COMPARISON OF ESCITALOPRAM A NEW SSRI WITH TCA, CLOMIPRAMINE IN MAJOR DEPRESSIVE DISORDER: A double blind study

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ABSTRACT:

Objective: To compare efficacy and side effects of a new Selective Serotonin re-uptake inhibitor antidepressant Escitalopram with Tricyclic antidepressants; Clomipramine in-patients suffering from major depressive illness.

Design: A prospective longitudinal study.

Setting: Outpatient Psychiatric Clinic at Services Hospital, Lahore.

Patients and Method: Patients between the age range of twenty to fifty five years suffering from Major depressive illness according to DSM-IV diagnostic criteria were included in the study. Ten patients receiving escitalopram were matched with ten patients from a larger sample of Clomipramine treated patients in regard to age, sex and diagnosis to create clinically comparable groups. Montgomery Asberg Depression rating scale and Demographic Performa on the formatted patterns were applied for assessing depression and other details. The raters who were from other group were blind to the patient’s medication status.

Results: The efficacy of both the drugs is comparable. The onset of action was earlier in escitalopram group. The side effects of a newer drug were much less than the older Tricyclic antidepressant NSSRI.

Conclusion: The new drug Escitalopram is better tolerated and has a rapid onset of action. The older TCA Clomipramine showed the same response if the patients tolerate side effects but it had relatively delayed onset of action.

Keywords: Depression, Escitalopram, Clomipramine, NSSRIs, TCAs

INTRODUCTION

The antidepressants are among the most widely prescribed psychotropic drugs. They are usually indispensable in the management of patients suffering from depressive and anxiety disorders. They are also useful in a number of other indications in neurotic disorders of older classification. However, the conventional Tricyclic antidepressants such as clomipramine, also have adverse effects, of which anticholinergic side effects is more serious in terms of frequency, persistence and overall impact on the well being of the patients.

The introduction of SSRI’s such as escitalopram, Paroxetine, Fluoxetine, Sertraline and Fluvoxamine have offered patients new alternatives in the psychopharmacological management of depressive disorders, although there is no complete agreement to the superiority of these drugs in terms of efficacy with the older drugs. Moreover, these drugs are expensive and all patients cannot afford them in developing countries like Pakistan.
Selective Serotonin re-uptake inhibitors have broadly replaced the older Tricyclic antidepressants type drugs as the first line treatment for depression. In addition the SSRI’s have proved efficacious for the treatment of several anxiety disorders.

Citalopram is a widely prescribed SSRI’s with an estimated exposure of more than 79 million patient. With the recent availability of large scale, Chiral separation technology, it has become possible to produce the active citalopram enantiomer. The active escitalopram the enantiomer was developed with the expectation that it would be essentially equivalent to that of citalopram at half the dose. However, in the initial clinical data as well as results from pre-clinical studies, suggested that escitalopram produced an earlier response than citalopram. Escitalopram 10-20 mg/day, achieved reduction in MADRS total scores that were significantly greater (p<0.05 to p<0.01) than placebo after 8 weeks treatment (primary end point). Analysis of the individual items on a rating scale, for example the MADRS or HAM-D, can provide a more detailed impression of the effect profile of an antidepressant. Escitalopram produced a greater numerical improvement in the score of each of the ten single items comprising the MADRS compared with placebo in the study by Wade et al, which used a fixed dose of 10 mg/day escitalopram. The score difference was statistically superior or eight out of ten items. Escitalopram also achieved numerical superiority compared with placebo for each MADRS item in a flexible-dose study.

There are studies other which show a statistically consistent difference with a quicker onset of action compared to SSRI after 3, 4 and 5 weeks of treatment in depressed patients. Percentage of patients responding to treatment on the Hamilton Depression Rating Scale following up to five weeks treatment with clomipramine 150mg/day and citalopram 40mg/day (9n+50) showed a significant difference from citalopram p<0.005. Preliminary data from the research indicates that newer SSRI’s are having least side effects as compared to the TCA’s but no specific superiority in efficacy and indications is ascertained. Number of trials also indicate that in certain disorders like anorexia nervosa patients associated with depressive illness are not responding to SSRI’s.

Tricyclic drugs are much cheaper than their counterparts and hence are affordable for majority of the patients but unfortunately because of the side effects, they are prescribed less and it is convenient for the doctor to prescribe a drug that does not need monitoring. Tricyclic antidepressants need regular monitoring and dose escalation is slow. The follow up is required on regular basis, this is good to ensure compliance, therapeutic alliance with the patients and also the safety and outcome of the patient.

The aim of the present study was to compare, in the clinical setting, the efficacy and the side effect profile of escitalopram with Clomipramine, as there has been no available data of such type in our set-up in Pakistan.

PATIENTS AND METHOD

Over a one year period, more than 100 outpatients of more than age 25 and meeting the following criteria were enrolled in a longitudinal, prospective study of the depressive illness: (1) Psychiatric diagnoses (based on DSM-IV criteria and confirmed by at-least two qualified psychiatrist) for which clomipramine antidepressant therapy was indicated; (2) Availability of reliable medical and pharmacological history from the patient, medical records, and or significant others; (3) Absence of severe physical illnesses that would preclude study assessments; (4) Willingness to participate and to give informed consent in writing. Baseline evaluation was done and clomipramine treatment was initiated. Dosage was standardized at 150mg/day. Follows up assessments were carried out on regular intervals for three months. Independent raters carried out the assessments, blind to the drug therapy as well as dosage.

Another group of ten patients meeting the
criteria of depressive illness according to DSM-IV diagnostic criteria and confirmed by two psychiatrists were selected for the escitalopram therapy that was 10mg/day. The same methodology was applied to this group as well which was previously considered for clomipramine therapy.

