

DOUBLE BLIND PLACEBO CONTROLLED CLINICAL TRIAL EXAMINING THE EFFECTIVENESS OF ST. JOHN'S WORT (*HYPERICUM PERFORATUM*) IN MILD TO MODERATE DEPRESSION

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ABSTRACT

Objective: To compare improvement in symptoms of mild to moderate depression after treatment with *Hypericum perforatum* (St. John's Wort extract) and placebo.

Design: Double blind randomized controlled trial.

Place and duration of study: This study was conducted at the outpatient department of psychiatry at Civil Hospital, Karachi from December 2006 to November 2007.

Subjects and Methods: This study is experimental, controlled randomized trial, done at out-patient department of Civil Hospital, Karachi on 112 patients who were assigned either St. John's Wort or placebo group for treatment. Depression was measured at weekly interval using Hamilton Depression Rating Scale (HAM-D) for six consecutive weeks along with concurrent side effects.

Results: 234 out of 350 initially selected patients were randomly assigned to two different groups A & B receiving St. John's Wort and placebo respectively. The efficacy of the treatments was evaluated after 14, 28 and 42 days of the treatments through changes in HAM-D score compared to Day 0. The Mean HAM-D score on Day 0 of St. John's Wort treated and placebo treated was 18.04 (SD=3.6) and 17.50 (SD=3.1) respectively. A marked reduction in HAM-D score was evident at 14 to 42 days of the treatment in both groups, however at day 42 the reduction in HAM-D score observed with St. John's Wort group was more from that of placebo.

Conclusion: St. John's Wort extract is more effective than placebo in the treatment of mild to moderate depression and have comparable safety and tolerability profile.

Key words: Double-blind randomized controlled trial, Depression, *Hypericum perforatum* (St. John's Wort), Placebo.

INTRODUCTION

Depression a common psychiatric disorder, affects mood, thoughts, physical health, and behavior of the

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patient¹. There is high prevalence of depression in Pakistani population attributable perhaps to peculiar socioeconomic conditions²⁻⁶. Among different barriers in successful treatment of depression two main are adverse effect of standard antidepressant and their high cost⁶. An effective, low cost, well tolerated antidepressant would thus be of tremendous clinical importance.

Many treatment strategies have been tried for these problems, including complimentary and alternative medicine (CAM). St. John's Wort (botanical name: *Hypericum perforatum*) is a herbal medicine that is being used for centuries⁷ and is highest OTC (over the counter) selling medicine in many developed countries⁸. It is one of the extensively studied natural product⁹ funded by prestigious organization like Center for Complementary and Alternative Medicine (NCCAM) of United States National Institute of Health. Scientific evidence regarding the

Table 1
Cost Comparison in Pak Rs. of St. John's Wort with other standard antidepressants

Ingredient	Price Tab		6 week Treatment Cost	
	Lowest	Highest	Lowest	Highest
Imipramine 25mg	0.86	1.16	108.08	146.67
Amitriptyline 25mg	0.75	0.94	126.00	158.47
St. John's Wort 450mg	3.96	—	332.50	—
Fluoxetine 20mg	4.70	37.80	197.40	1,587.60
Citalopram 20mg	9.90	49.97	415.80	2,098.74
Paroxetine 20mg	10.50	43.24	441.00	1,816.21
Sertraline 50mg	6.00	46.02	756.00	5,798.06
Venlafaxine 50mg	18.70	27.14	1,178.1	1,709.98
Fluvoxamine 100mg	25.00	37.84	1,050.00	1,589.20

Source: druginfosys.com

effectiveness of St. John's Wort for depression is inconsistent. There are many studies that support usefulness of St. John's Wort in treating mild to moderate depression^{10,12}. A meta-analysis of 23 randomized clinical trials of St. John's Wort extract, involving 1757 patients, revealed significant response as compared to placebo (15 placebo control trial)¹³ and equal efficacy in comparison to other antidepressants (8 antidepressant control trial). There are other clinical trials which revealed similar results in support of efficacy of St. John's Wort, but the study design and methodology have often been criticized¹⁴⁻¹⁶. Wolke¹⁷ considered the criticized issues in randomized multi-center double blind parallel group trial and in his trial he found St. John's Wort (500mg) is not only as effective as Imipramine (150mg) but also significantly better tolerated. Similar results were observed by Phillip¹⁸ in double blind placebo control comparison of St. John's Wort (1050mg) with Imipramine (100mg). Similar results have also been observed in comparative studies with Fluoxetine^{19,20}, Paroxetine²¹, and Citalopram²². One common finding of all studies was better tolerability of the St. John's Wort. Trautman-Sponse²³ concluded that when account of differing dose levels, standardization and methods of evaluation are taken into account then St. John's Wort extract is efficacious and well tolerated.

