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Pharmacology Section

# Comparative Evaluation of the Efficacy and Side Effects of Imipramine, Sertraline and an Ayurvedic Formulation in Patients of Depression

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## ABSTRACT

**Background:** Anti-depressant drugs which are used in the Allopathic system of medicine for the treatment of depression have side effects. Studies which have compared the efficacy and the side effects of Allopathic and Ayurvedic drugs in the treatment of depression have not been reported.

**Aims:** The aim of the present study was to compare the efficacy and the side effects of imipramine and sertraline which are the commonly prescribed drugs in the Allopathic system of medicine for the treatment of depression, with an Ayurvedic formulation.

**Settings and Design:** This study was an open labeled randomized clinical trial which involved 90 depressive patients who were divided into three groups of 30 each, for the administration of imipramine, sertraline, and an Ayurvedic formulation respectively. HAM-D scoring was done and a side effect checklist was also prepared.

**Materials and Methods:** The Ayurvedic formulation consisted of aqueous extracts of Brahmi, Shankhpuship, Malkangni and Jatamansi which were mixed in equal proportions (250 mg each). The Ayurvedic formulation was administered at a dose of 1000 mg orally in two divided doses; and imipramine and sertraline were administered at a dose of 150 mg each per day, to separate the groups of patients. The persons who abided by the inclusion and exclusion criteria were selected randomly. The effect of the treatments on the treated patients was repeatedly assessed at a continuous interval of two weeks for three months.

**Results:** The Ayurvedic formulation had negligible side effects and it was found to be effective at par with imipramine and sertraline at the end of three months.

**Conclusions:** The Ayurvedic formulation was found to be better as compared to imipramine and sertraline for the treatment of patients with mild to moderate depression, due to its lesser side effects.

**Key Words:** Depression, Imipramine, Sertraline, Brahmi, Shankhpushpi, Malkangni, Jatamansi, Clinical

## INTRODUCTION

Major depression is one of the most common psychiatric disorders. It is a chronic and a recurrent disorder [1]. According to the WHO, every year, 5.8% males and 9.5% females experience episodes of depression worldwide [2]. By 2020, it would be the second leading cause of disability, second to ischaemic heart disease [3]. It would fourth rank among all the medical illnesses in terms of its disabling impact on the world population [4]. Depression is common in people in their 20s, 30s, and 40s although depression can occur at any age. People who were born in the later part of the 20th century seemed to have higher rates of depression and suicide than those of the previous generation, in part, because of high substance abuse and the rising demands in the standards of living [5,6].

At least one in ten outpatients have major depression but most of the cases are unrecognized or inappropriately treated [7]. This imposes a large economic burden on the society, it decreases the productivity and the functional decline and it increases the mortality [8]. The appropriate therapy improves the daily functioning and the overall health of the patients with depression. Mood disorders are highly relapsing illnesses in many patients and they require long term therapy [9]. Allopathic drugs play a major role in satisfying the health care needs of the individuals. There is recurrence and relapse which are clinically relevant issues, mainly due to the side effect profiles which are faced with the allopathic drugs and their drug interactions in co-morbid conditions [10]. The choice of an anti-depressant is largely influenced by its side effect profile [11]. Although patients respond to the current drug therapy, imipramine or sertraline for the treatment of depression, these leave them with unresolved depression on long term treatment, as was depicted by earlier studies, due to a higher incidence of their side effect profiles [12].

Several drug utilization studies have documented that anti-depressants are usually taken at doses well below those which have been recommended. The possible explanation for the wide-spread under dosing is that depressed patients who are treated on an outpatient basis need to continue to work and function in the community and they cannot tolerate the adverse reactions that anti-depressants usually produce. With a low dose of anti-depressants, clinicians trade off a slightly reduced chance of improvement for a higher chance of avoiding adverse reactions, may be due to recurrence and relapse. The adverse effects increase significantly with doses [13].

