A COMPARATIVE STUDY OF THE EFFICACY AND SAFETY OF MIRTAZAPINE VERSUS AMITRIPTYLINE IN THE TREATMENT OF MAJOR DEPRESSION

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ABSTRACT

A clinical trial was undertaken to evaluate the antidepressant efficacy of Newer Antidepressant Mirtazapine in the treatment of major Depression in 39 patients in an O.P.D. setup. In addition to this clinical acceptability and safety profile of Mirtazapine as compared to that of Amitriptyline was also assessed. Mirtazapine usually described as Noradrenergic and specific serotonergic Anti depressant (NaSSA). Patients aged 18-65 years who fulfilled the diagnostic criteria for a single or recurrent major Depressive disorder (as defined by DSM IV) for a minimum of 2 weeks were enrolled at our study centre. Patient assessment were conducted at screening, baseline, end of week 1, week 2, week 3, week 4, week 5 & end of week 6 for the efficacy & safety Parameters; HRSD, CGI, Adverse event follow up, BP & Pulse. Three level statistical analysis were performed on all efficacy measures including ANOVA (An Analysis of variance). The result indicates that mirtazapine is effective in the treatment of major depression at the dosages range of 15-45 mg/day and it has efficacy equivalent to that of the standard TCA Amitriptyline, albeit, with a substantially better tolerability profile.

Key Words: Mirtazapine, NaSSA, Recurrent major Depressive Disorder, Efficacy, Tolerability Profile

Mirtazapine is an antidepressant with a unique pharmacological profile, usually described as noradrenergic and specific serotonergic antidepressant (NaSSA). It is an antagonist of central α₂ auto and heteroreceptors with a marginal affinity for α₁ - adrenoreceptors. The blockade of presynaptic inhibitory α₂ autoreceptors causes an increase in the release of noradrenaline. The subsequent excitation of α₁ receptors by noradrenaline which facilitate serotonin (5-HT) cell firing, and the direct blockade by mirtazapine of inhibitory α₂ heteroreceptors located on 5-HT terminals lead to an increase in the release of serotonin. As both 5-HT₂ and 5-HT₃ receptors are directly blocked by mirtazapine, serotonin acts at the other receptor subtypes, particularly 5-HT₁a. The resulting increase in both noradrenergic and serotonergic neurotransmission systems is thought to contribute to the antidepressant activity of mirtazapine (DSM-IV,1994; Bremner,1995). Mirtazapine has little affinity for D₁ and D₂ receptors and has marginal affinity for muscarinic cholinergic receptors. Although the compound has affinity for H₁ histaminergic receptors, its sedating effects are partially counterbalanced by its action on the noradrenergic system at usual therapeutic dosages (DSM-IV 1994; Bremner,1995; Ciollors
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The aims of the present study were:
1. To evaluate the antidepressant efficacy of mirtazapine in the treatment of major Depression in Indian Population and
2. To assess the clinical acceptability and safety of mirtazapine as compared to that of amitriptyline.

MATERIAL AND METHOD

Selection of patients: Patients aged 18-65 years, who fulfilled the diagnostic criteria for a single or recurrent major depressive disorder, as defined by DSM-IV for a minimum of 2 weeks, were enrolled at our study centre. The nature of depressive disorder was moderate or severe, without mood incongruent psychotic features. Pregnant or nursing women were not included in the study; and women of child bearing age were advised to use appropriate birth control methods during the trial period. All the patients signed an informed consent prior to the inclusion in the study.

Patients with a minimum total score of 15 on 17 item Hamilton Rating Scale for Depression (HRSD) at both the initial screening and pretreatment baseline were allowed to participate in the study. Only OPD patients were recruited for the study.

Patients with a history of alcohol dependence or substance abuse in the past 2 years, demonstrated a placebo response during screening (i.e. ≥ 20% decrease in HRSD score between screening and baseline) or patients displayed acute or unstable medical problem were not allowed to enter the study. The other exclusion criteria included hypersensitivity to SSRIs, previous use of mirtazapine, history of seizures, concomitant psychotropic medication, bipolar depression, other significant organic disease, clinically significant laboratory abnormalities, or other primary psychiatric diagnosis.