Besides many studies in support of efficacy of St. John's Wort, two large studies, one sponsored by NCCAM²⁴, showed that the herb was no more effective than placebo in treating major depression of moderate severity. An analysis of the results of 37 clinical trials concluded that St. John's Wort may have only minimal beneficial effects on major depression. However, the analysis also found that St. John's Wort may benefit people with minor depression; these benefits may be similar to those from standard antidepressants. Overall, St. John's Wort appeared to produce fewer side effects

than some standard antidepressants¹⁹. The issue of compliance becomes more important in patients with mild to moderate depression, who usually tend to discontinue medication due to side effect⁷.

Keeping in mind the aforementioned facts the primary objective of the study was to evaluate the efficacy of St. John's Wort 900 mg/day in local population during the 6 weeks of acute treatment. Secondary objectives were to assess the safety and tolerability of the treatments investigated. The principal outcome measure was the change in the total score on the Hamilton Rating Scale (HAM-D) 17-item version between day 0 and end point.

SUBJECTS AND METHODS

This was a 6-week randomized, double blind placebo controlled trial comparing the efficacy of St. John's Wort extract 300 mg with placebo in patients suffering from a mild to moderate depression. The investigation was conducted at the out patient department of psychiatry at Civil Hospital, Karachi. Ethical approval was taken before the start of the study and all patients provided written informed consent.

Sample Size

112 patients with mild to moderate depression were included in the study.

Sample Selection Technique

Systemic randomization / convenience.

Inclusion Criteria

Patients of both sexes, between the ages of 18 to 65 with no associated physical disease, who gave their consent, were recruited for the study.

Exclusion criteria

Any patients with depression secondary to organic illness and atypical cases that may carry different diagnosis were not included. Patient belonging out side of Karachi were also not included because of inherent difficulty in follow-up.

Clinical assessment

Base line investigation was carried out by Blood CPs & ESR, Serum Createnin and LFT

Mild to moderate depression was assessed according to International Statistical Classification of Diseases and Related Health Problems (ICD-10, 10th Revision, Version 2003; F32.0 Mild depressive episode or F33.0 Recurrent depressive disorder, current episode mild and F32.1 Moderate depressive episode or F33.1 Recurrent depressive disorder, current episode moderate). Participants were required to have a total score between the ranges of 15-22 on 17 item Hamilton Depression Scale (HAM-D).

Investigational Treatments

Film coated tablets containing 300 mg dry extract of St. John's Wort (*Hypericum perforatum*) were used. Tablets containing placebo (a mix of maize starch and dicalcium phopate) were indistinguishable from those containing St. John's Wort extract in all aspects of their appearance. During the 6 weeks of randomized treatment all patients took 3 film coated tablets per day, one in the morning, one in the afternoon and one in the evening.

Sample Selection Procedure

All consecutive patients enrolled at out patient department of psychiatry, were screened by OPD doctors. Newly diagnosed patients of depression were selected and Hospital Anxiety & Depression (HAD) scale was applied, patients having high score on HAD scale (> 11) were referred to the researcher.

Researcher assessed these patients in detail on semi structured psychiatric interview based on Present State Examination (PSE) questioner. The detailed psychiatric history of these patients was taken on standard format and diagnosis of depression was made according to ICD-10 criteria. Hamilton Depression Scale (HAM-D) was administered on these patients to find out severity of depression. Base line investigations such as complete blood count (CPC), erythrocyte sedimentation rate (ESR), serum createnin and liver function test (LFT) were carried out on selected cases to exclude concurrent illness.

The patients included in this study were divided randomly by balloting into two identical groups (A & B) each group was prescribed medicine labeled accordingly. One of these groups received St. John's Wort extract Tablets 300mg thrice daily, while other group was given placebo. Both the researchers and the patients were blinded to the treatment being offered. Test drugs were packaged in identical containers clearly marked

“Group A” and “Group B” under the supervision of a registered pharmacist, who did not participate in allocation of test drugs to the patients. The test drugs were shipped to the department of psychiatry at Civil Hospital where they were kept with the head researcher and were released once the patients were assigned to a particular group. The code of the medicine was sealed and placed in a secure location and was opened after compiling the data.

