Mollica et al. 1993). This definition of PTSD requires a score of 3 or 4 on at least one of four re-experiencing symptoms (criterion B), at least three of seven avoidance and numbing symptoms (criterion C), and at least two of five arousal symptoms (criterion D).
- To measure the level of depressiveness we used the Beck Depression Inventory (BDI) (Beck et al. 1996) a widely used self rated questionnaire for depression.
- To measure the level of anxiety we used the state-trait anxiety inventory (STAI), (Spielberger et al. 1970) a self-report questionnaire that evaluates feelings of apprehension, tension, nervousness, and worry.
- Side effects, as well as any concomitant medication, were monitored once a week, according to Medication List structured for the purpose of this study and Side Effects List.

Statistical analysis

For all variables, basic descriptive statistical parameters were first calculated (arithmetic mean and standard deviation). Two way-analyses of variance were also carried out, in which the drug treatment (tianeptine or fluoxetine) were "between group factor", and measurement period was "within-group factor". Statistical analysis was performed with SPSS software package.

RESULTS

43 patients started the treatment and 35 (82.5%) completed it. Four patients from each group dropped out due to various reasons. A patient from the tianeptine group insisted on stopping the medication after less than one week and continued only with psychotherapy. Two patients started consuming alcohol and ended the treatment. One patient dropped out due an allergic reaction to tianeptine.

In the fluoxetine group one patient withdrew from the treatment due to an allergic reaction, one due to significant side effects - severe and frequent nausea, one patient dropped out of the program as a whole, and one patient developed significant anxiety, which subsided after stopping fluoxetine to a level which allowed him to continue the therapeutic program.

18 patients on flouxetine and 17 patients on tianeptine completed the program. The two groups did not significantly differ in the dropout rate, although a somewhat stronger reaction to the drug, as a reason for dropout, was seen in patients taking fluoxetine.

Outcomes

Symptoms of PTSD

There was no statistically significant effect of group (tianeptine and fluoxetine) on the average HTQ scores of two measurements: HTQ scores for B symptoms ($F=0.02$; $p>0.05$), HTQ scores for C symptoms ($F=0.16$; $p>0.05$) and HTQ scores for D symptoms of PTSD ($F=0.88$; $p>0.05$).

There was no statistically significant effect of time (first and second measurement) on the average HTQ scores for both groups (tianeptine and fluoxetine): B symptoms ($F=0.76$; $p>0.05$), C symptoms ($F=2.26$; $p>0.05$) or D symptoms of PTSD ($F=0.04$; $p>0.05$).

There was no statistically significant interaction between the group (tianeptine and fluoxetine) and measurement periods - 2 measurements of HTQ-B symptoms ($F=2.97$; $p>0.05$), C symptoms ($F=0.47$; $p>0.05$) or D symptoms ($F=2.10$; $p>0.05$) (Table 1).

Level of depression

There was no statistically significant difference between the groups of participants in terms of average depressiveness measured by the BDI in each of the four measurements ($F=1.71$; $p>0.05$), nor was there statistically significant difference in depression level in each of the four measurements ($F=1.07$; $p>0.05$).

There was no statistically significant difference between the group (tianeptine and fluoxetine) and measurement periods (4 measurements of depression) ($F=1.16$; $p>0.05$) (Table 1.).

Level of anxiety

There was a statistically significant difference between the two groups of participants regarding their anxiety level measured with the STAI questionnaire ($F=4.14$; $p<0.05$) (Table 1.).

Table 1. Arithmetic means, standard deviations, main and interaction effects of two-way ANOVA for Beck Depression Inventory (BDI), State-Trait Anxiety Inventory (STAI), Harvard Trauma Questionnaire (HTQ) between groups of participants (fluoxetine and tieneptine) and results of the LSD post-hoc test