Trial Design: Patients meeting the initial inclusion criteria entered a one week placebo screening phase. At the end of one week placebo washout period, patients returned for their final screening procedures. All the patients who satisfied the inclusion and exclusion criteria were then randomized to either mirtazapine or amitriptyline treatment in an open, parallel group study design.

The study drug was supplied in bottles containing seven day supply. Patients in the mirtazapine group received mirtazapine 15 mg tablets, and patients in the amitriptyline group received amitriptyline 25 mg tablets.

Target dosage ranges of 15 mg to 45 mg daily for mirtazapine and 25 mg to 150 mg for amitriptyline were predetermined, and the lowest effective dose was to be maintained throughout the 6 week portion of the study.

Clinical Laboratory Investigations: Clinical laboratory investigations (urine analysis, haematology, biochemistry, ECG and chest X-ray) were conducted at screening and at the end of the study. All required clinical laboratory investigations were done by approved professional laboratory.

Storage: During the trial, the trial drug was kept in a secured place. The trial drug was not supplied to any one except the co-investigators or deputy involved in the study. Detailed account to use of the drug with date and patient number was maintained. Unused drug was returned to the monitor after the study was completed.

Associated Treatment: Full information concerning the name, dosage, duration of the other concomitant therapy was recorded.

Adverse Event management: At each follow-up visit, the patients were asked for any possible adverse events. Any reported side effects were reported in the adverse event form. Any serious/life-threatening side effects were to be informed to the sponsors representative immediately. Details of adverse event management (Corrective therapy, change in dosage, withdrawal of drug, etc.), were clearly reported in the case record form. Also the severity of side effects were also mentioned.

The number and percentage of patients experiencing each specific event for Treatment-Emergent-Signs and Symptoms (TESS) (defined...
as experience that appeared for the first time during the study) were calculated for both treatment groups. The number and percentage of patients reporting any adverse experience were computed for both the treatment groups.

**Patient Assessment:** Patient assessments were conducted at screening, baseline, end of week 1, week 2, week 3, week 4, week 5 and end of week 6 for the efficacy and safety parameters: HRDS, CGI, adverse event follow-up, B.P. and pulse.

General physical examination and medical and psychiatric history were conducted at screening only. Clinical laboratory evaluations were conducted at screening at the end of trial.

The primary efficacy variables were the 17-item HRSD and the CGI- Improvement scale. Responder status was defined as improvement during treatment of ≥ 50% on the HRSD total scores. In the case of CGI- improvement scale, responder status was defined as improvement to a score of 1 (very much improved) or 2 (much improved). A sustained response was defined as improvement that once observed persisted until the end of trial. A final 17-item HRSD total score of 8 or less defined remission.

**Statistical Methods:** Three basic statistical analysis were performed on all efficacy measures. An analysis of variance (ANOVA) for baseline ratings to assess the equivalence of the treatment groups at the beginning of the study. ANOVA of pre-treatment versus post-treatment to examine the response produced by each drug over time. An ANOVA for each assessment to evaluate the differences between the treatment groups.

**RESULTS**

**Patient Disposition:** Forty patients who fulfilled the inclusion criteria were recruited for the trial. At the start of the drug period, the mirtazapine group consisted of 21 patients, and the amitriptyline group, 18 patients. All randomized patients who received study drug comprised the intent-to-treat safety population. There were 3 drop outs in mirtazapine group resulting in an intent-to-treat efficacy population of 18 mirtazapine treated and 18 amitriptyline treated patients.

**Demographic and Baseline Characteristics:** Physically healthy patients only were enrolled for the study. No significant differences were detected between mirtazapine and amitriptyline groups on any demographic, diagnostic or psychiatric history variables, as shown in Table-II.

