EFFICACY AND TOLERABILITY OF TIANEPTINE IN DEPRESSED PATIENTS WITH CARDIO-VASCULAR DISEASES

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Abstract

The symptoms of depression and those of cardiovascular disease (CVD) overlap substantially. Differentiating between dimensions of depressive symptoms may improve our understanding of the relationship between depression and physical health, in order to find a more adequate antidepressant treatment for patients having both depression and cardiovascular disease.

Our aim was to assess the efficacy, tolerability and safety of tianeptine in depressed patients with moderate and severe cardio-vascular disorders.

The present survey is an observational naturalistic study conducted in patients with important cardio-vascular disorders who underwent evaluation for depressive symptoms, using the Montgomery Asberg Depression Rating Scale (MADRS) and the self-evaluation Hospital Anxiety and Depression Scale (HADS). The MADRS and HADS were used to examine the efficacy of tianeptine after 28 days of antidepressant therapy. Tolerability of tianeptine and its effects on cardiovascular system was assessed.

Fifty eight hospitalized patients meeting DSM-IV TR (Diagnostic and Statistical Manual of Mental Disorders, forth edition, text revision) criteria for major depressive disorder, severe or moderate episode, who also had important cardio-vascular disorders: arterial hypertension, cardiac failure and ischemic heart disease were included in the study. Cardio-vascular disorders were clinically stable under specific treatment. Two ECG were performed: one at baseline and one after two weeks of treatment. The patients received 3 tablets of tianeptine 12.5 mg per day, and were monitored for 28 days regarding both efficacy and tolerability of the treatment.

The efficacy of the treatment was assessed using the Montgomery Asberg Depression Rating Scale (MADRS), the self-evaluation Hospital Anxiety and Depression Scale (HADS) and the Clinical Global Impression Improvement Scale (CGI-I), in the first day and after 7, 14, 21 and 28 days of tianeptine treatment. The tolerability and safety were observed by monitoring the vital signs (blood pressure, pulse, respiratory frequency) and the adverse effects. For all patients, an ECG was performed after 2 weeks of treatment with tianeptine and was compared with the one made before admission, in order to monitor possible changes in heart conduction.

After 4 weeks, 76% of the patients presented a very good improvement at CGI-I Scale, as 21% presented a good improvement. The mean MADRS total score decreased by 40% from baseline in patients with severe depressive episodes, and by 50%, in those who had moderate depressive episodes. There were no significant changes registered on the ECGs. There was a good tolerability of tianeptine, the adverse effects registered had mild intensity and left no sequelae.
Tianeptine appears to be as an efficient treatment in severe and moderate depression in patients with concomitant serious cardio-vascular disorders, and was well tolerated, with no important cardio-vascular adverse effects. Further studies are necessary to confirm these observations regarding the efficacy and tolerability of tianeptine in this group of patients.

Rezumat

Simptomele depresiei și cele ale tulburărilor cardio-vasculare se pot supraopune deseori. Diferențierea simptomelor depresive poate contribui la înțelegerea legăturii dintre manifestările depresiei și starea somatică și este necesară în alegerea tratamentului optim pentru pacienții care prezintă atât depresie cât și tulburări cardio-vasculare.

Scopul acestui studiu a fost acela de a evalua eficacitatea, tolerabilitatea și siguranța tianeptinei la pacienții cu depresie și tulburări cardio-vasculare moderate sau severe.

Acest studiu observațional, naturalist a inclus pacienți cu tulburări cardio-vasculare importante, care au fost evaluați pentru simptome depresive, folosindu-se scala de evaluare Montgomery Asberg Depression Rating Scale (MADRS) și scala de auto-evaluare Hospital Anxiety and Depression Scale (HADS). Scalele au fost utilizate pentru a evalua eficacitatea tianeptinei după 28 de zile de tratament antidepresiv. Tolerabilitatea și efectele tianeptinei asupra sistemului cardio-vascular au fost, de asemenea, urmărite.


