CLINICAL TRIAL ON DIFFERENT ADJUVANT TREATMENT IN UNIPOLAR DEPRESSION

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Abstract. Depressive disorders are considered to be clinical entities frequently seen in medical practice, causing a very high level of disease burden and are expected to show a rising trend during the coming 20 years. Symptoms of depressive episode in both recurrent depressive disorder and bipolar affective disorder are similar. Despite these similarities, recent studies show that depressive episode who appears in both disorders, is different regarding etiology, course and adjacent neurochemical processes. The therapeutic plan used for the treatment of depression usually combines an antidepressant with a benzodiazepine. The current study investigates the therapeutic efficiency of clonazepam versus diazepam in association with paroxetine used to treat the depressive episode – Major Depressive Disorder.

Keywords: depressive episode, therapeutic efficiency, clonazepam.

Introduction

Depressive disorders are clinical entities frequently encountered in clinical practice, depression being one of the major causes of disability worldwide. World Health Organization recently conducted a study which showed that globally, depression is one of the most disabling diseases. Specialists from Bethesda Public Health Institute warn that in 2020, depression will become the second cause of death after cardiovascular disorders.

Although the clinical features of the depressive episode are identical both in recurrent depressive disorder and in bipolar disorder - depressive episode, the two clinical entities differ in terms of etiology, of neurochemical basis and of evolution. This assertion is supported by findings of several studies. For example, in 2000, Morishita, S. and Aoki, S. conducted a study that compared the effect of adding clonazepam to antidepressants in unipolar depression and bipolar depression, noting that, after four weeks, the percentage of the clinical response obtained was eight times as great in patients with unipolar depression as in those with bipolar depression. These results led to the idea that differences in clinical response are due to the particular psychopathological processes underlying the two types of depression. (1)

According to current therapeutic recommendations regarding the drug option in major depressive episode, the first step consists in choosing an antidepressant as monotherapy. If until almost 30 years ago, tricyclic antidepressants represented the treatment of choice in depressive episodes, in the last two decades the use of SSRIs (selective inhibitors of serotonin reuptake) has been considered a turning point in the treatment of depressive disorders. They are considered first-line therapeutic agents for the treatment of depressive episodes in affective disorders. Their advantages are clear: they are well tolerated; they allow individual reintegration into society and improve quality of life. Most selective reuptake inhibitors of serotonin are administered in one dose, which increases patient compliance. Fluoxetine, the first SSRI, was discovered more than two decades ago, being, from then until now, the
most prescribed drug in the U.S. among all tricyclic antidepressants, MAOIs and SSRIs. After several years, sertraline and paroxetine have become almost as widely used as fluoxetine. Currently there are six SSRIs, namely: fluoxetine, sertraline, paroxetine, fluvoxamine, citalopram, and escitalopram. (2)

Regardless of the drug class to which they belong, antidepressant agents manifest their effect after a latency period that can range from 7-10 days to three weeks. Delay in emergence of therapeutic response cannot be explained by the pharmacokinetic profile of antidepressant agents because the peak plasma drug concentration (and possibly intracerebral concentration too) is usually reached in seven days. Clinical improvement that occurs earlier than that can be explained by the decrease in anxiety symptoms that accompany depressive episodes and by obtaining an improved sleep caused by the sedative action inherent in antidepressants. Recent studies show that antidepressants’ action is explained by the adaptive changes they induce in the adrenergic, serotonergic, and GABA-B receptors. The literature of preclinical studies has suggested that GABA levels may be decreased in induced animal depression model. Furthermore, some studies have shown low levels of GABA in plasma and cerebrospinal fluid in patients with depression. However, antidepressants, mood-stabilizers, electro-convulsive therapy, and GABA agonists have the capacity to reduce the induced depressive behavior in animals, being effective in patients with unipolar and bipolar depression by increasing GABAergic brain activity. (3), (4), (5).