**Patient Treatment:** The average daily dose range of mirtazapine at the end of the trial was 22.89±10.45 mg and for amitriptyline the same was 75.00±0.00 mg (Dose range 25-150mg).

**Primary Efficacy**

**Hamilton Rating Scale for Depression (HRSD):** Mirtazapine group showed a slightly higher level of depression than amitriptyline as measured by the HRSD total score at baseline. A summary of total score changes from baseline to end point in HRSD is given in table 1.

By the end of week 3, mirtazapine group showed a mean decrease of more than 18.19 points on the HRSD total score, while the amitriptyline group showed a mean decrease of 10.66. By the end of week-6 (endpoint) the total reductions in the HDRS score as compared to baseline were 26.20 and 14.44 for mirtazapine and amitriptyline respectively. The percentage reduction in the mean HRSD score for mirtazapine was 89.91% while that for amitriptyline was 54.04%.

**Clinical Global Improvement Scale (CGI)**

Both mirtazapine and amitriptyline groups were comparable in total CGI score at baseline. A summary of total score changes from baseline to end point in CGI is given in Table-II.

The percentage reduction in the mean CGI score for mirtazapine was 70.78% while that for amitriptyline was 43.11%.

**Tolerability:**

Treatment emergent adverse events were reported by 28.57% (N=6) of mirtazapine treated patients and 94.45% (N=17) of amitriptyline treated patients. The most common events are summarized in Table-VI. The majority of all adverse
events in both treatment groups were mild to moderate and did not lead to discontinuation of the treatment.

Two mirtazapine treated patients (9.52%) each reported headache and nausea; one (4.76%) each reported sedation, vertigo, anxiety, sleep disorder and dyspepsia. Twelve (66.67%) amitriptyline treated patients reported of dry mouth; eleven (61.11%) reported of constipation; five (27.78%) each reported of sedation, vertigo and urinary retention; two (11.11%) reported sleep disorder and impotence; one (5.56%) reported each of headache, giddiness, anxiety, blurring of vision, tremor, anorexia, postural hypotension, bitterness of mouth, abdominal pain and diarrhoea.

Overall Evaluation of tolerability by the investigator and the patient.

At the end of the study an overall assessment of tolerability was made by the investigator as well as the patient, this assessment was based on the number and severity of adverse effects and likelihood of a causal relationship, the drug could be assessed as having excellent, good, moderate or bad tolerability.

In the mirtazapine group as per the investigator's evaluation, 33.34% (N=6) of the patients who completed the treatment showed excellent tolerability and 66.67% (N=12) exhibited a good tolerability, mild adverse event was reported in 6 patients (28.57%).

In the amitriptyline group as per the investigator's evaluation about 38.88% (N=7) showed a good tolerability, 55.56% (N=10) showed a moderate tolerability and 5.56% (N=1) showed a bad tolerability mild to moderate adverse event was observed in 17 patients (94.44%).

In the overall evaluation of tolerability by the patient, 27.78% (N=5) of the patients who completed the treatment in the mirtazapine group...
stated the drug to have an excellent tolerability and 72.23% (N=13) stated it to have a good tolerability.

In the amitriptyline group 33.34% (N=6) reported a good tolerability, 61.11% (N=11) reported a moderate tolerability and 5.56% (N=1) reported a bad tolerability.

**Overall Evaluation of Efficacy by the Investigator**

For the overall assessment of the treatment acceptability and efficacy the protocol defined four categories: very good, good, moderate, unchanged or worse.

