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Efficacy of whole system ayurveda management protocol in major depressive disorder- A randomized controlled clinical trial

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ABSTRACT

Background: Major Depressive Disorder (MDD) is one of the common depressive disorder. MDD has high co-morbidity and has greater implications on quality of life. Whole system Ayurveda management protocol *(WSAP)* is explored for it's possible role in management of MDD.
Objective: To evaluate the efficacy of Whole system Ayurveda management protocol on Major Depressive Disorder.
Material and Methods: Study was a randomized controlled trial. Total 50 patients of MDD meeting the DSM V criteria, age group 20–70 years of either sex participated in the study. They were randomly divided into two groups, control group received Escitalopram 10 mg twice a day and Ayurveda group was on WSAP. Interventions were for 60 days. Assessments were done through various clinical parameters like Hamilton Depression Rating Scale (HDRS), Hamilton Anxiety Rating Scale (HARS), Brief psychiatric rating scale (BPRS), Pittsburgh Sleep Quality Index (PSQI), WHO Quality of Life- BREF (WHOQOL-BREF), Clinical Global Improvement scale (CGI), UKU Side effect scale. Assessments during intervention was on every 15th day.
Results: Study showed that Ayurveda group produced significant outcome improvement compared to control group in HDRS ($p = 0.01$), HARS ($p = 0.03$), PSQI ($p = 0.03$), WHOQOL-Bref ($p < 0.001$) and UKU side effect scale ($p = 0.02$). Both the group showed improvements in all the parameters except in WHOQOL-Bref where Ayurveda group only showed improvements ($p < 0.001$). Effect size showed large effect in WHOQOL-Bref. Mild side effects were reported in control group and none in Ayurveda group.
Conclusion: WSAP was effective in management of MDD and had better side effect profile. Further studies needed.

1. Introduction

Depression is one of the most common disorders in primary care as well as in community settings that is of public health concern. Incidence has increased by around 50% in the last 30 years and around 264 million individuals of all ages are affected currently [1]. According to WHO, 5% of adults suffer from depression globally [2]. MDD will create greater societal and economic burden globally by 2030 [3]. A large Indian study showed that the life time and current prevalence of depressive disorder in India was 5.25% and 2.68% respectively [4]. Treatment gap for depression was 79.1% and 23 million adults are affected at any given time. Depression is more common in women of age group between 40 to 49 years, lower economic background, divorced, widows, separated, urban areas with population more than 1 million. More than 66% of sufferers reported disability in work place (67.3%), social (68.6%), family life (70.2%) and difficulty in daily living was in 20.9% [4]. A south Indian study reported that the overall prevalence of depression as 15.1% [5].

Depression has multi risk factors like biological, psychological, social, cultural and economic etc. Pathology includes disruption in hypothalamus pituitary axis, increase in cortisol, oxidative stress, low grade systemic inflammation etc. Globalisation and westernisation have altered the lifestyle in a great way. Life style changes include more sedentary, consumption of poor diet, sleep/wake cycle pressures and

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sleep deficiency, substance misuse, psychosocial pressures like increased competition, time pressures, social isolation, decreased intimacy with family and friends, stress etc, may lead to depression and life style disorders like obesity. Life stye disturbances can increase in proinflammatory cytokines, interferon gamma, reactive oxygen and nitrogen species, low levels of antioxidants, may damage mitochondria and mitochondrial DNA, this results in neurodegeneration and decreased neurogenesis [6]. Poor quality of diet and diet patterns are associated with depression [7].

MDD has heterogeneity and is subdivided into melancholic and atypical depression. Melancholic patients have decreased non reactivity of mood to circumstances, decreased appetite, loss of weight, insomnia and early morning awakenings, diurnal variation is worse in the morning and improves with the day. Plasma cortisol norepinephrine are elevated. They have severe depression along with poor outcomes and respond better to Electro convulsive therapy, tricyclic antidepressants. Atypical patients have significant mood reactivity, fatigue, anxiety, increased appetite and increased weight, hypersomnia. Diurnal variation is best in the morning and deteriorates with the day. It is associated with decreased sympathetic activity, early age of onset and chronic course of disease, less severe depression, higher comorbidity with anxiety and substance abuse, higher prevalence in female [8].