Eficacitatea tratamentului a fost evaluată folosindu-se scalele MADRS, HADS și scala de Impresie Clinică Globală - îmbunătățire(CGI-I). Acestea au fost aplicate pacienților în prima zi și după 7, 14, 21 și 28 de zile de tratament cu tianeptină. Tolerabilitatea și siguranța au fost observate monitorizându-se semnele vitale: tensiunea arterială, aluna ventilator, frecvența respiratorie, precum și apariția eventualor efecte secundare. Toți pacienții au efectuat un examen EKG după două săptămâni de tratament, care a fost comparat cu cel efectuat înainte de spitalizare, pentru a evidenția posibile tulburări de conducere cardiacă.

După 4 săptămâni de tratament, 76% dintre pacienții au prezentat ameliorare foarte bună pe scala CGI-I, iar 21% dintre ei o ameliorare bună. Scorul median total al MADRS a scăzut cu 40% față de baseline la pacienții cu episod depresiv sever și cu 50% la cei care au prezentat episod depresiv moderat. Nu s-au înregistrat modificări semnificative la examenul EKG, comparativ cu cel efectuat înaintea includerii în studiu. Tianeptina a fost bine tolerată, efectele secundare înregistrate au fost de intensitate ușoară și s-au rezolvat fără sechele.

În studiul nostru, tianeptina s-a dovedit a fi un tratament eficient în depresia severă și moderată, la pacienții cu tulburări cardio-vasculare asociate; a fost bine tolerată de pacienți, nu s-au înregistrat efecte adverse cardio-vasculare majore. Sunt necesare studii suplimentare, care să confirme observațiile privitoare la eficacitatea și tolerabilitatea tianeptinei la acest grup de pacienți.

Keywords: Depression, tianeptine, cardio-vascular comorbidities
Introduction

Depression and cardiovascular disease

The coexistence of depression and cardiovascular disease (CVD) has been well established [1,4]. The prevalence rates of depression in patients with cardiovascular disease are ranging from 16% to 23%.

Although knowledge about the etiology, biology, and treatment of depression and CVD has increased in the past 2 decades, the exact mechanisms linking these 2 illnesses have yet to be established. Research has demonstrated that depression and CVD may each precede the other, that they may develop concurrently, and that early signs of CVD may be mistakenly diagnosed for depressive symptoms. Even in the absence of clearly described mechanisms for their relationship, the coexistence of depression and CVD is associated with a worse CVD prognosis [7,9].

Depression is associated with several physiological disturbances that could contribute to adverse cardiac outcomes [11,13]. Patients with depression have high sympathetic tone, hypercortisolemia, elevated catecholamine levels, abnormal platelet activation, increased inflammatory markers, and endothelial dysfunction. It is interesting that these physiological dysfunctions are present in depressed patients who do not have cardiac diseases (i.e., these mechanisms may be linked to depression itself), and even when not currently depressed, patients with a history of depression have at least some of these abnormalities (e.g., platelet activation) as compared with patients who are not depressed [2].

Recent advances in biological psychiatry have included the discoveries of numerous neurochemical, neuroendocrine, and neuroanatomic alterations in unipolar depression. Proposed as important adjuncts in the diagnosis of depressed subjects, some of these biologic markers may reflect important pathophysiologic alterations that contribute to the increased vulnerability of depressed patients to CVD. These include sympathoadrenal hyperactivity, diminished heart rate variability (HRV), ventricular instability and myocardial ischemia in reaction to mental stress, as well as alterations in platelet receptors and/or reactivity [8,10].

Rumsfeld et al [12] suggested several hypothesis: depression could be a causal risk factor, directly related to cardiovascular disease and outcome. Or depression could be a risk marker, indirectly related to cardiovascular disease through behavioral variables. Or depression is a secondary event, elicited by major medical events such as cardiac surgery.

