Therapeutic effects of two antidepressant agents in the treatment of posttraumatic stress disorder (PTSD)

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Abstract

Posttraumatic stress disorder (PTSD) is a psychiatric disorder characterised by an acute emotional response to a traumatic event or situation involving severe environmental stress (natural disasters, wars, epidemics, rape, assaults, physical torture, catastrophic illness or accident), which may be identified in cognitive, affective or sensory motor activities. The objective was to perform a pilot clinical trial designed to compare the effects of older (tricyclic) and newer "second-generation" (selective inhibitors of serotonin uptake) antidepressants in the treatment of PTSD. A total of 20 hospitalised chronic military combat Bosnian veterans with PTSD symptoms were randomly assigned into two groups of 10 patients each. One group was treated with amitriptyline hydrochloride (AMYZOL®) 75 mg/day as a representative of older antidepressants and the other with fluoxetine hydrochloride 60 mg/day (OXETIN®) as a representative of newer antidepressants. Those drugs were administered by mouth two or three times-a-day in equally divided doses for at least 8 weeks. Favourable response was achieved in 70% of patients treated with amitriptyline hydrochloride and 60% of patients treated with fluoxetine hydrochloride. Amitriptyline hydrochloride was more effective in the treatment of acute PTSD symptoms (emotional numbing, startle reaction, nightmares, flashbacks, intrusive thoughts, vulnerability, poor impulse control or irritability and explosiveness). Fluoxetine hydrochloride showed a greater efficacy in the treatment of chronic PTSD symptoms (avoidance and numbing symptoms, hyperarousal, nightmares and a feeling of guilt).

Key words: Posttraumatic stress disorder, amitriptyline, fluoxetine, PTSD total scores

Introduction

Posttraumatic stress disorder (PTSD) is a psychiatric disorder characterised by an acute emotional response to a traumatic event or situation involving severe environmental stress (natural disasters, wars, epidemics, rape, assaults, physical torture, catastrophic illness or accident), which may be identified in cognitive, affective or sensory motor activities (DSM-III, 1980). It has been reported that prevalence of PTSD among Vietnam veterans was approximately 67% (YEHYDA, 1999), in people experiencing natural disasters or catastrophes 30% (YEHYDA, 1999), and in women experiencing sexual abuse or sexual assault (rape) between 57% and 80% (REGEHR, 1999).

According to DSM-III criteria the precipitating event in PTSD should be "outside of range of usual human experience." However, there is evidence that a PTSD-like syndrome can occur following more usual life traumas (e.g. bereavement) (HOROWITZ et al., 1980). Using an experimental approach, BLANCHARD et al. (1982) have reported that heart rate response to audiotape of combat sounds successfully differentiated normal from PTSD patients in 95.5% of cases. Systolic blood pressure and forehead electromyographic response also differed between groups.

In DSM-IV (1994) are described three subtypes of PTSD:

- *Acute (duration of symptoms less than 3 months)*
- *Delayed (onset at least 6 months after trauma) and*
- *Chronic (duration of symptoms 3 or more than 3 months).*

Data sources (DAVIDSON et al., 1985; GREEN et al., 1985; SIERLES et al., 1983) indicate that there is a high prevalence (75-84%) of concurrent psychiatric diagnoses in PTSD patients. The most common disorders found were alcohol or drug abuse (60%), depression (20%), generalised anxiety disorders (14%) and antisocial personality (11%).

Objective

Since pharmacotherapy of PTSD may include the administration of antidepressant agents, the objective of this study was to perform a pilot clinical trial designed to compare the effects of the representatives of older and newer antidepressants in the treatment of PTSD.

Methods (patient and trial characteristics)

Type of trial
A pilot randomised single blind trial.

Patient selection
A total of 20 hospitalised chronic military combat Bosnian male veterans between 25-50 years of age.