Pharmacology and psychological treatments are first line managements strategies. Conventional management of MDD is through Tricyclic antidepressants and serotonin reuptake inhibitors (SSRIs). Other therapies include cognitive behaviour therapy, trans cranial magnetic stimulation (TMS). A first-line course of antidepressant treatment is not enough to bring about remission in 68% of cases, and between 15 and 30% of depressive episodes do not respond to appropriate trials of two antidepressants [9]. From 95.5% at one month to 52.6% at two months to 18.9% at six months, treatment adherence dropped sharply [10]. Treatment adherence is affected due to the delayed onset of effectiveness and side effects. Residual symptoms causes increased functional derangements, suffering, morbidity and mortality.

Patients are increasingly using Complementary and Alternative Medicine (CAM) therapies in depression. A study reported 40% patients used CAM therapies but most did not report it to their family physicians [11]. Review study on Complementary and alternative medicine on MDD showed St John's wort and regular exercise as effective interventions [12]. Ayurveda science advocates whole system approach in disease management, as it integrates components of physical, mental, emotional, psychosocial and patient's preferences in diagnostic and therapeutic applications. Ayurveda management of depression through whole system includes medications, counselling, working on emotions, thought process, cognitions, code of conduct, life style management through daily regimen, spiritual practises like mantra/music, yoga etc. These includes principles of environmental, behavioural and psychological components. They are exercise, recreation, relaxation and meditative techniques, sleep, environment, socialization, cessation of habits like alcohol, tobacco etc. These also form the components of life style medicine [13] and can play a beneficial role. Exercise has shown to be an effective intervention in depression [14]. High stress levels can cause depression [15]. Hence, this study was planned to evaluate the effect of whole system Ayurveda approach (WSAP) in MDD.

2. Materials and methods

Patients from the outpatient department of KLEU Shri B M K Ayurveda Hospital, Belagavi, Karnataka India were enrolled in the study. Reporting of study is as per the CONSORT statement guidelines [16].

2.1. Patients

Patients (n = 50) diagnosed as Major Depressive Disorder as per DSM V criteria [17] were enrolled from outpatient department of KLEU Shri B M K Ayurveda Hospital, Belagavi.

Patients of 20–70 yrs of either sex were enrolled in the study. Patients with other Axis I disorders like schizophrenia, psychosis, anxiety disorders etc were excluded. Patients with Axis II disorder like personality disorders, depression with psychotic symptoms, use of psychotropic's therapy/drugs within the past period of 4 weeks, with other comorbid medical complications like hypertension, diabetes mellitus, pregnant or lactating women were excluded in the study. Patients with evidence of active suicidal ideation were excluded. Suicidal assessment of ideation, plan, behavior, intent were done and was screened through suicide risk screening tool (Suicide Risk Assessment Guide [18]).

2.1.1. Screening methods

Study brochures, information contents were displayed in the reception, psychiatry unit and other areas of the hospital. Soft copy of the same were circulated in the social media platforms. Information was shared during both in house and out house camps. AP and BRT communicated to all the information seekers in person. Patients meeting the diagnostic criteria (n = 62) of MDD (DSM V) were screened to enroll 50 patients. 50 patients participated in the study. A thorough clinical assessments were conducted and data was recorded in case record form.

2.2. Research design

Study design is a randomized controlled parallel group study. Randomization was through block design, 25 blocks of two were done. The patient allocation in control and test groups was in the 1:1 ratio. Random sequence generation was through an online software. Sequence generation and sealing was done by Principal Investigator. Sealed opaque envelopes were used for allocation concealment and it was blinded to the investigators. Separate research team carried out randomization, distribution and administration of study related materials. Adherence was assessed through the adherence charts and through unused medications. Assessment through assessment parameters was carried out by investigators on every 15th day of interventions.