Sometimes depression may be a secondary development in cardiac patients, whereby patients with more severe cardiac disease or a heavier burden of comorbid conditions may become depressed in reaction to their
illnesses. In this case, adverse outcome is the result of the greater disease burden but not of depression itself. There are some factors that do not sustain this explanation, at least as a unique mechanism for the association between depression and cardiovascular outcomes [12]. Other studies, including the one of Mallik et al [5] have used robust risk adjustment for cardiac and noncardiac disease burden in their analyses. Taking into account for these variables does not appear to eliminate the relationship, and this is supporting the conclusion that depression is an independent predictor of outcome. Furthermore, depression precedes cardiovascular disease in many cases.

Major depression and depressive symptoms, although commonly encountered in medical populations, are frequently underdiagnosed and undertreated in patients with cardiovascular disease. This is of particular importance because several studies have shown depression and its associated symptoms to be a major risk factor for the development of CVD.

Treatment of depression in patients with CVD improves their dysphoria and other signs and symptoms of depression, improves quality of life, and perhaps even increases longevity.

Treatment with tianeptine in depressed patients with cardiovascular disease

Tianeptine is an antidepressant which was synthesized by French researchers, being developed and marketed since the late 1980s. Tianeptine acts as a glutamate modulator, regulating glutamate release and therefore increasing plasticity in the brain.

Evidence suggests that tianeptine acts to prevent and even reverse stress-induced neural damage, promoting both neuronal survival and synaptic plasticity, which has been manifested by reduction of stress-induced dendritic atrophy, and reverses the stress-induced decrease of neurogenesis and hippocampal size in an animal model of depression. Furthermore, sustained use of tianeptine tends to normalise the hypothalamic-pituitary-adrenal system [6].

Double blind studies comparing tianeptine with imipramine and amitriptyline have shown the effectiveness of tianeptine's antidepressor action, its properties of non-specific symptoms related to behaviour disorders (anxiety, inhibition) and its action on somatic complaints expressed by depressed patients. Due to its pharmacological properties, tianeptine could be an effective antidepressant in cases of depression with cardiovascular disease and could lead to good therapeutic response in these patients.
Materials and Methods

This observational naturalistic study evaluated 58 male and female inpatients admitted on Ward III of the Clinical Hospital of Psychiatry “Prof.Dr.Alexandru Obregia”, Bucharest, Romania, presenting major depressive disorders, severe or moderate episodes. These patients also had important cardio-vascular disorders: arterial hypertension, cardiac failure and ischemic heart disease, which were clinically stable under specific treatment. The study was conducted according to the principles of the Declaration of Helsinki (1964) and its amendment (Tokyo 1975, Venice 1983, Hong Kong 1989) and the Good Clinical Practice (GCP) rules. The clinical protocol was reviewed and approved by the Ethics Committee of the Hospital. All subjects gave their written informed consent prior to the study.

Depressive symptoms were assessed using the Montgomery Asberg Depression Rating Scale (MADRS) and the self-evaluation Hospital Anxiety and Depression Scale (HADS) and the Clinical Global Impression Improvement Scale (CGI-I).

Apart from specific cardio-vascular therapy, the patients received 3 tablets of tianeptine per day, and were monitored for 28 days regarding both efficacy and tolerability of the treatment.

Two ECGs were performed to each patient, one before admission and another one after 2 weeks of treatment with tianeptine, its effects on cardiovascular system being also examined. The mean period of hospitalization was of 3 weeks. Those who were discharged were followed as outpatients until the end of the observation period.

Results and Discussion

Demographic data (gender, age) can be observed in table I.