PTSD assessment
- DSM-IV (1994) and ICD-X (1994) diagnostic criteria
- Bosnia-Herzegovina version of Harvard Trauma Questionnaire (HTQ) (1998)
- Standard Psychiatric Interview (SPI)

Inclusion criteria
- Only DSM-IV diagnostic criteria proven PTSD
- Only ICD-X diagnostic criteria proven PTSD
- Only HTQ diagnostic criteria proven PTSD
- Only SPI diagnostic criteria proven PTSD

Exclusion criteria
- History of alcohol and/or drug abuse
- History of depression
- History of generalised anxiety
- History of personality disorder (antisocial personality)

Drug administration
Patients with proven PTSD were randomly assigned into two groups. Each group of 10 patients was treated with one of two investigated antidepressants, which were administered by mouth two or three times-a-day in equally divided doses for at least 8 weeks:
- One group was treated with amitriptyline hydrochloride (AMYZOL®) 75 mg/day t.i.d.
- The other group was treated with fluoxetine hydrochloride (OXETIN®) 60 mg/day b.i.d.

Results

Favourable response was achieved in 70% of patients treated with amitriptyline hydrochloride and 60% of patients treated with fluoxetine hydrochloride.

Amitriptyline hydrochloride produced a marked decrease of emotional numbing and other acute PTSD symptoms including startle reaction, nightmares, flashbacks, intrusive thoughts, vulnerability, poor impulse control or irritability and explosiveness.

Fluoxetine hydrochloride showed a greater efficacy in the treatment of chronic PTSD symptoms (avoidance and numbing symptoms, hyperarousal, nightmares and a feeling of guilt).

PTSD total scores before and after administration of amitriptyline hydrochloride and fluoxetine hydrochloride are shown in Figs. 1, 2, 3 and 4.

Discussion

Treatment of PTSD consists of behaviour therapy, pharmacotherapy, and psychotherapy. The pharmacotherapy of PTSD is not well established. Broad treatment guidelines are not curative, but instead are directed at ameliorating PTSD symptomatology. The positive symptoms, including re-experiencing the event and hyperarousal, often respond to pharmacotherapy. Negative symptoms,

Figure 1. PTSD total scores by age of patients before administration of amitriptyline hydrochloride (AMYZOL®) 75 mg/day p.o.

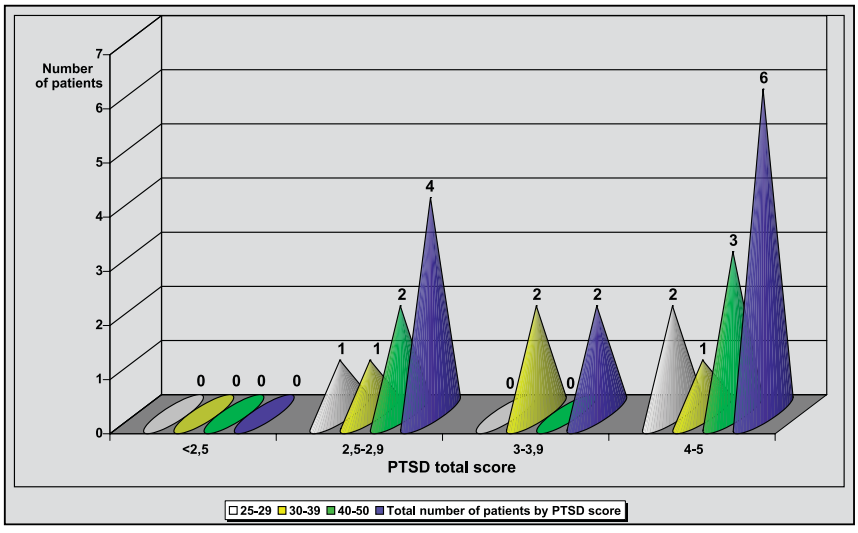
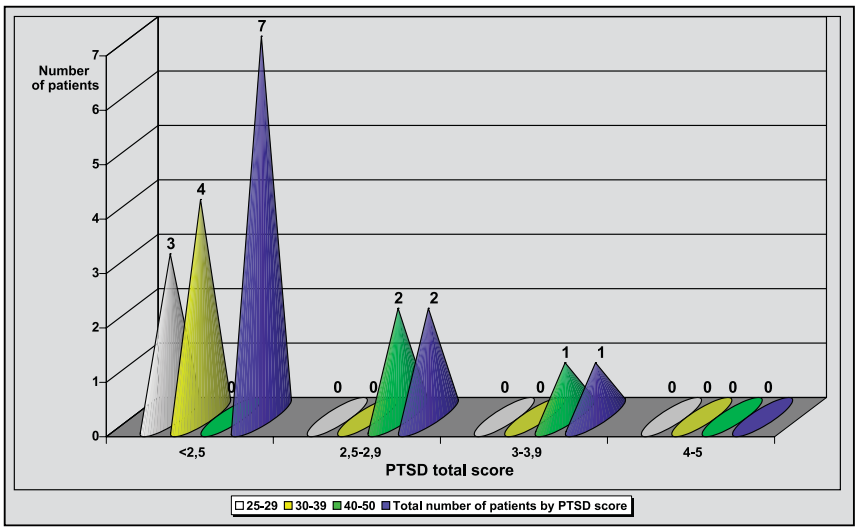