A number of plants have been reported to possess anti-depressant-like activity by pre-clinical and clinical studies. Brahmi (*Bcopa monniera*) has been reported to possess an anti-depressant-like activity in rats [14] and it is a well established cognitive enhancer [15] in clinical studies. Shankhpushpi (*Convolvulus pluricaulis*) has been reported to possess an anti-depressant-like activity in mice [16] and in clinical studies [17]. Malkangni (*Celastrus paniculatus*) has been reported to possess an antistress activity in mice [18] and in

clinical studies [19]. Jatamansi (*Nardostachys jatamansi*) has been reported to possess an anti-depressant-like activity in mice [20]. But a combination of these plants has not been evaluated and compared for its effectiveness and side effects; with the commonly employed allopathic drugs (imipramine and sertarline) for the treatment of patients with depression.

Keeping in view the above facts, the present study was carried out to evaluate the efficacy, the side effect profile and the usefulness of an Ayurvedic formulation which comprised of aqueous extracts of Brahmi, Shankhpushpi, Malkangni and Jatamansi which were mixed in equal proportions [21], and to compare this with the representative drugs like tricyclic anti-depressants and selective serotonin reuptake inhibitor classes of anti-depressants, that is, imipramine and sertraline respectively.

## MATERIALS AND METHODS

### Drugs

Brahmi, Shankhpushpi, Malkangni and Jatamansi were procured from the Padmnabham Ayurved Hospital and Research Centre, Jaipur (Rajasthan). Imipramine hydrochloride (Sun Pharma) and sertraline hydrochloride (Unichem) were used as the standard anti-depressant drugs.

### Preparation of the Extract

The extract was prepared by mixing 1 part of each herb (Brahmi, Shankhpshp, Makangni, Jatamansi) with 8 times distilled water and by keeping it overnight. This mixture was heated till the extract was reduced to 1/8th of its volume. The final extract was filtered through a sieve. The filtrate was dried by using a water bath. The dried extract was formulated into tablets (vatis), each of 125 mg strength.

### Study design

This study was conducted on 90 patients with major depression, who scored 25 or more on the HAM-D scale, who were in the age group of 18-60 years, keeping in mind the following inclusion and exclusion criteria.

**Inclusion criteria:** The patients were entered into the study if the following criteria were met:

1. The subject should be able to comprehend the consent form and he/she should provide a written informed consent prior to commencing any study specific assessments and procedures.
2. Males and females should meet the age criteria at the time of the consent.
3. The patient should be diagnosed as a case of “depression” by a well qualified psychiatrist.
4. The subject must meet the DSM-IV criteria for depression.
5. The subject should have a HAM-D total score of 17 at both the screening and the baseline visits.

**Exclusion criteria:** The subjects were not enrolled in the study if the following criteria were met:

1. Subjects with a history of manic illness or schizophrenia, any other major psychotic disorders or dementia homicidal or suicidal patients.
2. Anything that suggests unresponsiveness to pharmacotherapy or non-compliance with the protocol (antisocial or borderline personality disorder).
3. The patient does not satisfy the scoring criteria for major depression.
4. The subject’s depression is due to some medication or chronic debilitation illness. (hypothyroidism, Parkinson’s disease, chronic pain)
5. Subjects with a past history of seizure disorder or brain injury (traumatic or disease related), any condition that predisposes to seizures, medications that lower the seizure threshold,; subjects undergoing alcohol withdrawal or a sedative or those who suffer from a cardiac problem,
6. Subjects with disorders that interfere with the action, absorption, distribution and metabolism or excretion of the treatment drug.
7. Any medical condition that interferes with the accurate assessment of the safety or efficacy of the drugs which are under study.
8. A medically significant history of any adverse effects of the drug which was being used or with its closely related compound.
9. Subjects on any other medication that has the potential to interact with the drugs under study e.g. benzodiazepines, other sedatives or hypnotics and other psycho-active medicines, including psychoactive herbal treatment and nutrition supplements.
10. Subjects with any kind of cardiac aliment e.g. coronary artery disease, congestive heart failure, hypertension; chronic alcoholics and patients with a suicidal tendency or substance abuse or dependence,
11. Subjects with a systolic blood pressure of > 150mm of Hg or a diastolic blood pressure of > 95mm of Hg at either the screening visit or the baseline visit,
12. The subjects should not be participating in any other clinical trial in which they were or would be exposed to an investigational drug or non-investigational drug or device for studies which were related or unrelated to the present illness.
13. The subject is non-compliant with the study visit schedule or with the study procedures e.g. illiteracy, planned vacation, planned hospitalizations during the course of the study, etc.