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>( n=58 )</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender ratio</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>60% (n=35)</td>
</tr>
<tr>
<td>Female</td>
<td>40% (n=23)</td>
</tr>
<tr>
<td><strong>Age groups</strong></td>
<td></td>
</tr>
<tr>
<td>25-34 years old</td>
<td>7% (n=4)</td>
</tr>
<tr>
<td>35-44 years old</td>
<td>20% (n=12)</td>
</tr>
<tr>
<td>45-54 years old</td>
<td>27% (n=16)</td>
</tr>
<tr>
<td>55-64 years old</td>
<td>46% (n=26)</td>
</tr>
</tbody>
</table>

The majority of the included patients were male, mostly because of the specificity of the ward, and the highest percentage among age groups was observed for patients between 55-64 years old.
Patients met DSM-IV TR (Diagnostic and Statistical Manual of Mental Disorders, forth edition, text revision) criteria for major depressive disorder, severe and moderate depressive episodes. They also had important cardio-vascular disorders: arterial hypertension, cardiac failure and ischemic heart disease, as seen in the table II.

Table II

<table>
<thead>
<tr>
<th>Psychiatric diagnosis</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major depressive disorder, Moderate depressive episode</td>
<td>28</td>
</tr>
<tr>
<td>Major depressive disorder, Severe depressive episode</td>
<td>30</td>
</tr>
<tr>
<td>Cardio-vascular disorders</td>
<td></td>
</tr>
<tr>
<td>Arterial Hypertension 2nd degree</td>
<td>18</td>
</tr>
<tr>
<td>Arterial Hypertension 3rd degree</td>
<td>12</td>
</tr>
<tr>
<td>Heart failure NYHA II class</td>
<td>9</td>
</tr>
<tr>
<td>Heart failure NYHA III class</td>
<td>5</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>14</td>
</tr>
</tbody>
</table>

NYHA – New York Heart Association

Patients included in this study presented both severe or moderate depressive episodes, and different associated cardio-vascular disorders. Arterial hypertension was the most frequent disorder, 31% had arterial hypertension 2nd degree (n=18) and 21% arterial hypertension 3rd degree (n=12). Heart failure was also a frequent disorder. The degree of heart failure was classified using the New York Heart Association (NYHA) functional classification. The patients also had heart failure NYHA II class (n=9) and NYHA III class (n=5), while 14 patients presented ischemic heart disease.

The depressive symptoms improved during the 28 days of treatment, the total mean MADRS score decreased with about 40% from baseline in patients with severe depressive episode, from 35.2 to 19.7, and over 50%, in those who had moderate depressive episode, from total mean score of 27.5 to 12.6, at the end of the study.

The mean MADRS, HADS and CGI-S total scores at baseline and at the end of the study are as follows:

Table III

<table>
<thead>
<tr>
<th>Severe depressive episode</th>
<th>Moderate depressive episode</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>End of study</td>
</tr>
<tr>
<td>MADRS</td>
<td>35.2</td>
</tr>
<tr>
<td>HADS</td>
<td>31.2</td>
</tr>
<tr>
<td>CGI-S</td>
<td>5.6</td>
</tr>
</tbody>
</table>
The figure 1 shows the improvement of mean MADRS total scores in both groups of patients, with severe and with moderate depression, after 4 weeks.

The mean HADS total scores also improved, from 31.2 at baseline to 14.5 after 28 days of treatment, in the patients with severe depressive episode, and from 25.2 to 10.6, in the group having moderate depressive episode as seen in figure 2.

The figure 3 illustrates the favorable evolution of the depression total mean sub-scores on HADS in both groups of patients, with severe as with moderate depression, from baseline until the end of the study period.
The improvement of the total mean sub-scores of depression on HADS, in both groups of patients

The next figure shows the evolution of the total mean sub-scores of anxiety on HADS, in the patients with severe and those with moderate depression, from baseline to the end of the study (figure 4).

CGI-S Scale was used at baseline and then weekly until the end of the study, on the 28th day of treatment. An important improvement of the
patient’s overall clinical condition was observed in CGI-S scale, with a decrease after 4 weeks of total mean scores of 59% in the group with severe depressive episode and of 63% in the one with moderate depressive episode as seen in figure 5.