Measurement	Tianeptine		Fluoxetine		F	LSD test
	M	SD	M	SD		p
BDI 1st measurement	33.76	10.19	34.27	10.27	$F_{between\ groups}=1.71$ $F_{over\ time}=1.07$ $F_{interaction}=1.16$	N.S.
BDI 2nd measurement	30.90	14.17	36.18	11.98		
BDI 3rd measurement	32.57	13.95	39.36	9.45		
BDI 4th measurement	31.00	15.45	35.04	14.02		
STAI 1st measurement	64.57	8.46	66.57	6.89	$F_{between\ groups}=4.14$* $F_{over\ time}=0.80$ $F_{interaction}=1.26$	0.537
STAI 2nd measurement	59.04	21.67	69.95	8.39		0.003*
STAI 3rd measurement	59.19	21.51	69.59	8.39		0.041*
STAI 4th measurement	57.76	25.14	66.00	17.94		0.022*
1st Harvard B measurement	3.05	1.46	2.50	1.71	$F_{between\ groups}=0.24$ $F_{over\ time}=0.76$ $F_{interaction}=2.97$	N.S.
2nd Harvard B measurement	2.81	1.81	3.23	1.60		
1st Harvard C measurement	13.71	6.45	13.50	6.79	$F_{between\ groups}=0.16$ $F_{over\ time}=2.26$ $F_{interaction}=0.48$	N.S.
2nd Harvard C measurement	14.81	9.26	16.45	6.44		
1st Harvard D measurement	11.14	3.42	10.82	3.72	$F_{between\ groups}=0.88$ $F_{over\ time}=0.04$ $F_{interaction}=2.10$	N.S.
2nd Harvard D measurement	9.71	5.71	11.91	4.15		

*p<0.05; N.S. – not significant

The post-hoc test results (Table 1) showed statistically significant differences in anxiety level in the second, third and fourth measuring. Participants who were taking tianeptine showed significantly lower level of anxiety, but there was no statistically significant interaction between the group (tianeptine and fluoxetine) and measurement periods (4 measurements) (F=1.26; p>0.05) nor was there any statistically significant change in the level of anxiety within the groups in all of the four measurements (F=0.80; p>0.05).

Additional medication

Use of all medication was monitored as reported by the patients. The drugs were prescribed by GPs on patient's request or the patients bought them themselves. All reported drugs could be classified in four groups: anxiolytics, hypnotics, other psychoactive drugs (other antidepressants, neuroleptics and the like) and analgesics. In the majority of cases the anxiolytics used were diazepam and oxazepam.

73.8% of patients were taking anxiolytics at inclusion (68.2% in the fluoxetine group and 80.0% in the tianeptine group). After the first month these percentages increased to 86.4% and 89.5%, after after three and half months of treatment they increased to 89.5% and 94.7% for fluoxetine and tianeptine respectively. After that, the percentages did not change until the end of the research. The differences between these values were not significant.

At inclusion, analgesics were being received by 50% of patients in the fluoxetine group and by 45.5% of patients in the tianeptine group. The difference in percentages was not significant (p=0.062). One month later, this percentage increased to 77.3% in the fluoxetine group, while the percentage in the tianeptine group remained unchanged. Three and a half months later, these values increased to 84.2% and 57.9%, and at the end of the research they were at 88.9% in the fluoxetine group and 55.6% in the tianeptine group, and the difference was significant (p=0.025).

Side effects

The most frequent complaints reported by the patients were dry mouth and taste disturbances in the fluoxetine group (9 patients) and a mild bitter taste in the tianeptine group (10 patients). Nausea was reported by 14 patients on fluoxetine and 10 patients on tianeptine. Only in one case the severity of this disturbance was such that it led to withdrawal from treatment. These adverse events were reported during the first month of treatment. 22.7% and 28.6% patients in each group experienced muscle cramps. Fatigue, headache, chest tightness and respiratory difficulties appeared with a lower incidence, below 10%. Two patients, one from each group, developed an allergic reaction and stopped taking the drug. The difference between the two treatments regarding the incidence of adverse events was not significant.

DISCUSSION

There was no statistically significant difference for re-experiencing symptoms (B), avoidance and numbing symptoms (C) and arousal symptoms (D) of PTSD nor

was there any statistically significant difference in depression level in all of the measurements conducted during the therapy. However, anxiety level in the group taking tianeptine was significantly lower compared to the group taking fluoxetine.