Figure 2. PTSD total scores by age of patients after administration of amitriptyline hydrochloride (AMYZOL®) 75 mg/day p.o.



such as avoidance and withdrawal, are usually resistant to medication. Due to the overlapping symptoms between PTSD and other psychological disorders, pharmacological treatment usually involves antidepressants (BLEICH, 1986).

Since pharmacotherapy of PTSD may include the administration of antidepressant agents, the objective of this study was to perform a pilot clinical trial designed to compare the effects of the representatives of older and newer antidepressants in the treatment of PTSD.

Amitriptyline hydrochloride (AMYZOL®) and fluoxetine hydrochloride (OXETIN®) were representatives of older (tricyclic) and newer "second-generation" (selective inhibitors of serotonin uptake) antidepressants, respectively.

The mechanism of action of amitriptyline in man is thought to be inhibition of the membrane pump mechanism responsible for uptake of noradrenaline and serotonin in adrenergic and serotonergic neurons. This drug has very high ability to block serotonin uptake and moderate activity with respect to noradrenaline uptake. The diminution of monoamine oxidase (MAO) activity partially elucidates the antidepressant effect of amitriptyline (REYES and LISANSKY, 1984). Fluoxetine has been demonstrated to be a specific inhibitor of serotonin reuptake in vitro and in vivo in man and animals (LEMBERGER et al., 1978; LEMBERGER et al., 1978a; STARK et al., 1985).

The results of this pilot clinical trial are in agreement with other data sources. According to HTQ (1998), individuals with DSM-IV PTSD scores and/or total scores of > 2.5 are considered symptomatic for PTSD. This is the

Figure 3. PTSD total scores by age of patients before administration of fluoxetine hydrochloride (OXETIN®) 60 mg/day p.o.

