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EFFICACY, TOLERABILITY AND SAFETY OF TIANEPTINE IN SPECIAL POPULATIONS OF DEPRESSIVE PATIENTS

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SUMMARY

Background: *Tianeptine, a new generation antidepressant, possesses a unique mechanism of antidepressive action and has a specific pharmacokinetic profile. The aim of this study was to determine the efficacy, tolerability and safety of tianeptine in a "fragile" population of depressive patients: (1) a group of elderly patients and (2) a group with comorbid alcohol addiction.*

Subjects and methods: *This was an open multicentric eight-week study of tianeptine efficacy, tolerability and safety including patients with mild to moderate depression (DSM-IV), age ≥55 years (group 1; n=45) or with comorbid alcohol addiction (group 2; n=32). Assessments was made with the following rating scales; MADRS, HAM-A and CGI for efficacy and DESS for tolerability.*

Results: *After eight-week tianeptine therapy, remission (MADRS ≤12) was established in 51.1% and 84.4% patients, respectively. On day 7, the therapy led to a significant decrease of MADRS. On endpoint, there were significant differences on HAM-A, CGI-I and CGI-S scores ($p<0.01$). No adverse effects with frequency ≥ 10%, were registered. A lower tolerability of tianeptine was registered in a group of elderly (nausea 4.5%, leg fatigue 4.4%, irritability 2.2%, bursts of crying and sadness 2.2%), while only 3.1% depressive patients with comorbid alcohol addiction had dizziness.*

Conclusion: *This is the first clinical study to evaluate tolerability, efficacy and safety of tianeptine in a special population of depressive patients in the region. The study showed that tianeptine had good efficacy in treatment of mild to moderate forms of depression in special populations of depressive patients (elderly population and patients with comorbid alcohol addiction). The drug was well tolerated.*

Key words: *tianeptine – depression - alcohol addiction*

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INTRODUCTION

Tianeptine is a tricyclic antidepressant, but with a few structural modifications. The drug has a unique mechanism of action as a glutamatergic modulator, especially in the hippocampus and cortex (Reagan et al. 2007, Svenningsson et al. 2007). Also, tianeptine modulates the neuro-endocrine response to stress (on the hypothalamic-hypophysis-adrenal axis – HPA), by down-regulation of gluocorticoid receptors, type 1, followed by decrease in concentration of corticotropine releasing factor (CRF) in the hypothalamus and adrenocorticotropic hormone (ACTH) in the plasma (Wilde and Benfield, 1995). Moreover, it impacts structural plasticity on the cell population altered in depression (McEwen et al. 2002, Fuchs et al. 2004).

Existing clinical studies confirmed tianeptine's antidepressant efficacy and favorable profile of adverse effects. Therefore, the drug may be recommended for treatment of depressive disorders and dysthymia, including cases with associated anxiety disorders (Wagstaff et al. 2001, McEwen & Olie 2005). The advantage of tianeptine compared to most other antidepressants, is a low rate of adverse effects (AE) such as: sleep disturbances, weight changes and sexual dysfunctions (Lôo et al. 1990, Guelfi 1992). Furthermore, its antidepressive and anxiolytic

effectiveness has been shown in some populations of depressive subjects with comorbidities. For example, Drobizhev et al. (2000) gave evidence for its efficacy and safety in depressive patients with coronary heart disease, Vorob'eva and Shavlovskaia (2005) showed a significant decrease of frequency and severity of headache attacks in patients with headaches and concomitant mild depression, while Levin (2007) found improvement in tianeptine treated patients with both depression and Parkinson's disease.

Comorbidity of depression and alcohol addiction is very common and it is usually associated with somatic complications (Di Sclafani et al. 2007, Hazen et al. 2008, Kroch et al. 2004). The old age population is also at an increased risk either of depression or/and somatic dysfunctions (Maâlej et al. 2008). Safe treatment of these special ("fragile") populations needs to be proven by controlled clinical studies. Thus, the aim of this study was to determine the efficacy, tolerability and safety of tianeptine in a special population of depressive patients: (1) a group of elderly patients and (2) a group with comorbid alcohol addiction.

SUBJECTS AND METHODS

This was a multicentric, open, eight-week study of tianeptine efficacy, tolerability and safety in special populations of depressive patients, divided into two groups. The research was performed in three clinical centers in Belgrade (Institute of Psychiatry University Clinical Centre, Institute of Mental Health and Psychiatric clinic at the Military Academy), during a six month period (December 2006 - June 2007). There are no fundamental differences between the centers: they all belong to academia, cover general psychiatric pathology, provide secondary and tertiary prevention and serve Belgrade and its surroundings by following common diagnostic manuals (ICD X and DSM IV) and therapeutic guidelines of the Serbian Medical Society - Psychiatric Section.