The data gathered from escitalopram group was compared with ten matched clomipramine treated patients on two critical factors; age and length of treatment. It was ascertained that none of the patients in both the groups had ever received an SSRI or TCA before they were enrolled in this study. The treatment was open label, determined by the patient’s physician.

Assessments were done at baseline, 1 week and 2,3,4 and 6 weeks with MADRS. Interrater reliability was evaluated at random intervals throughout the study for the MADRS, obtaining an average interclass correlation coefficient of 0.84. The raters were blind or masked to the patient’s medication status.

**Statistical analysis:**
We performed t test and chi square tests to assess difference in baseline demographic and clinical characteristics between the escitalopram and clomipramine groups; life table analysis. All the statistical tests were two tailed and the alpha level was set at p = >0.05. We used the SPSS 10 version software for analysis.

## RESULTS

Table-I compares the baseline demographic and clinical characteristics of the escitalopram and the clomipramine groups. The patients matched on age, sex and diagnosis. The two groups were also similar in terms of gender, race, education, proportion of patients who were antidepressant naïve at baseline and baseline MADRS scores. Both groups of Escitalopram and clomipramine received the median daily dose of 10 mg/day and 150mg/day respectively.

Life table analysis of the six weeks risk for any side effects for the matched groups revealed a significant higher incidence of side effects in the clomipramine group, the p value was 0.05 (Table-II). The side effects profile when statistically analyzed showed a significant difference. In the escitalopram group only two patients developed a mild allergic reaction, the drug however was continued, as the sensitivity problem was not significant to reduce or discontinue the drug. In clomipramine group all the subjects had multiple side effects, sedation, postural hypotension, sexual disturbances, palpitations, profuse sweating & increased blood pressure were the major side effects.

The comparison of weekly improvement of both the groups indicates that the improvement started earlier in escitalopram, which is also significant on statistical analysis of these groups Table-III. The improvement however, had a similar degree at the end of fourth week. Both the groups showed that the mean scores of

### Table-I: Comparison of Escitalopram and Clomipramine treated patients

<table>
<thead>
<tr>
<th>Demographic or baseline measures</th>
<th>Escitalopram Mean</th>
<th>Clomipramine Mean</th>
<th>Matched t test or chi square</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>30.2</td>
<td>30.1</td>
<td>&gt;0.5</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>75.6</td>
<td>80.3</td>
<td>&gt;0.5</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>24.4</td>
<td>19.7</td>
<td>&gt;0.5</td>
<td></td>
</tr>
<tr>
<td>Education (years)</td>
<td>9.4</td>
<td>9.2</td>
<td>&gt;0.5</td>
<td></td>
</tr>
<tr>
<td>%anticholinergic side effects</td>
<td>0.9</td>
<td>43.2</td>
<td>&lt;0.5*</td>
<td></td>
</tr>
</tbody>
</table>

### Table-II: Comparison of Escitalopram and Clomipramine

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean</th>
<th>Standard Deviation</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Escitalopram</td>
<td>1.20</td>
<td>2.57</td>
<td>4.02</td>
<td>&lt;.05*</td>
</tr>
<tr>
<td>Clomipramine</td>
<td>6.11</td>
<td>2.89</td>
<td>4.02</td>
<td>&lt;.05*</td>
</tr>
</tbody>
</table>

### Table-III: MADRS scores in two drugs

<table>
<thead>
<tr>
<th>MADRS</th>
<th>Escitalopram Mean scores</th>
<th>Clomipramine Mean scores</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 1</td>
<td>43.0</td>
<td>42.7</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Week 2</td>
<td>36.7</td>
<td>41.8</td>
<td>&lt;0.05*</td>
</tr>
<tr>
<td>Week 3</td>
<td>27.1</td>
<td>37.7</td>
<td>&lt;0.05*</td>
</tr>
<tr>
<td>Week 4</td>
<td>18.5</td>
<td>19.3</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Week 6</td>
<td>12.6</td>
<td>13.1</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>
MADRS in improvement had a similar range at the end of six weeks and this comparison is not significant (Figure 1).

**DISCUSSION**

To the best of our knowledge, this is the first study in Pakistan comparing escitalopram with clomipramine in well-matched groups of the patients using a prospective, longitudinal design. The patients were treated with antidepressants in appropriate doses and assessed prospectively at regular intervals in a standardized manner by “blind” raters. One limitation of the study was that it was not a double blind placebo controlled trial. Rather, this was as study blending with more closely resembling actual clinical practice. The mean length of follow-up was relatively short hence the results reflect the short-term benefits. Longer follow-up will help ascertain the risk and benefits in later stages of treatment and at variable doses.8

The majority of the patients enrolled in the study were anti-depressant naïve. The MADRS scores had a drop much earlier in the escitalopram group at the week two and three than clomipramine group. The mean scores were same later at six weeks; this shows a rapid onset of action in the escitalopram and improvement in the depressive symptoms. The improvement had a steady escalation in escitalopram group however, in the clomipramine if the patient tolerated the drug in the first three to four weeks then the comparison of improvement was same in the course of time.3

The clomipramine group had multiple side effects and in the escitalopram group no side effects were seen. This shows that this drug is safe in multiple cases and in a wide range of age group.

In studies of depressed inpatients the antidepressants effect of Clomipramine was found to be superior to that of SSRI’s, citalopram and Paroxetine. We also found that Clomipramine is very effective in our indoor patients.

In summary, our results suggest that the escitalopram is safer than clomipramine in terms of side effects in almost all groups of age ranges. The efficacy is almost the same of both the drugs. The clomipramine is cheaper and where economic considerations are significant, it may be the first choice of treatment.

Tricyclic antidepressant are still one of the better options that ensures the good prognosis of the various psychiatric disorders if prescribed properly and patients are monitored as well.

**REFERENCES**