Sample size was calculated from a previous study [19]. Primary outcome of the current study was used to calculate sample size. Total sample was 50, 25 in each arm with 5 % alpha error (two tailed) and 85 % power and estimated effect size of d = 0.84.

2.2.1. Intervention

Recruited patients were randomly divided into two interventional groups. Control group (n = 25) received Escitalopram 10 mg bd with water and Ayurveda group (n = 25) received whole system Ayurveda management protocol (WSAP). Escitalopram was procured from Rich field (India) I Pharmaceuticals Pvt Ltd. Batch No 9046 TNI.

2.2.2. Whole system Ayurveda management protocol-

MDD protocol was planned by PI consisting of diagnostic and therapeutic protocol for depression. (PI has already prepared a protocol on Irritable bowel syndrome and published the study). These protocol are in sync with principles and practices in Ayurveda and are commonly used by most of the Ayurveda clinicians. However Ayurveda practices lack protocol documentation, preparation and testing. Diagnostic protocol was subdivided into dosha and srotas. The protocol based practice was developed and was being used by the PI in Psychiatric OPD of the institute since 2015.

2.2.3. These protocols were fine tuned before initiating the study

Literature search of MDD was made and all manifestations were compiled. MDD publications DSM V Criteria were considered. Thesis and publications related to *vishada* and *kaphaja unmada* were reviewed. *vishada* and *kaphaja unmada* manifestations were compiled. *Kaphaja unmada* manifestations occurring in MDD were screened. MDD manifestations were compiled and Ayurved equivalent terms were considered.

2.2.4. Whole system Ayurveda diagnostic protocol –

These manifestations were subclassified on the basis of d*osha* and *srotas.* Ayurveda assessment of MDD can be closely related to *Kaphaja Unmada* in severe depressive cases and in less severe depressive cases to vishada. *Kaphaja Unmada* has predominant kaphaja manifestations and vishada has more of *Vata kaphaja* manifestations [20]. Hence Ayurveda assessments of MDD revealed to form two sub clusters. Hence diagnostic protocol has two subcomponents *Kapha*, *Tama pradhana* (KT)and *Vata Raja* dosha along with *Kapha Tama dosha* (VRKT). Developed diagnostic protocol was subjected to review by physicians handling depression (MDD, DSM V criteria) in their clinical practise (with minimum of 5 years' experience). Each of the 8 physicians (Seven ayurveda physicians and 1 psychiatrist) were presented with the 35 manifestations and was open to additions/modifications. Asked them to rate (1–5, minimum to maximum) on relevancy to MDD. Relevancy of 4 and above were considered and manifestations considered were 31. Eight physicians concurred with 31 manifestations and 2 manifestations were concurred by 5 physicians, another 2 were concurred by 3 physicians. Hence 31 manifestations were considered. Seven ayurveda physicians were subjected to relevancy of diagnostic protocol subcomponents (*dosha, srotas*), (1–5, minimum to maximum). All physicians concurred with the *dosha* and *srotas* subcomponents classification.

Manifestations under dosha and srotas subcomponents (1–5, minimum to maximum) were presented to 7 physicians. Relevancy of 4 and above were considered. 29 manifestations along with their dosha and srotas subclassifications were accepted by all, 2 manifestations were accepted by 4 physicians. Hence 29 manifestations along with their dosha and srotas subclassifications were considered in the final diagnostic protocol. *Srotas* (systems) involved were *manovaha* (channels of mind), *rasavaha* (channels of body fluid), *mamsavaha* (channels of muscles), *medovaha* (channels of fat), *shukravaha* (reproductive system), *purishavaha* (excretory system), *annavaha* (gastrointestinal system), *pranavaha* (respiratory system). Melancholic presentations have resemblance to KT and atypical depression to VRKT subgroups of WSAP.