Enhancement of antidepressant treatment through benzodiazepines is one of the strategies used by physicians. One of them concerns the Hamilton Scale in which about one third of the items assess symptoms of anxiety. Associating benzodiazepines to antidepressant agents often provides a reduction in the Hamilton-D scale score by 30% within a few days, if the appropriate doses are used. BZDs’ role of increasing GABA activity may allow a significant improvement of some of the depression symptoms.

Besides the therapeutic benefit of combining benzodiazepines with antidepressant agents, another question that has worried some researchers was whether certain benzodiazepines have some antidepressant properties. It seems that some BZD, besides the anxiolytic and sleep induction actions, also have an antidepressant action which can be explained in terms of involvement of the GABA system in depression. Data from literature supports this theory. Petty, F. et al. (1995) have conducted a meta-analysis comparing the action of some benzodiazepines (alprazolam, diazepam, chlordiazepoxide) with the action of classical antidepressant agents in the treatment of depression, noting that alprazolam is useful in the treatment of depression in patients in whom standard antidepressant medication is contraindicated, poorly tolerated or ineffective. (6),(7).

This study aims to determine whether clonazepam has a higher efficacy compared to diazepam in treating major depressive episode in recent depressive disorder.

Materials and methods

Selection criteria

Study subjects were inpatients from the 6-th ward of the Clinical Psychiatric Hospital “Prof. Dr. Alexandru Obregia”, between the years 2006-2009, age between 18 and 60 years, and of female sex. Patients were only female due to the profile of the ward - the ward has 70 beds for women and only 5 beds for men. All patients fulfilled DSM-IV-TR criteria for severe major depressive episode without psychotic symptoms. At admission patients showed good general condition.

Patients with psychotic symptoms and those with a history of manic or hypomanic episode were excluded. Although the clinical features of the depressive episode are similar both in recurrent depressive disorder and in bipolar disorder - depressive episode, it seems that the two clinical entities differ in terms of etiology, of neurochemical basis and of evolution. Sorting out patients to exclude psychotic symptoms and mixed states was done by obtaining data of history (from both patients and their family, when this was possible), clinical interview and application of the Young Mania Rating Scale (11 items) that had scores below 12 in all patients included in the trial.

Patients with mental retardation, with severe somatic comorbidity, with alcohol or drug abuse in the last 12 months were not taken into the trial. Also, patients with maximum blood pressure lower than 100 mmHg and greater than 160mmHg at the admission were not taken into the trial either.

During treatment, all patients in the fertile age group were gynecologically consulted and pregnancy tests were done to rule out the presence of an ongoing pregnancy.

Trial methodology

We formed two randomized groups of 50 patients each. The distribution of the patients into the two groups was done randomly in chronological order of their admission and of meeting the inclusion and exclusion criteria. The study group received a dose of paroxetine of 20mg/day and clonazepam...
1mg/day. The control group received a dose of paroxetine of 20mg/day and diazepam in an average dose of 20mg/day. According to the tables of equivalence, it may be considered that diazepam and clonazepam were administered in quasi-equivalent doses (0.5 mg clonazepam is equivalent to 10mg diazepam). (8), (9). We intended to use moderate doses of benzodiazepines in order not to produce notable side effects that would discomfort the patient. It is known that unpleasant experiences in the first days after treatment initiation due to adverse drug reactions is one of the factors that lead to poor compliance and abandonment of long-term treatment. (10). The patients received a dose of 20mg of paroxetine for several reasons. One of them is that 20mg/day represents the producer's recommended usual dose for the treatment of the depressive episode. Moreover, several studies showed that patients treated with higher doses than 20mg/day of paroxetine had no greater benefit than those treated with 20 mg/day. In 2009, Ruhe, H. G. et al. presented a study explaining why increasing the dose of over 20mg/day paroxetine does no additional therapeutic benefit in the treatment of major depressive episode. Although paroxetine plasma concentrations increase with dose, serotonin transporters in the membrane of serotonin neurons are almost entirely occupied by the 20mg/day doses of paroxetine. (11)

Paroxetine was administered in one dose and benzodiazepines were administered in two divided doses, in the morning and in the evening.