Patients were followed up weekly for 6 weeks to assess improvement of symptoms, side effects of drug and adjustment of dosage. HAM-D was repeated on 2nd, 4th and 6th week to see improvement.

A specially designed check list was used for recording adverse effects which included nausea, dizziness, drowsiness, dryness of mouth and skin allergies, there was also space provided for recording any other adverse effects reported during the course of the treatment.

Patients were thoroughly questioned about adverse events in a general inquiry during each visit. These were recorded & concurrent illness was also dealt with.

Statistical Analysis

Statistical analysis was done to correlate different therapeutic variables (active drug and placebo) with reference to the severity of depression (according to rating scale used in this research) by using t-test.

RESULTS

In this 6-week double blind placebo controlled study the efficacy of St. John's Wort was compared to placebo in mild to moderate cases of depression. Total 234 patients out of 350 initially selected for the study were randomly assigned to two different groups A & B. Both groups were almost homogenous in terms of mean age and gender; there were more female patients than male in both groups (Table 2). Patients assigned to group 'A' received St. John's Wort 300 mg thrice daily. Patients in group 'B' received same dose of placebo. Patients in both groups were observed on weekly follow-up basis for 6 weeks. 35 patients from St. John's Wort treated and 76 patients from placebo treated did not maintain the 6 weeks follow-up and the primary reason for this premature termination of the treatment could not be traced out (Figure 1).

Efficacy

The efficacy of the treatments was evaluated after 14, 28 and 42 days of the treatments through changes in HAM-D score compared to Day 0. The Mean HAM-D score on Day 0 of St. John's Wort treated and placebo treated was 18.04 (SD =3.6) and 17.50 (SD =3.1) respectively as shown in Table 3. A marked reduction in HAM-D score was evident at 14 to 42 days of the treatment in both groups, however at day 42 the reduction in HAM-D score observed with St. John's Wort group was different from that of placebo (Figure 2). The percentage

Table 2
Base line characteristics of patients with mild to moderate depression treated with St. John's Wort (SJW) 300 mg thrice daily or placebo

Characteristics	Treatment		P - Value
	SJW (n=56) Mean (SD)	Placebo (n=56) Mean (SD)	
Age (years)	33.89 (10.884)	36.29 (12.478)	0.28
HAD Score	17.83 (4.573)	17.57 (3.996)	0.7
HAM-D Score at inclusion	18.04 (3.593)	17.50 (3.116)	0.4
Sex	% (n)	%(n)	
Male	23.2 (13)	21.4 (12)	
Female	76.8 (43)	78.6 (44)	