2.2.5. Whole system Ayurveda therapeutic protocol –

PI formulated therapeutic protocol on the basis of accepted diagnostic protocol. Subclassified as dosha (2 classification), Srotas (8), Sub classification of srotas (12), therapy as drugs (64), *satwawajaya* (counselling), Music/Mantra, Exercise, Yoga and diavivyapashraya. *Manavaha Srotas* (24 drugs), *nidra* (4 drugs), *pranavaha* (4 drugs), *rasavaha* (7 drugs), *raktavaha* (6 drugs), *Mamsavaha* (6 drugs), *medavaha* (4 drugs), *purishvaha* (10 drugs), *Annavaha* (4 drugs), *Shukravaha* (6 drugs). Total number of drugs were 62 and their usage was in protocol was in 75 instances. 11 drugs had multiple applications in protocol. Drugs were based on the clinical experience of PI, frequent usage, availability in the pharmacy unit of the institute.

Seven physicians were subjected to relevancy of therapeutic protocol (1–5, minimum to maximum). Components *dosha* (2 classification), *srotas* (8), Sub classification of *srotas* (12), therapy as drugs (62), *satwawajaya* (counselling), Music/Mantra, Exercise, Yoga and *diavivyapashraya* were scored for relevancy. There was acceptance dosha (2 classification), Srotas (8), Sub classification of srotas (12), therapy as drugs (68), *satwawajaya* (counselling), Music/Mantra, Exercise, Yoga and *diavivyapashraya.* 64 drugs were accepted by everyone and hence 64 drugs were considered remaining 4 drugs were accepted by 4 physicians. Dosage, duration, integration of the protocol subcomponents were discussed. Finalised protocol was subjected to departmental and institutional presentations. Inputs, suggestions, comments were noted. Dosage, duration, integration of the protocol were discussed. All the drugs used were from classical text books of ayurveda. Drugs were procured from GMP certified Ayurveda pharma companies. Dosage and vehicle used were as per the classical texts of ayurveda. However Satwawajaya, music/mantra, exercise and yoga was advised in all the patients. Patients with severe depression (HDRS> 24) additional counselling sessions were conducted. (Annexure 1).

2.2.6. Pilot testing of the protocol-

Pilot testing of the protocol was assessed in 6 patients of MDD by PI. Feasibility and applicability of diagnostic and therapeutic protocol were assessed and were found to be satisfactory.

Intervention duration was 60 days and follow up assessments were made on every 15th day during the intervention. All participants were detailed with nature and design of the study. Informed consent was obtained. The study was approved by the Institutional Ethics Committee (Protocol Id BMK/18/PG/KC/04, KLEU BMK Ayurveda Mahavidyalaya Belagavi, Date of Approval June 03, 2019. CTRI Registration Number CTRI/2019/06/019,892). Data collection was from February 2020 to May 2021. Patients were informed to adhere to the intervention protocol and contact investigators for any issues. Patients were informed to report any existing manifestations causing considerable distress or any new manifestations. These were evaluated for the possible adverse events. Contingency measures for in place like management of adverse effects at out patient or inpatient levels in the hospital. Suicidal assessment of ideation, plan, behavior, intent were done and was screened through suicide risk screening tool. (Suicide Risk Assessment Guide [18]).

2.3. Criteria for assessment

2.3.1. Primary outcome measure

Hamilton Depression Rating Scale (HDRS) [21].

2.3.2. Secondary outcome measure

The secondary outcomes measures were Hamilton Anxiety Rating Scale (HARS) [22], BPRS-Brief Psychiatric Rating Scale [23], Pittsburgh Sleep Quality Index (PSQI) [24], WHO Quality of Life- BREF (WHO-QOL-BREF) [25], Clinical Global Improvement scale (CGI) [subcomponents include severity (CGI-S), efficacy index (CGI-EI), Global Improvement (CGI-GI)] [26], Udvalg for Kliniske Undersogelser (UKU) side effect scale [27].

Assessments through the clinical assessment scales were conducted at every 15th day that includes baseline, 15th, 30th, 45th and 60th day. Outcome of the interventions were assessed as remission (HDRS<7), responders (>50 % improvement, but not achieved remission), partial responders (25–49 % improvements, symptoms negatively effecting their functioning), non responders (<25 % improvement) on the basis of HDRS [28].