Patients were evaluated at admission and on the 14-th day in both groups because studies have shown that therapeutic benefit brought by antidepressants is felt after an average interval of 10-14 days.

**Choosing the measurement scales**

Hamilton Depression Rating Scale was introduced in 1960 by Hamilton and became the most used scale in the field, being by far the most used international scale and an instrument of communication between investigators. It is used especially in psychopharmacological studies, in a standard procedure of rating the severity of symptoms and sensitivity to change. It is commonly used in analytical or comparative studies.

The most commonly reported score in scientific papers is the total score. Total score can range from 0-50 when the 17 items scale is applied, and it may be in the range of 0-62 for the 21 items scale. (12),(13), (14).

For the Romanian language population and for the English language population as well, scores below 7 indicates absence of depression; between 7-17 mild depression; between 18-24 moderate depression and above 25 severe depression.

**Efficiency measurement**

Evaluation of efficacy was achieved through:

- measuring the changes in the total score of Hamilton Depression Scale at 14 days from the time of admission and comparing the values from the two groups;
- measuring the changes in CGI severity score after 14 days, comparing it to the score at the admission and comparing the values in the two groups;
- determining the percentage of patients whose HAM-D score was lower than 50% compared with the one at the admission in the two groups studied;
- comparing (counting) the items that had the greatest decrease (improvement) in the study group compared to the control group.

**Statistical analysis**

Both for the 17 criteria of the Hamilton scale and for the 3 criteria of the CGI scale, recorded data for each group and for each assessment time (T1 and T2) have fulfilled the conditions of normal distribution and equality of variants.

First, each criterion was statistically analyzed separately, and afterwards we conducted the overall analysis of the scores obtained by the two groups at the times T1 (admission) and T2 (after 14 days) of the study. We assessed the distribution of patients according to the difference between the initial and the final score for each criterion and overall. Testing a possible association between the scores recorded and the type of treatment of each group was performed using Pearson’s chi-square test.

We used unpaired Student’s t-test (independent samples - homoscedastic) to statistically assess the differences between the overall scores recorded for the two groups (control and study) - Hamilton scale.

The level of statistical significance was set at a p value of 0.05.

On admission, the two groups were comparable in terms of the average value of the Hamilton scale score (25.82 in the control group and 25.84 and in the study group) and of the average value of the CGI severity score (5.48 in the control group and 5.52 in study group).

**Results**

In both groups, the Hamilton scale score had lower values after 14 days (time T2) than at admission time, which demonstrates that, in both groups, patients’ condition improved during the 14 days.
In the control group, the average value of the Hamilton scale score after 14 days was 14.6 (compared to 25.82) and in the study group it was 10.90 (compared to 25.84). (Tabel I)

Comparing the results of the two groups (T1-T2 for the control group and study group respectively) showed statistically significant differences between the evolution of the two cohorts (p <0.005).

Mean CGI severity score after 14 days was 3.38 in the control group (compared to 5.48 at the admission) and 2.96 in study group (compared to 5.52 at the admission).

At T2 moment of the trial, the distribution of the patients according to the criterion „CGI severity of illness“ was presented in tabel II

- 2% of the control group patients and 14% of the study group patients obtained a score of two points – at the limit between normal and pathological;
- 62% of the control group patients and 76% of the study group patients scored three points – slightly ill;
- 32% of the control group patients and 10% of the study group patients scored 4 points - moderately ill;
- 4% of the control group patients and none of the patients in the study group scored 5 points - severely ill.

Applying Pearson’s chi-square test showed that there was a significant correlation between the treatment administered and the test score obtained under criterion „severity of illness“ at time T2 of the study (χ² = 12.97, df = 3, p = 0.001). Thus, it can be argued that under treatment with Clonazepam, patients achieved statistically significant improvements of this criterion.

At T2 moment of the study, the distribution of the patients according to criteria „CGI favorable global trend“ was as following presented in tabel III

38% of the control group patients and double the percentage of the study group patients obtained a score of one point - very much improved;
54% of the control group patients and 24% of the study group patients obtained a score of 2 points - much improved;
4% of the control group patients and none of the patients in the study group obtained a score of 3 points - slightly improved.