The patients who were randomly assigned to a 12 week trial with the imipramine group received a dose of 75-150 mg/day, those in the sertraline group received a dose of 50-150 mg/day and the third group was the group that were given an Ayurvedic formulation in the dose of 500 mg twice a day.

### Recruitment of the Patients

The present study was approved by the ethics committee of SMS Medical College, Jaipur, vide letter number No. 4/MC/EC/JPR/2005. The patients were classified according to their demographic profiles (age and gender, marital status, occupation, education, religion, type of family and domicile). They were put on treatment by any of the three drugs (imipramine, sertraline and the Ayurvedic formulation) after they were diagnosed to have a major depressive disorder and after qualifying for the inclusion and exclusion criteria. They were followed up for a period of three months. The follow up of these patients was done on after every week for the first two weeks and in the 4th, 6th, 8th, 10th and 12th week thereafter. In the follow up period, the patients were re-examined for improvement in their signs and symptoms, as was mentioned in the case report form. The patients did not receive any other drug for the management of depression during the whole study period. Any side effect which was experienced by the patient

during the treatment period was recorded. On the unlikely event of a serious adverse effect, the treatment was stopped and the necessary corrective measures were taken.

The patients were screened for their HAM-D scores and a side effect checklist was filled. The HAM-D scores and the side effects which were presented were recorded on each visit after examining the patient. The patients' conditions at the end of the treatment were compared to their conditions at the baseline level on the HAM-D score.

### Statistical Analysis

The values were expressed as mean ± S.D. The data was analyzed by one-way ANOVA, followed by Dunnett's post hoc test. A P value of <0.05 was considered as statistically significant.

## RESULTS

### Demographic Profile

1. The gender and ages of all the groups have been shown in [Table/Fig-1]. All the groups included adults who were between 18 to 16 years of age. The different age groups were treated with different treatments (imipramine, sertraline and the Ayurvedic formulation). A total of 30 patients were administered the drug in each group. The mean age of the patients in each of the drug treated groups has been shown in [Table/Fig-2].
2. The marital status of the subjects in each group of the treatment has been depicted, and there was no difference between the three groups (imipramine, sertraline and the Ayurvedic formulation), as regards their marital status [Table/Fig-3].
3. The occupation of all the 30 patients in each treatment group (Imipramine, Sertraline or the Ayurvedic formulation) has been presented in [Table/Fig-4].
4. The educational status of all the 30 subjects for each treatment group (Imipramine, Sertraline or the Ayurvedic formulation) has been presented in [Table/Fig-5]. When the educational status of the subjects who were included in the three treatment groups were compared, it was evident from the table that the three groups had a similar distribution pattern; however, there is a tendency among the patients with a higher educational status to take the Ayurvedic treatment.
5. The religion of the patients in the three treated groups (Imipramine, Sertraline or the Ayurvedic formulation) has been presented in [Table/Fig-6]. It is clear from the table that the Muslims were not inclined to the Ayurvedic treatment, which can be explained by the fact that the choice of therapy in the Muslim religion is not Ayurveda but Unani (the Unani system of medicine is similar to the Ayurvedic system of medicine).
6. The type of family in the three treated groups (Imipramine, Sertraline or the Ayurvedic formulation) has been presented in [Table/Fig-7]. From this table, it is clear that approximately over 60% of the subjects belonged to nuclear families in each treatment group.
7. The distribution according to domicile of all the 30 subjects in each treatment group (Imipramine, Sertraline or the Ayurvedic formulation) has been presented in [Table/Fig-8]. Approximately 76.67% of the patients were from urban areas, who were inclined to take the Ayurvedic treatment and 60% of the patients were from the rural areas, who had an inclination towards the allopathic treatment.