The use of additional medication did not change during the treatment in neither of the groups. The difference was obtained in the use of analgesics - the group receiving tianeptine was taking fewer analgesics than the group receiving fluoxetine. Side-effects appeared equally in both groups, but they were low in intensity and did not lead to termination of the treatment.

Tianeptine and fluoxetine were equally efficient regardless of the fact their mechanism of action was different, which was confirmed by results of other research (Onder, Tural & Aker 2006). However, none of them led to significant reduction in posttraumatic symptom intensity at the end of the treatment.

Unlike most of the studies that appear in literature, this study followed efficacy of pharmacotherapy during 5 and a half months in parallel with an intensive trauma-specific psychotherapy program. The obtained results should be viewed in the given context. Most of the therapy evaluations so far have pointed to similar outcome, especially when it comes to veterans (Cahill et al. 2008). Surprisingly enough, the patients are satisfied with the treatment, in spite of the fact that their symptoms have not dropped and the improvements are perceived in better relationships with their environment (Moro et al. 1995, Lečić-Toševski & Draganic-Gajic 2005). The structure of the program has several stages.

The aim of the first stage of such psychotherapeutic programs is to bring down the defenses that repress traumatic memories, then to start working through the traumatic experience in the middle stage and finally to obtain a separation reaction. The actual task of the therapy is to initiate the mourning process and the working through of traumatic events, which continues even after the end of treatment (Moro & Frančišković 1999). Integration of the traumatic event is a long-term process, which can sometimes last a lifetime (Wilson & Beverly 1993). In case of multiple traumatization, as a combat-related trauma, it is clear that it takes more than a few months to open and work through the traumatic stories.

One of the options is to establish a pattern for working through the patient's experience, which the patient then adopts for further work. A lack of a more significant effect on the symptom reduction can be related to the negative social context in which the therapy program takes place (Ljubotina et al. 2007). In addition, financial difficulties put a large number of veterans in a situation where they literally live on disability benefits. In such conditions, suggestive questionnaires, as PTSD questionnaires usually are, HTQ not excluded, become subjected to strong bias (Frueh et al. 1996).

It should be kept in mind that in this type of work, depending on its stage, patients are brought to a state of an increased anxiety and initiation of the mourning process leads to a rise of depression. However, such effect did not appear, and medications might be one of the reasons. Tianeptine produced a stronger anxiolytic effect during the measuring. These results are comparable to researches which show that SSRI antidepressants have an anxiolytic effect, which was also confirmed for tianeptine (Zohar et al. 2000). It is important to realize that antidepressants effectiveness in PTSD is not simply mediated trough improvement in anxiety and depression, and that PTSD symptoms respond independently from the anxiolytic or antidepressant effect (Hageman et al. 2001).

The records on additional medications indirectly point to the severity of anxiety and depression. Use of anxiolytics, hypnotics, other psychoactive drugs and analgesics was monitored. Anxiolytic effect can also be monitored in an increased use of analgesics, especially because they are most often taken for the pain syndrome, lumbalgia and tension headache, which can be understood as somatic equivalents of anxiety (Gelenberg 2000). A mild usage of analgesics can be observed, with a tendency towards greater analgesic consumption in the fluoxetine group. This indicates that tianeptine is more efficient in arresting somatic anxiety than fluoxetine, which confirms the literature data about tianeptine as an especially effective antidepressant in treating psychosomatic patients (Svenningsson et al. 2007).

Side-effects reported by patients in our research confirmed the relatively mild profile of side-effects both in fluoxetine and tianeptine. These side-effects are mostly known, which is in accordance with the literature data (Stahl 2008).

This research has its limitations. Above all, the research included a small sample which does not allow for making generalizations. Furthermore, the examination was conducted only during the combined therapy program in which patients go through a psychologically stressful working through of traumatic events, which could increase the symptoms. Drug dosages were not changed during the program, which can influence the drug effectiveness in some patients. Finally, the sample included veterans, and most of them lived in frustrating circumstances which certainly might have produced an effect on the research outcome. However, in spite of the limitations, our results demonstrate that tianeptine has the same effect as fluoxetine when it comes to treating PTSD-affected veterans, with a significant effectiveness in treating anxiety and its somatic equivalents.

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