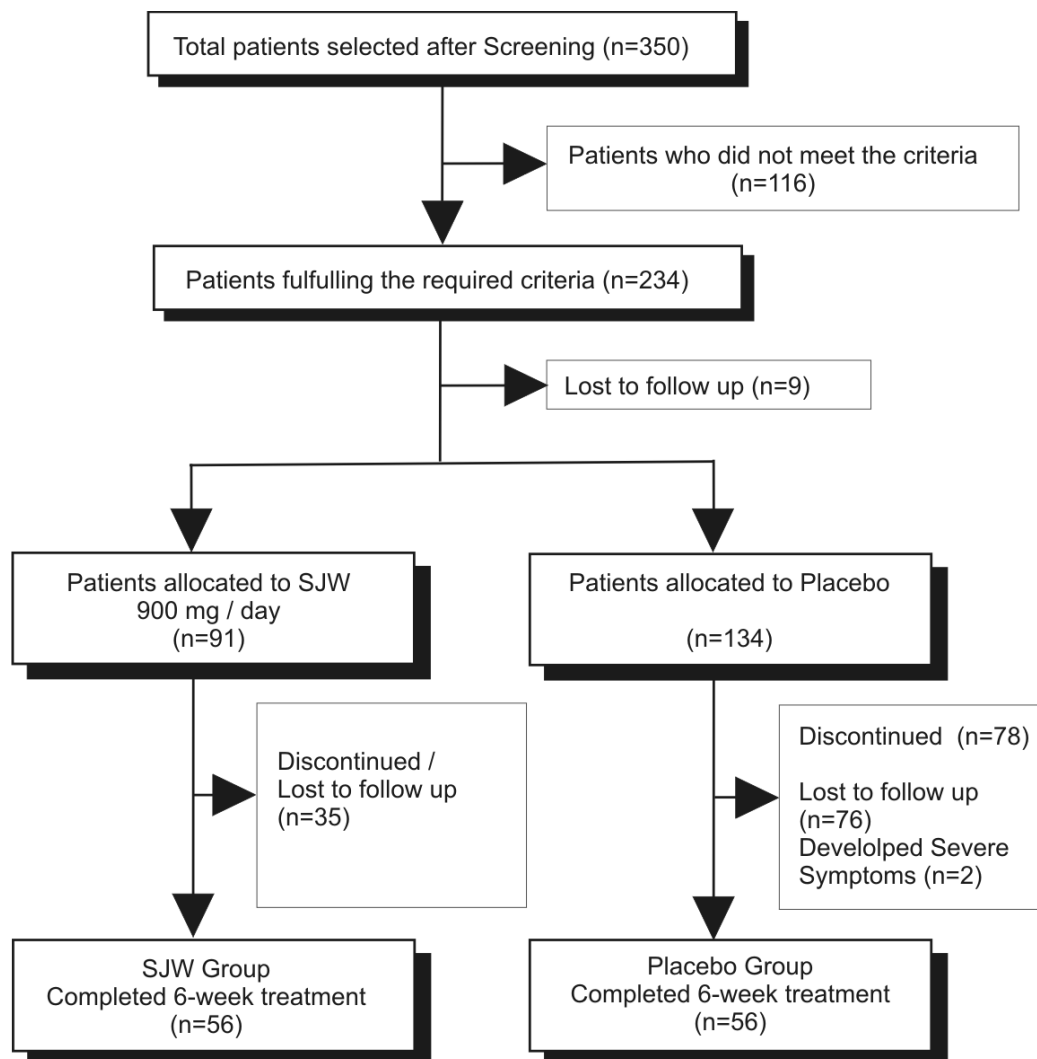


Fig. 1: Screening and follow-up compliance of the patients with mild to moderate depression treated with St. John's Wort 300 mg thrice daily or placebo.

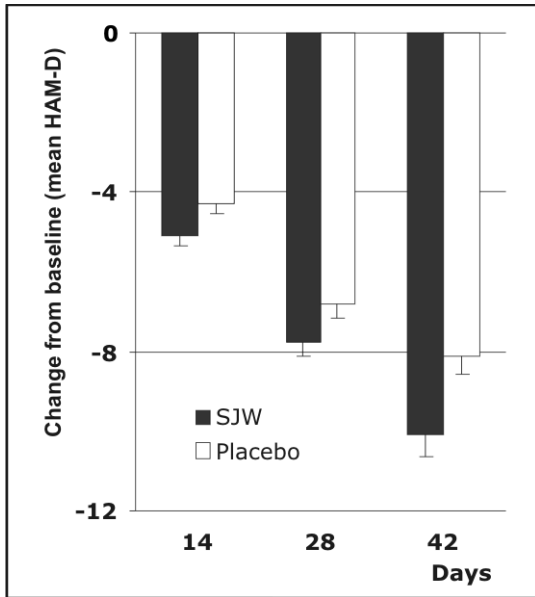


Fig. 2: Change from base line in mean HAM-D scores in patients with mild to moderate depression after 14, 28 & 42 days of treatment with SJW and Placebo.

reductions for both treatments are shown in Figure III; the data demonstrate that patients treated with St. John's Wort exhibited greater improvements as compared to placebo treated group, indicating effectiveness of St. John's Wort in the treatment of mild to moderate depression.

Safety and tolerability

A good tolerability profile was observed with both the treatments. Nausea and headache were the most common side effects reported in both groups of the patients. However dry mouth and dizziness was more frequent with St. John's Wort treatment, compared to placebo (Table 3). The incidence and severity of the ad-

Table 3

Number of patients with mild to moderate depression who experienced adverse effects during 6 weeks treatment with St. John's Wort (SJW) 300 mg thrice daily or placebo.