**Effect of imipramine, sertraline and the Ayurvedic formulation per se on the depression scores of the patients at different visits:**

There was a significant progressive decrease in the depression scores from the 3rd visit to the 6th visit for the imipramine treated group and from the 2nd visit to the 6th visit for the sertraline and the Ayurvedic formulation treated groups; indicating the significant anti-depressant property of imipramine, sertraline and the Ayurvedic formulation *per se* in the patients [Table/Fig-9]. The more the 'q' value for the Dunnett's post hoc test was, the higher was the decrease in the depression scores of the patients. At visits 3, 4 and 5, sertaline had the highest 'q' value and so it showed the best anti-depressant activity as compared to imipramine and the Ayurvedic formulation. But at visit 6 (after 3 months), the Ayurvedic formulation has the highest 'q' value and so it showed the best anti-depressant activity as compared to imipramine and sertraline.

**Side effects which were observed for imipramine, sertraline and the Ayurvedic formulation per se in the patients:**

The most commonly reported adverse effects in the decreasing order of their incidence in the imipramine treated patients were sedation, dry mouth, tachycardia, abdominal discomfort, tremors, sexual dysfunction, weight gain, urinary retention and agitation. The most common adverse effects of sertraline in the descending order of their incidence were nausea, abdominal discomfort, dry mouth, weight gain, sexual dysfunction and tachycardia. The largest difference between imipramine and sertraline in the incidence of their side effects was the incidence of nausea in the sertraline treated patients. The incidence of the adverse events was slightly higher for the imipramine treated subjects.

The Ayurvedic formulation virtually had the least side effect profile in comparison to imipramine and sertraline. Sedation, tremors and abdominal discomfort were much less in the Ayurvedic formulation treated group as compared to the imipramine and the sertarline groups. Other side effects like dry mouth, urinary retention, weight gain, agitation, tachycardia, nausea and asexual dysfunction were not reported with respect to the Ayurvedic formulation [Table/Fig-10].

| Age group (in yrs) | Imipramine | | | Sertraline | | | Ayurvedic formulation | | |
|---|---|---|---|---|---|---|---|---|---|
| | Male | Female | Total | Male | Female | Total | Male | Female | Total |
| 20-29 | 4 (13.33) | 4 (13.33) | 8 (26.67) | 6 (20.00) | 3 (10.00) | 9 (30.00) | 5 (16.67) | 1 (3.33) | 6 (20.00) |
| 30-39 | 8 (26.67) | 3 (10.00) | 11 (36.67) | 3 (10.00) | 7 (23.33) | 10 (33.33) | 4 (13.33) | 5 (16.67) | 9 (30.00) |
| 40-49 | 2 (6.67) | 5 (16.67) | 7 (23.33) | 3 (10.00) | 3 (10.00) | 6(20.00) | 5 (16.67) | 7 (23.33) | 12 (40.00) |
| 59+ | 1 (3.33) | 3 (10.00) | 4 (13.33) | 2 (6.67) | 3 (10.00) | 5 (16.67) | 3 (10.00) | 0 (0.00) | 3 (10.00) |
| Total | 15 (50.00) | 15 (50.00) | 30 (100.00) | 14 (46.67) | 16 (53.33) | 30 (100.00) | 17 (56.67) | 13 (43.33) | 30 (100.00) |

**[Table/Fig-1]:** Distribution according to age and sex of various group subjects
Figures in brackets indicate percentage values.

| Group | No. of patients | Age (Mean ± SD) in years |
|---|---|---|
| Imipramine treated | 30 | 36.10 ± 9.71 |
| Sertraline treated | 30 | 36.33 ± 10.50 |
| Ayurvedic formulation treated | 30 | 38.67 ± 9.20 |

**[Table/Fig-2]:** Age of various drug treated patients
Figures in brackets indicate percentage values.

| Marital Status | Group | | |
|---|---|---|---|
| | Imipramine treated | Sertraline treated | Ayurvedic formulation treated |
| Married | 27 (90.00) | 26 (86.67) | 29 (96.67) |
| Unmarried | 3 (10.00) | 4 (13.33) | 1 (3.33) |
| Total | 30 (100.00) | 30 (100.00) | 30 (100.00) |