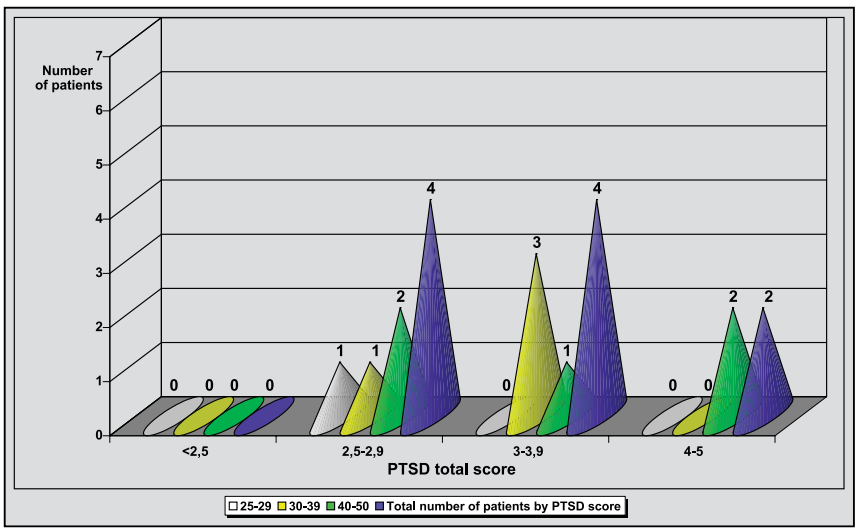
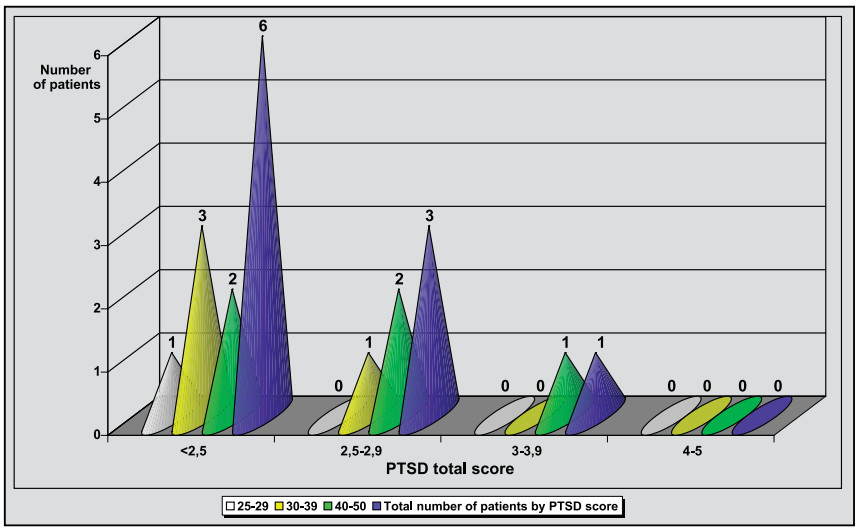


Figure 4. PTSD total scores by age of patients after administration of fluoxetine hydrochloride (OXETIN®) 60 mg/day p.o.



reason why PTSD total scores before and after administration of two antidepressant agents were scored. It has been found that before administration of both antidepressants all patients had PTSD total scores between 2.5 -5. At the end of treatment 70% of patients treated with amitriptyline hydrochloride and 60% of patients treated with fluoxetine hydrochloride had PTSD total scores < 2.5.

FALCON et al. (1985) have conducted uncontrolled clinical trial using amitriptyline hydrochloride and have reported that this drug had beneficial effects in treatment of PTSD in combat veterans.

In a double-blind study by DA VIDSON et al. (1990) that compared amitriptyline and placebo in 46 veterans with PTSD, modest benefits were reported. With an average daily dose of 169 milligrams, statistically significant improvement was seen after 4 weeks in the depression scale and after 8 weeks of treatment in the depression and anxiety scales. However, no significant improvements were noted on the intrusiveness scale.

CONNOR et al. (1999) have published that in a 12-week, double-blind study, fluoxetine (10 mg daily) was more effective than placebo for treating post-traumatic stress disorder (PTSD). It has been reported that on the Duke Global Rating (Duke) for PTSD, significantly more patients reached a score of 1 (no symptoms) during treatment with fluoxetine than placebo (59% versus 19%; $p < 0.0005$). The Davidson Trauma Scale (DTS) total scores were also significantly lower in patients treated with fluoxetine compared to placebo. The onset of beneficial effects was observed at 2 weeks on the Duke scale and at 4 weeks on the DTS. This study included only civilians, primarily women, who fulfilled DSM-IV criteria for PTSD.

Conclusions

A pilot clinical trial, designed to compare the effects of the representatives of older and newer antidepressants in the treatment of PTSD, was performed.

Two antidepressants used were:

- Amitriptyline hydrochloride (AMYZOL®) as a representative of older (tricyclic) antidepressants
- Fluoxetine hydrochloride (OXETIN®) as a representative of newer (selective inhibitors of serotonin uptake) antidepressants.