Statistical analysis of these data has shown a close correlation between the treatment administered and the test score obtained under the criterion: „positive global evolution“ (χ² = 13.09, df = 2, p = 0.001). Patients treated with clonazepam obtained significantly better scores for the criterion „positive global evolution“ than patients treated with diazepam.
Determining the percentage of the patients whose HAM-D scores were less than 50% compared to the time of the admission in the 2 studied groups

Thus,

In the control group, treated with diazepam, at T2 moment of the trial, 29 patients obtained a decrease of less than 50% in the HAM-D score, compared with the initial scores (T1). The remaining 21 patients of the control group achieved overall reductions greater than 50% in the HAM-D score compared with the initial scores (T1).

In the group study, only one patient achieved a decrease of less than 50% in the overall HAM-D score, while all other patients (49) have achieved reductions greater than, or equal to 50% in the overall HAM-D score, compared with the scores originally obtained. (Tabel IV)

<table>
<thead>
<tr>
<th>The percentage difference between the initial score (T1) and the final score (T2)</th>
<th>Control group</th>
<th>Study group</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50%</td>
<td>29 (58%)</td>
<td>1 (2%)</td>
<td>30</td>
</tr>
<tr>
<td>≥50%</td>
<td>21 (42%)</td>
<td>49 (98%)</td>
<td>70</td>
</tr>
<tr>
<td>Total</td>
<td>50</td>
<td>50</td>
<td>100</td>
</tr>
</tbody>
</table>

Tabel IV

Item analysis

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Item name</th>
<th>Results obtained from comparing the two groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Depressed mood</td>
<td>chi-square Pearson's test p&gt;0.50</td>
</tr>
<tr>
<td>2</td>
<td>Feelings of guilt</td>
<td>chi-square Pearson's test p=0.005</td>
</tr>
<tr>
<td>3</td>
<td>Suicide</td>
<td>chi-square Pearson's test p=0.010</td>
</tr>
<tr>
<td>4</td>
<td>Insomnia: early in the night</td>
<td>chi-square Pearson's test p&lt;0.025</td>
</tr>
<tr>
<td>5</td>
<td>Insomnia: middle of the night</td>
<td>chi-square Pearson's test p&lt;0.001</td>
</tr>
<tr>
<td>6</td>
<td>Insomnia: early hours in the morning</td>
<td>chi-square Pearson's test p&gt;0.50</td>
</tr>
<tr>
<td>7</td>
<td>Work and activities</td>
<td>chi-square Pearson's test p&gt;0.25</td>
</tr>
<tr>
<td>8</td>
<td>Retardation</td>
<td>chi-square Pearson's test p&gt;0.25</td>
</tr>
<tr>
<td>9</td>
<td>Agitation</td>
<td>chi-square Pearson's test p=0.01</td>
</tr>
<tr>
<td>10</td>
<td>Anxiety psychic</td>
<td>chi-square Pearson's test p&lt;0.001</td>
</tr>
<tr>
<td>11</td>
<td>Anxiety somatic</td>
<td>chi-square Pearson's test p&lt;0.001</td>
</tr>
<tr>
<td>12</td>
<td>Somatic symptoms gastro-intestinal</td>
<td>chi-square Pearson's test p=0.10</td>
</tr>
<tr>
<td>13</td>
<td>General somatic symptoms</td>
<td>chi-square Pearson's test p&gt;0.25</td>
</tr>
<tr>
<td>14</td>
<td>Genital symptoms</td>
<td>chi-square Pearson's test p&gt;0.50</td>
</tr>
<tr>
<td>15</td>
<td>Hypochondriasis</td>
<td>chi-square Pearson's test p&gt;0.05</td>
</tr>
<tr>
<td>16</td>
<td>Loss of weight</td>
<td>chi-square Pearson's test p&gt;0.10</td>
</tr>
<tr>
<td>17</td>
<td>Insight</td>
<td>chi-square Pearson's test p&gt;0.50</td>
</tr>
<tr>
<td>Global score</td>
<td>Student’s t-test - p&lt;0.001; chi-square Pearson’s test p&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