**[Table/Fig-3]:** Distribution of marital status of various group subjects
Figures in brackets indicate percentage values

| Occupation | Group | | |
|---|---|---|---|
| | Imipramine treated | Sertraline treated | Ayurvedic formulation treated |
| House wife | 3 (10.00) | 7 (23.33) | 13 (43.33) |
| Business | 3 (10.00) | 6 (20.00) | 8 (26.67) |
| Unemployed | 9 (30.00) | 8 (26.67) | 0 (0.00) |
| Laborer | 6 (20.00) | 6 (20.00) | 2 (6.67) |
| Farmer | 6 (20.00) | 1 (3.33) | 2 (6.67) |
| Service | 0 (0.00) | 0 (0.00) | 5 (16.67) |
| Professional | 2 (6.67) | 2 (6.67) | 0 (0.00) |
| Student | 1 (3.33) | 0 (0.00) | 0 (0.00) |
| Total | 30 (100.00) | 30 (100.00) | 30 (100.00) |

**[Table/Fig-4]:** Distribution of occupation of various group subjects
Figures in brackets indicate percentage values

## DISCUSSION

In the present study, imipramine, sertraline and the Ayurvedic formulation produced a significant anti-depressant effect in patients with mild to moderate depression. At the end of three months, the Ayurvedic formulation produced the highest anti-depressant activity as compared to imipramine and sertraline. Further, the Ayurvedic formulation had the least side effects. The depression was diagnosed according to the guidelines which were set by the American Psychiatric Association that followed the DSM-1V criteria [22].

| Educational status | Group | | |
|---|---|---|---|
| | Imipramine treated | Sertraline treated | Ayurvedic formulation treated |
| Middle | 12 (40.00) | 14 (46.67) | 8 (26.67) |
| Secondary | 5 (16.67) | 4 (13.33) | 0 (0.00) |
| Sr. Sec | 5 (16.67) | 7 (23.33) | 6 (20.00) |
| Graduate & above | 8 (26.67) | 5 (16.67) | 16 (53.33) |
| Total | 30 (100.00) | 30 (100.00) | 30 (100.00) |

**[Table/Fig-5]:** Distribution of educational status of various group subjects
Figures in brackets indicate percentage values

| Religion | Group | | |
|---|---|---|---|
| | Imipramine treated | Sertraline treated | Ayurvedic formulation treated |
| Hindu | 28 (93.33) | 27 (90.00) | 30 (100.00) |
| Muslim | 2 (6.67) | 3 (10.00) | 0 (0.00) |
| Total | 30 (100.00) | 30 (100.00) | 30 (100.00) |

**[Table/Fig-6]:** Distribution of religion of various group subjects
Figures in brackets indicate percentage values.

| Type of family | Group | | |
|---|---|---|---|
| | Imipramine treated | Sertraline treated | Ayurvedic formulation treated |
| Nuclear | 20 (66.67) | 18 (60.00) | 22 (73.33) |
| Nuclear Extended | 10 (33.33) | 12 (40.00) | 8 (26.67) |
| Total | 30 (100.00) | 30 (100.00) | 30 (100.00) |

**[Table/Fig-7]:** Distribution of type of family of various group subjects
Figures in brackets indicate percentage values

| Area | Group | | |
|---|---|---|---|
| | Imipramine treated | Sertraline treated | Ayurvedic formulation treated |
| Rural | 18 (60.00) | 16 (53.33) | 7 (23.33) |
| Urban | 12 (40.00) | 14 (46.67) | 23 (76.67) |
| Total | 30 (100.00) | 30 (100.00) | 30 (100.00) |

**[Table/Fig-8]:** Distribution according to domicile of various group subjects
Figures in brackets indicate percentage values

The most common problems of clinical relevance which were encountered by the physicians and the patients, ever since the first anti-depressants came to be known, until the present time, are their side effect profile and their onset of action, apart from the others that are also of importance, namely their efficacy, recurrence,