The sample consisted of 77 subjects divided into two groups. *Group 1* (n= 45) included subjects older than 55 years, who meet the criteria for mild or moderate depression according to DSM-IV (APA, 1994). *Group 2* (n=32), included depressive patients older than 18 years, who meet the criteria for mild or moderate depression and comorbid alcohol addiction according to DSM-IV (APA 1994). The subjects included in the study were consecutively admitted as in- or outpatients with the aforementioned clinical characteristics, from all the aforementioned centers, in the period December 2006 - March 2007. Before entering the study, patients gave their informed consent.

The exclusion criteria were: other types of depression (i.e. dysthymia and double depression), severe risk of suicide, acute or chronic psychosis, dementia, previous history of drug abuse or dependence, chronic somatic illness and pregnancy. For the evaluation of depressive symptomatology, the Montgomery-Asberg Depression Rating Scale – MADRS (Montgomery and Asberg 1979) was used. Anxiety was assessed by the Hamilton Anxiety Rating Scale - HAMA (Hamilton 1959). To estimate the severity of the disorder Clinical Global Impression - CGI-S was used (Guy 1976), while therapeutic efficacy was evaluated by CGI-I (Guy 1976). To measure tolerability and safety of the medication Discontinuation Emergent Signs and Symptoms – DESS scale was used (Rosenbaum et al. 1998). The DESS is a clinician-rated 43-item checklist that is used to evaluate signs and symptoms possibly associated with discontinuation or interruption of treatment, and it spans a broad spectrum of discontinuation symptoms. We assessed only symptoms that occurred during the use of the study medication.

The baseline visit (T0) included a semi-structured psychiatric interview, MADRS and CGI assessment. Tianeptine was than prescribed in the dose of 37.5mg, t.i.d. (3x12.5mg). During the study, the use of anxiolytic medication was permitted if necessary, but only $\leq$ 3 days continuously. Neither the use of antidepressants other than tianeptine, nor psychotropic or non-psychiatric drugs were permitted. Two follow-up visits were performed on day 7 (T1) and on day 56 (T2), by same rater. Both visits included all the aforementioned instruments, plus CGI-I and DESS scales. T2 evaluation was also performed in all cases of tianeptine discontinuation for more than 3 days for any reason. No dropouts were recorded during the study.

The study was approved by a local Ethical Committee.

RESULTS

A total of 77 (47 male and 30 female) patients who entered the study have completed the eight week protocol. Group 1 (n = 45) consisted of

subjects with a mean age 65.1±6.7 years, the majority of whom were retired, married males, with high school education The mean age of the subjects in group 2 (n = 32) was 47.4±9.5 years, with gender distribution in favor of male subjects (62.2%), mostly married, employed and high school educated. On the inclusion visit, the severity of depression (MADRS) in both group was moderate (29.4±6.8 and 29.81±5.74, respectively). The level of HAM-A was 20.7±6.4 in group 1 and 23.03±6.74 in group 2, while the mean CGI score 4.4±0.8 in group 1 and 4.7±0.8 in group 2 reflected illness of moderate intensity (see Table 1 for more details).

Table 1. Baseline patients' characteristics

	Group 1, n=45	Group 2, n=32
Age (mean ± SD)	65.1±6.7	47.4±9.5
Gender, male n (%)	28 (62.2)	19 (59.4)
Marital status n (%)		
Single	4 (8.9)	6 (18.8)
Married	20 (44.4)	20 (62.5)
Divorced	4 (8.9)	6 (18.8)
Widowed	17 (37.8)	0 (0.0)
Educational level		
primary school	9 (20.0)	5 (15.6)
secondary school	24 (53.3)	17 (53.1)
high school	3 (6.7)	2 (6.3)
university	9 (20.0)	8 (25.0)
Employment status		
No employed	11 (24.4)	2 (6.3)
Employed	6 (13.3)	24 (75.0)
Retired	28 (62.2)	6 (18.8)

Table 2. Mean (± SD) MADRS, CGI-S, CGI-I scores during the study in both groups

	Group 1			Group 2		
	T0	T1	T2	T0	T1	T2
MADRS	29.4±6.8	24.6±8.0	12.7±7.1	29.8±5.7	23.7±5.9	9.5±4.3
HAM-A	20.7±6.3	-	9.5±4.6	23.0±6.7	-	8.6±4.2
CGI-S	4.4±0.8	4.2±0.9	3.3±0.8	4.7±0.8	4.1±0.8	3.3±0.9
CGI-I	-	3.1±0.6	2.3±0.8	-	2.6±0.6	2.0±0.5

Legend: T0 - baseline; T1 - week 1; T2 - week 8; MADRS (T0-T1 t=8.86; p<0.01; T0-T8 t=12.07; p<0.01); HAM-A (T0-T1 t=11.451, p<0.01; T0-T8t=17.610; p <0.01); CGI-I (T0-T1 t=7.097; T0-T8 p<0.01; t=5.299; p<0.01);

The mean (± SD) MADRS, HAM-A, CGI-S, CGI-I scores at the baseline; week 1 and week 8 are showed on table 2.