![CGI-S total mean scores at baseline and after 28 days of therapy, in both groups of patients](image)

Figure 5

After 4 weeks, 76% of the patients were very much improved since the initiation of treatment on CGI-I Scale (CGI-Improvement), and 21% were much improved. A small percentage of the patients (3%) were minimally improved from the baseline, on CGI-I scale (Table IV).

<table>
<thead>
<tr>
<th>CGI-Improvement (CGI-I)</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very much improved</td>
<td>76% (n=44)</td>
</tr>
<tr>
<td>Much improved</td>
<td>21% (n=12)</td>
</tr>
<tr>
<td>Minimally improved</td>
<td>3% (n=2)</td>
</tr>
</tbody>
</table>

Table IV

Improvement of the symptoms after 4 weeks, from baseline, on CGI-I Scale

Tianeptine was well tolerated, and the registered adverse effects were mild to moderate (Table V). The most frequent reported adverse effects in our study were gastro-intestinal symptoms such as nausea, constipation, diarrhea, vomiting, and dry mouth, observed during the treatment with tianeptine. The patients who had adverse effects recovered with no sequelaes.
In our study two ECGs were performed for each patient, one at baseline and another one after 2 weeks of treatment with tianeptine. There were no significant changes registered on the ECGs, comparing with those performed before antidepressant treatment.

There were no clinically significant changes of existing cardio-vascular disorders.

In patients from our study, the blood pressure values did not change significantly, during the 4 weeks period of observation. There was no need of changing the doses of cardio-vascular therapy, for the patients, during the observation period.

**Conclusions**

Different studies demonstrated that the coexistence of depression and cardiovascular disease is well established. Depression is frequently associated with several physiological disfunctions that could contribute to adverse cardiac outcomes [11,3].

There are few antidepressants that a physician can use to treat safely depressed patients with associated cardio-vascular disorders.

In several studies, tianeptine proved to be an effective antidepressant for patients with depression and cardiovascular disease, leading to a good therapeutic response.

In our study, we found out that tianeptine has a good efficacy in improving depressive symptoms, both in severe and moderate depressive episode, in patients having serious cardio-vascular disorders, which were confirmed by the change of total mean scores of MADRS, HADS and CGI-S, from baseline until the end of the study.

The mean MADRS total score was decreased with about 40% from baseline in patients with severe depressive episode, and with over 50%, in those who had moderate depressive episode, at the end of the study. A significant improvement was observed in mean HADS total scores, which

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**Table V**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Percentage (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>12% (n=7)</td>
</tr>
<tr>
<td>Constipation</td>
<td>10% (n=6)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>12% (n=7)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>7% (n=4)</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>14% (n=8)</td>
</tr>
</tbody>
</table>

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decreased with over 50%, compared to baseline. No important side effects were registered, and more important, no important cardio-vascular adverse effects were reported.

Our study evidenced both the efficacy of tianeptine and the safety and tolerability of this antidepressant in patients having cardiovascular disorders and undergoing specific treatment.

The two ECG’s performed to each patient, one before inclusion and the second one after two weeks of antidepressant therapy showed no significant changes. The patients also didn’t need additional cardiovascular treatment while they were included in this study.

There were few adverse effects registered, including nausea, constipation, diarrhea, vomiting, and dry mouth, which had mild to moderate intensity and were resolved with no sequaeles.

In this study tianeptine confirmed its efficacy and safety in the treatment of severe and moderate depression in patients with concomitant serious cardio-vascular disorders. The advantages presented by our data and conclusions are represented by the fact that it is a naturalistic study, which is closer to the clinical reality than the controlled studies.

Nevertheless, our study has some methodological limitations, being an open study, with a relatively small number of patients, and a short follow-up period of time.

Further studies are required to strengthen these data.

There are no easy solutions in treating depressed patients with important cardiovascular disorder, and it is very important to pay attention to both benefits and potential risks, when choosing one treatment or another.

As a conclusion, we can say that tianeptine may be a first line treatment option, when managing cases of depression and associated cardio-vascular disorders.

References


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