Adverse Effects	SJW (n=56)	Placebo (n=56)
Nausea	16 (28.5%)	8 (14.3%)
Dry mouth	8 (14.3%)	0 (0.0%)
Headache	16 (28.5%)	16 (28.5%)
Dizziness	12 (21.4%)	4 (7.1%)
Palpitations	4 (7.1%)	0 (0.0%)
Photosensitivity	4 (7.1%)	4 (7.1%)

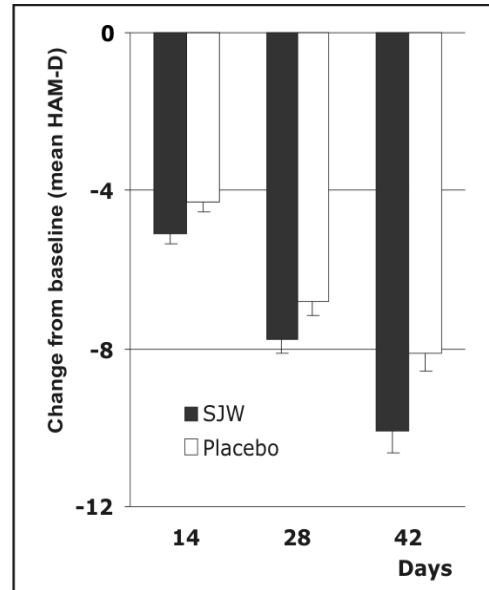


Fig.3: Percentage drop in HAM-D score in patients with mild to moderate depression after 6 weeks treatment with SJW and Placebo

verse effects observed were not to the extent that would make the patients reluctant in taking the medication. In the placebo treated group 2 patients were withdrawn prematurely because of the development of severe symptoms of depression.

DISCUSSION

Efficacy

The results of this study demonstrate the efficacy of 300 mg thrice daily of St. John's Wort as compared to placebo in patients with mild to moderate depression at the interval of 6 weeks. This finding was stable across several validated investigators. Over the first four weeks, the mean decreases in HAM-D scores were nearly the same with no statistical difference. It was about 7.7 points in St John's Wort group and 6.8 in placebo group. Over the full 6 weeks, mean decreases in HAM-D scores were approximately 10 points for St John's Wort group and 8 points for the placebo group; the difference of 2 points was significant.

On a descriptive level, the antidepressant effects of St. John's Wort and placebo were comparable during the first four weeks of treatment, indicating that without a placebo run in phase, factors other than the pharmacological action of St. John's Wort extract may have initially contributed to the observed relief of depressive symptoms. However, the majority of patients randomized to placebo showed only limited or no improvement between day 28 and day 42.

The drop in mean HAM-D scores after 42 days treatment with St. John's Wort (900mg/day) in our study

were comparable with results reported by Kasper et al²⁵ with St. John's Wort (1200mg/day) for same duration of treatment. However there was a minor difference in the placebo group of our and the Kasper study. The drop in mean HAM-D scores in the placebo group in the present study was slightly higher than reported by Kasper for placebo group.

Safety and tolerability

For both treatment-groups, the highest frequencies of adverse events were observed during the first two weeks of acute treatment. Because this effect was observed in both treatment groups, it is likely to have been related to a non-specific, non-drug-related effect based on the patients' and investigators' expectations or to the patients' initial severity of depression (known to increase vulnerability to various kinds of adverse experiences). During the 6-week acute treatment, the St. John's Wort group showed a relatively higher frequency of adverse events than the placebo group. Potentially attributable adverse events included gastrointestinal disorders, headache, dizziness, dry mouth, and photosensitivity reactions (Table-3). Number of patients complaining of headache was identical (28.5%) in both groups this appears more because of the symptoms of depression than due to adverse effect of active drug. In the Kasper²⁵ study St. John's Wort extract had no meaningful influence on laboratory measures, physical findings, vital signs or ECG parameters.

CONCLUSION

Although larger sample size is needed, the findings from our current study demonstrate that both treatments alleviated the symptoms of mild to moderate depression but St. John's Wort 900 mg was more effective than placebo in the treatment of mild to moderate depression. Both treatments showed comparable safety and tolerability profile, however there was a slightly higher incidence of side effects in St. John's Wort group compare to placebo.

Given the low cost of St. John's Wort extract it may have a role in treatment of patients with mild to moderate depression who cannot afford standard antidepressants or who cannot tolerate standard antidepressants due to adverse effects.

DECLARATION OF INTERESTS

The study was funded by Medics Laboratories including provision of Deprisin[®] Tablets (St. John's Wort) 300 mg and manufacturing of placebo with similar shape and color.

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