### TABLE 3

| Adverse Event       | Mirtazapine (N=21) | Amitriptyline (N=18) |
|---------------------|--------------------|----------------------|
|                     | Number  | %     | Number  | %     |
| Dry mouth           | 0       | 0     | 12      | 66.67 |
| Constipation        | 0       | 0     | 11      | 61.11 |
| Sedation            | 1       | 4.76  | 5       | 27.78 |
| Vertigo             | 1       | 4.76  | 5       | 27.78 |
| Urinary retention   | 0       | 0     | 5       | 27.78 |
| Headache            | 2       | 9.52  | 1       | 5.56  |
| Giddiness           | 0       | 0     | 1       | 5.56  |
| Anxiety             | 1       | 4.76  | 1       | 5.56  |
| Sleep disorder      | 1       | 4.76  | 2       | 11.11 |
| Dyspepsia           | 1       | 4.76  | 0       | 0     |
| Impotence           | 0       | 0     | 2       | 11.11 |
| Blurring of vision  | 0       | 0     | 1       | 5.56  |
| Tremor              | 0       | 0     | 1       | 5.56  |
| Anorexia            | 0       | 0     | 1       | 5.56  |
| Postural            | 0       | 0     | 1       | 5.56  |
| Hypotension         | 0       | 0     | 1       | 5.56  |
| Bitterness of mouth | 0       | 0     | 1       | 5.56  |
| Abdominal pain      | 0       | 0     | 1       | 5.56  |
| Diarrhoea           | 0       | 0     | 1       | 5.56  |
| Nausea              | 2       | 9.52  | 0       | 0     |

In the mirtazapine group, 66.67% (N=12) of the patients who completed the treatment showed very good response, 27.78% (N=5) showed good response and 5.56% (N=1) showed moderate response.

In the amitriptyline group 44.45% (N=5) showed good response, 50.00% (N=9) showed moderate response and 5.56% (N=1) were non responders.

**DISCUSSION**

The result of the study indicates that mirtazapine is effective in the treatment of depression at the dosage range of 15-45 mg/day. The average dose used at the end of the study was 22.89±10.45 mg/day.

In several studies mirtazapine has demonstrated efficacy equivalent to that of other commonly prescribed tricyclic antidepressants, such as amitriptyline (Hamilion, 1960; Khan, 1995; MarThla et al., 1995; Montgomery, 1995; Mullin et al., 1996). There is some evidence of faster onset of action with mirtazapine that with the selective serotonin reuptake inhibitors (SSRIs). Mirtazapine was more effective than the SSRI fluoxetine at weeks 3 and 4 of therapy and it was also more effective than paroxetine and citalopram at weeks 1 and 2, respectively, in short-term assessments (6 to 8 weeks). Mirtazapine had equivalent efficacy to the SSRIs at study endpoint. Preliminary data suggest that the drug may be effective as an augmentation or combination therapy in patients with refractory depression. Mirtazapine displays a favourable tolerability profile, with virtually no anticholinergic, antiadrenergic or serotonergic adverse events. Complaints of drowsiness, appetite increase, dry mouth and weight gain were the only adverse events reported significantly more frequently than with placebo (Zivkov & Jongh, 1996).

Large differences in efficacy between both the treatment groups were not observed, the primary treatment outcome of this study suggest that mirtazapine is equally efficacious as amitriptyline. Mirtazapine produced some initial therapeutic benefit over amitriptyline as measured by HRSD score throughout the six-week study. In the secondary efficacy variable (CGI) also mirtazapine showed benefit. Also mirtazapine showed significant clinical response at the end of three weeks of treatment. In addition to overall improvement in depressive symptoms and depressed mood, both mirtazapine and
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Amitriptyline were equally effective in reducing anxiety, sleep and vegetative disturbances associated with depression, as assessed by changes in respective HRSD factors. The response and recovery time with Mirtazapine was relatively shorter as compared to Amitriptyline.

Considering the side effect profile, mirtazapine was better tolerated than amitriptyline. Only six patients (28.57%) reported side effects. However, only one patient had to discontinue the study due to the suicidal attempt & subsequently had to switch over to ECT. In the amitriptyline group, 17 patients (94.45%) reported side effects. Dry mouth, constipation, sedation, vertigo and urinary retention were the major reported side effects with amitriptyline.

Our study demonstrated that mirtazapine has efficacy equivalent to that of the standard tricyclic drug amitriptyline in the treatment of moderately to severely depressed outpatients but with a substantially better tolerability profile.

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