| Groups | Visit | | | | | | |
|---|---|---|---|---|---|---|---|
| | Screening | I | II | III | IV | V | VI |
| Imipramine | 27.83 ± 2.30 | 27.00 ± 2.66 | 25.90 ± 3.31 | 21.70 ± 4.18[a] (q = 5.962) | 19.37 ± 4.65[a] (q=8.228) | 17.07 ± 5.11[a] (q=10.465) | 13.67 ± 4.74[a] (q=13.772) |
| Sertraline | 25.87 ± 1.18 | 25.93 ± 1.21 | 23.93 ± 1.98[a] (q = 3.437) | 21.70 ± 1.99[a] (q= 7.388) | 19.30 ± 3.00[a] (q = 11.640) | 16.90 ± 1.18[a] (q= 15.893) | 14.23 ± 3.51[a] (q= 20.623) |
| Ayurvedic formulation | 25.33 ± 1.22 | 25.27 ± 1.00 | 23.97 ± 1.30[b] (q=2.865) | 23.20 ± 1.70[a] (q=4.487) | 21.97 ± 2.14[a] (q=7.078) | 20.43 ± 2.75[a] (q=10.322) | 14.60 ± 2.11[a] (q=22.603) |

**[Table/Fig-9]:** Effect of imipramine, sertraline and Ayurvedic formulation on mean scores of patients at various visits
n=30 in each group. Values are expressed as Mean ± S.D. Data was analyzed by one-way ANOVA followed by Dunnett post hoc test.
F(6, 203) = 55.05; p<0.0001 (Imipramine)
F(6, 203) = 128.2; p<0.0001 (Sertraline)
F(6, 203) = 124.61; p<0.0001 (Ayurvedic formulation)
a P<0.01 as compared to screening; b P<0.05 as compared to screening.

| S. No. | Side Effects | Imipramine | Sertraline | Ayurvedic formulation |
|---|---|---|---|---|
| 1 | Dry mouth | 18 (60.00) | 2 (6.67) | 0 (0.00) |
| 2 | Urinary Retention | 3 (10.00) | 0 (0.00) | 0 (0.00) |
| 3 | Weight gain | 4 (13.33) | 2 (6.67) | 0 (0.00) |
| 4 | Sedation | 20 (66.67) | 0 (0.00) | 1 (3.33) |
| 5 | Agitation | 3 (10.00) | 0 (0.00) | 0 (0.00) |
| 6 | Tremors | 5 (16.67) | 0 (0.00) | 2 (6.67) |
| 7 | Tachycardia | 12 (40.00) | 1 (3.33) | 0 (0.00) |
| 8 | Abdominal discomfort | 9 (30.00) | 3 (10.00) | 1 (3.33) |
| 9 | Nausea | 0 (0.00) | 8 (26.67) | 0 (0.00) |
| 10 | Sexual dysfunction | 4 (13.33) | 2 (6.67) | 0 (0.00) |

**[Table/Fig-10]:** Side effects observed for imipramine, sertraline and Ayurvedic formulation

n =30 in each group; figures in brackets indicate percentage values.

relapse, onset of action, co-morbidity of the mood disorders and other associated medical conditions [23-24]. While analyzing all the associated problems that have to be faced in the course of the treatment with allopathic anti-depressant drugs, alternative systems of medicine need to be explored for a better management of depression.

Imipramine, a representative drug from the tricyclic anti-depressant group and Sertraline, a representative drug from the selective serotonin reuptake inhibitor group were compared with an Ayurvedic preparation (an aqueous extract of four herbal drugs namely Brahmi, Shankhpushpi, Malkangni and Jatamansi which were mixed in equal proportions). In the present study, the onset of action of sertraline and the Ayurvedic formulation was reported at visit 2, but it was reported only at visit 3 in the imipramine treated patients. The anti-depressant effect of the Ayurvedic formulation was the best at the end of three months. Previous studies on herbal drugs also have documented their therapeutic potentials in the treatment of mental disorders [15,17,19].

An interesting finding in our study was the side effect profile of the Ayurvedic formulation, which was virtually negligible and its anti-depressant effect was best at the end of three months, which indicated that the Ayurvedic formulation could be a promising drug for mild to moderate depression. However, in acute cases of depression with marked psychomotor retardation or suicidal tendencies, where one has to choose a drug with a rapid onset of action, sertraline, followed by imipramine becomes a better choice [23].

## CONCLUSION

The Ayurvedic formulation which was administered for 3 successive months showed the best anti-depressant effect as compared to the two allopathic drugs, namely, imipramine and sertraline, at the end of three months in patients with mild to moderate depression. The Ayurvedic formulation had negligible side effects. Further studies can be undertaken to evaluate the anti-depressant efficacy of the Ayurvedic formulation in severe cases of depression.

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