Improvement in patients of both groups was shown after the first week of treatment and continued throughout the study duration. In both groups,a paired t-test comparing baseline MADRS scores with scores on week 1 (t=8.86; p<0.01 and t=12.07; p<0.01, respectively) and week 8 showed that the differences became significant (t=8.861; p<0.01 and t=18.932, p<0.01, respectively). In addition, the improvement was confirmed by CGI-I (t=7.097; p<0.01 and t=5.299; p<0.01, respectively).

In Group 1, 23 (51.1%) patients were considered to have entered remission by week 8, while remission was defined as a MADRS score of ≤12. In Group 2, remission was achieved in 32 (84.4%) patients by the end of the study (week 8).

In addition, the mean values in HAM-A at the baseline, showed significant reduction of anxiety over the eight week of follow up in both groups (t=11.451, p<0.01 and t=17.610; p<0.01, respectively).

During the trial, adverse effects in both groups were rare. In Group 2 (depressive subjects with comorbid alcohol addiction) only one patient (3.1%) complained of dizziness, while in older subjects with depression the complaints were: nausea (4.4%), leg fatigue (4.4%), headache (4.4%), irritability (2.2%) and bursts of crying and sadness (2.2%).

DISSCUSION

Only a few studies have evaluated tianeptine effects in special populations of depressed patients (Marey et al. 1991). This is the first study in the region to assess efficacy, safety and tolerability of the drug in a special, "fragile" population of patients with depression: the elderly and alcohol addicts. Our study showed that tianeptine significantly reduced depressive symptomatology. The majority (84.4%) of patients with alcohol addiction and mild to moderate depression met the criteria for remission (MADRS ≤ 12) after 8 weeks treatment with tianeptine, additionally confirmed by value/rate change of CGI-S and CGI-I. Also, major improvement was evident within a group of elderly, i.e. more than a half (51.1%) significantly improved in MADRS, followed by increase in CGI-S and CGI-I.

At the same time, we proved that the administration of tianeptine led to a statistically important reduction of anxiety symptoms estimated by HAM-A, in both groups ($t=11.451$, $p<0.01$ and $t=17.610$; $p<0.01$, respectively). By the study design we were able to exclude all patients whose level of anxiety was high so that they needed addition of an anxiolitic drug for more than three days, but no one was excluded due to this reason. This could be an indirect argument for the anxyolitic efficacy of the drug. Similarly, Lôo et al. (1988), found that tianeptine possesses anxiolytic activity, and added that it was not accompanied by any impairment of vigilance, as it was in case with amitriptyline.

In our study, during an eight-week tianeptine trial, side effects that appeared after tianeptine administration in the elderly were the following: nausea (4.4%), leg fatigue (4.4%), headache (4.4%), irritability (2.2%) and bursts of crying and sadness (2.2%). However, not even one of the treated patients in the study was excluded due to the side effects.

So far, studies have shown quite rare side-effects of tianeptine in the elderly**.** Thus, Saiz-Ruiz et al. (1998) found that side-effects were found in only 11.7% of older patients, with no changes in laboratory or ancillary safety parameters. In subjects with alcohol addiction and comorbid depression in our study, we also found good tolerability of tianeptine – dizziness was the only side effect that occurred during the study, and it was evident in 3.1% of the treated patients.

There are many arguments to favor tianeptine administration in subjects with alcohol dependence: (1) neurochemical studies showed that there was an interaction between alcohol and glutamate, (2) pharmacological studies confirmed that tianeptine leads to reduction of alcohol consumption in animals, and (3) depression was a common comorbid disorder in alcohol addicts (Favre et al. 1997).

CONCLUSION

Tianeptine, as an atypical antidepressant, is classified as a glutamatergic modulator and is not an enhancer of the synaptic reuptake of serotonin (Reagan et al. 2007, Svenningsson et al. 2007). The antidepressive action of tianeptine is more directly related to both central neuronal remodeling and restoration of neuronal plasticity.

The clinical effectiveness of tianeptine in the treatment of major depression, bipolar disorder, and dysthymia or adjustment disorder has been extensively reviewed (Brink et al. 2006). Clinical trials also show that tianeptine is well tolerated, with no significant sedation, anticholinergics and cardiovascular effects and does not produce changes in hematological, renal or hepatic function, nor does it cause increase in body weight. It is also important that, unlike the majority of tricyclic antidepressants, tianeptine does not cause impairment in cognitive and psychomotor functioning. Furthermore, it differs from most other antidepressants in the fact that it is not primarily metabolized by the hepatic cytochrome P450 system, indicating less likelihood of drug-drug interactions. All the aforementioned characteristics are of special value for vulnerable patients who are particularly prone to the side-effects of psychotropic drugs (Malka et al. 1992), such as elderly patients or alcohol addicts ("fragile" population). This is the first clinical study to evaluate the effects of tianeptine in these special populations of depressive patients in the region. The study showed that tianeptine had good efficiacy, and that it was safe and well tolerated in the treatment of mild to moderate forms of depression in these special populations of depressive patients (elderly population and patients with comorbid alcohol addiction). This simple open trial serves as a good basis for future placebo-controlled studies of tianeptine in these special patient populations.

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