PTSD total scores before and after administration of amitriptyline hydrochloride and fluoxetine hydrochloride were assessed.

Of two antidepressants used, more favourable response was achieved with amitriptyline hydrochloride (70%) than with fluoxetine hydrochloride (60%).

Amitriptyline hydrochloride was more effective in the treatment of acute PTSD symptoms, while fluoxetine hydrochloride was more effective in the treatment of chronic PTSD symptoms.

References

1. BLANCHARD, E.B., KOLB, L.C., PALLMEYER, T.P. and GERARDI, R.J. (1982): A psychophysiologic study of posttraumatic stress disorder in Vietnam veterans. Psychiatr. Q., (Psychiatric Quarterly), 54: 220-229.

2. CONNOR, K.M., SUTHERLAND, S.M., TUPLER, L.A. et al. (1999): Fluoxetine in posttraumatic stress disorder. Br. J. Psychiatr., 175: 17-22.

3. DAVIDSON, J.R.T., SWARTZ, M., STORCK, M., KRISHNAN, K.R.R. and HAMMETT, E. (1985): Phenomenology and family history of posttraumatic stress disorder. Am. J. Psychiatry, 142: 90-93.

4. DSM-III (1980): American Psychiatric Association, Committee on Nomenclature and Statistics: Diagnostic and Statistical Manual of Mental Disorders, 3rd ed.(DSM-III). American Psychiatric Association, Washington, DC.

5. DCM-IV (1994): American Psychiatric Association. Committee on Nomenclature and Statistics: Diagnostic and Statistical Manual of Mental Disorders, 4th ed. (DSM-IV). American Psychiatric Association, Washington, DC.

6. FALCON, S., RYAN, C., CHAMBERLAIN, K. et al. (1985): Tricycles: possible treatment for posttraumatic stress disorder. J. Clin. Psychiatry, 46: 385-389.

7. GREEN, B.L., LINDY, J.D. and GRACE, M.C. (1985): Posttraumatic stress disorder: toward DSM-IV. J. Nerv. Ment. Dis., 173: 406-411.

8. HOROWITZ, M.J., WILNER, N., KALTREIDER, N. and ALVAREZ, M.A. (1980): "Signs and symptoms of posttraumatic stress disorder". Arch. Gen. Psychiatry, 37: 85-92.

9. HTQ (1998): Harvard Trauma Questionnaire Bosnia-Herzegovina Version, Harvard Program in Refugee Trauma, Harvard School of Public Health, Harvard Medical School, Department of Psychiatry, University of Sarajevo.

10. ICD-X (1994): International Classification of Diseases, 10th ed. (ICD-X). Geneva: World Health Organisation.

11. LEMBERGER, L., ROWE, H., CARMICHAEL, R. et al. (1978): Fluoxetine, a selective serotonin uptake inhibitor. Clin. Pharmacol. Ther., 23: 421-429.

12. LEMBERGER, L., ROWE, H., CARMICHAEL, R. et al. (1978a): Pharmacological effects in man of a specific serotonin reuptake inhibitor. Science, 199: 436-437.

13. REGEHR, C. and MARZIALI, E. (1999): Recovery from sexual assault: A relational perspective. J.Nerv. Ment. Dis., 187: 618-623.

14. REYES, E. and LISANSKY, J. (1984): Effects of tricyclic antidepressants on platelet monoamine oxidase activity. Clin. Pharmacol. Ther., 35: 531-534.

15. SIERLES, F.S., CHEN, J.J., Mc FARLAND, R.E. and TAYLOR, M.A. (1983): Posttraumatic stress disorder and concurrent psychiatric illness: A preliminary report. Am. J. Psychiatry, 140: 1177-1179.

16. STARK, P., FULLER, R.W. and WONG, D.T. (1985): The pharmacological profile of fluoxetine. J. Clin. Psychiatry, 46: 7-13.

17. YEHUDA, R. (1999): Biological factors associated with susceptibility to PTSD. Can. J. Psychiatry, 44: 34-39.