Tabel V

Analysis of the 17 items of the Hamilton scale at 14 days showed that some items (feelings of guilt, suicide, insomnia: early in the night, insomnia: middle of the night, agitation, anxiety psychic, anxiety somatic) showed significant differences between the two groups compared with other items (depressed mood, insomnia: early hours in the morning, work and activities, retardation, somatic symptoms gastrointestinal, general somatic symptoms, genital symptoms, hypochondriasis, loss of weight, insight) which have similar variations between the two groups after 14 days of treatment.

Discussion

Patients in both groups had improved during the 14 days of treatment. Mean CGI severity score was 2.96 (compared to 5.52 at admission) in the study group and 3.38 (compared to 5.54 at admission) in the control group. CGI scores after 14 days indicate that both groups of patients had CGI severity corresponding to the status of „slightly ill” to „moderately ill”. This was expected because both groups received combined therapy recommended by currently existing guidelines regarding the treatment of depressive episode of the recurrent depressive disorder. (13) (14) (15).
After 14 days, in terms of CGI improvement score, 76% of the study group patients were „very much improved” compared to only 38% of the control group patients. This can be explained by a higher therapeutic efficiency of clonazepam than diazepam in combination with paroxetine in improving depressive symptoms.

According to studies in the literature on the effectiveness of different drugs or combinations of drugs used in treating depressive episodes, clinical response, defined by a decrease of 50% or more of the initial score on the HAM-D scale, is assessed on a minimum of 21 days. (16) In the present study we observe that the percentage of patients who had a HAM-D score less than, or equal to 50% of the initial value at the admission is 98% in the study group compared to 42% in the control group after 14 days of treatment. Almost 100% of the patients treated with paroxetine and clonazepam had a clinical response in only 14 days, which leads to the idea that clonazepam is superior to diazepam in clinical improvement of depressive symptoms.

14 days after admission, some items showed a significantly greater reduction in the study group compared to the control group. These items are: feelings of guilt, suicide, insomnia: early in the night, insomnia: middle of the night, agitation, anxiety psychic, anxiety somatic. These items can be considered both as an expression of anxiety in depressive states as well as possible side effects of the SSRIs. (17) The significantly greater improvement accomplished by clonazepam, leads to the idea that clonazepam is superior to diazepam in reducing anxiety and insomnia symptoms of depression but also in reducing the possible side effects of SSRIs.

There were items that didn't have significant differences between the two groups in 14 days: depressed mood, insomnia: early hours in the morning, work and activities, retardation, somatic symptoms gastro-intestinal, general somatic symptoms, genital symptoms, hypochondriasis, loss of weight, insight. These items are less influenced by the selected anxiolytic agent than by the antidepressant agent.

Conclusions

This study demonstrates that clonazepam represents a first choice benzodiazepine in combination with paroxetine in the short-term treatment of depressive patients. After a period of 14 days, clonazepam induced a clinical response in 98% of patients treated with paroxetine and clonazepam, compared to the clinical response in only 42% of the patients treated with paroxetine and diazepam. The difference in clinical response between the two groups of patients can be explained by a greater influence of clonazepam than diazepam on anxiety and insomnia components of depression, but also by a possible shortening of paroxetine treatment latency realized by clonazepam.

The combination clonazepam - paroxetine represents a more effective therapeutic strategy than the combination diazepam - paroxetine in controlling anxiety and insomnia symptoms in patients with depressive episode. This observation is supported by data from literature that mentions that the association between antidepressants and some benzodiazepines lead to better compliance and more rapid improvement of depressive symptoms. (18), (19), (20). Additional beneficial effect of benzodiazepines associated with antidepressants is consistent with the theory involving GABAergic system in depression; this could be another direction for the development of new antidepressant agents.

References

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