2.4. Statistical methods

Statistical analysis was conducted through SPSS Version 25.0(IBM Corporation, Chicago, Illinois, United States). Between groups homogeneity was assessed through $\chi 2$ test. Two way repeated measure Analysis of Variance (rmANOVA) with Bonferroni post-hoc test was used to compare the groups across different time points. Within group comparison at two time points was with paired T test. Group comparison at a time point was with independent sample *t*-test. Treatment outcome was assessed by noting the differences between pre with post treatment. Partial Eta Square method was used for calculating effect size, treatment effect was through the outcome from baseline to 60th day of intervention. Interpretation of effect size measures was: 0–0.2 minimal, 0.2–0.5 as small, 0.5–0.8 as medium, and above 0.8 as large effect size [29]. Values reported are as mean ± standard deviation. Statistical significance was set at $p < 0.05$.

3. Results

Number of patients recruited in the study were 50. Two patients from Control group and a patient from Ayurveda group dropped out of the study. Drop out was due to translocation to other town in a patient and unable to visit because of personal commitments in 2 patients. (Fig. 1).

The base line features like mean age ($p = 0.85$), gender (0.56), socio-

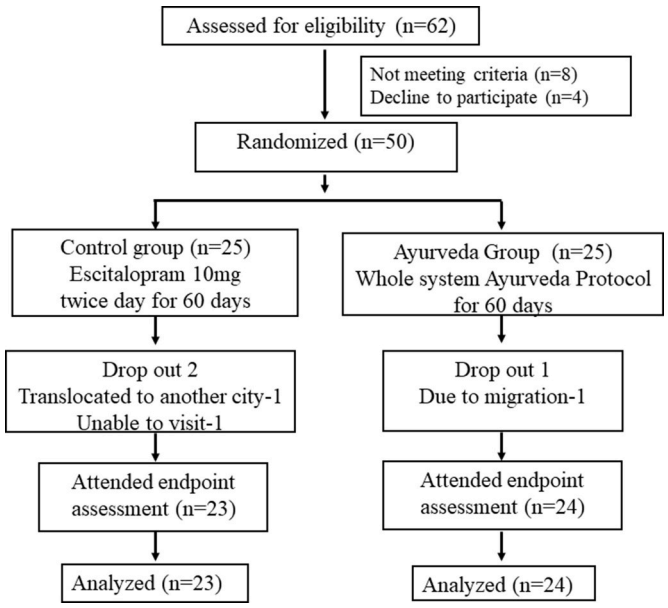

Fig. 1. Subject flow chart through the study.

economic status (0.30), educational status (0.75), marital status (p = 0.83), *Agni* status (p = 0.21), prakirti (p = 0.07), weight (p = 0.58), BMI (p = 0.83), duration of illness (p = 0.75) were comparable between the groups (Table 1) (Fig. 1). Base line clinical features like HDRS (p = 0.84), HARS (p = 0.99), BPRS (p = 0.07), PSQI (p = 0.71), WHOQOL-Bref (p = 0.18). CGI severity (p = 0.25) were comparable between the groups (Table 2).

3.1. Primary outcome

Assessments on HDRS showed that outcomes in Ayurveda group was better compared to control group (p = 0.01). Both the groups showed significant improvement in HDRS at all the four time points. In control group, improvements were at 15th day (p = 0.002), 30th, 45th and 60th day (p < 0.001). In Ayurveda group, improvements were at 15th day, 30th, 45th and 60th day (p < 0.001). Effect size was moderate (Table 3).

3.2. Secondary outcomes

In parameters of HARS (p = 0.03), PSQI (p = 0.03) and WHOQOL-Bref (p < 0.001) significant difference was observed between groups. Outcomes in Ayurveda group was better than control group. Outcomes in other parameters like BPRS (p = 0.22), CGI-severity (p = 0.77), CGI-GI (p = 0.69), CGI-EI (p = 0.28) were comparable between groups. Improvements in both the groups were in all the time points in HARS, BPRS, PSQI and CGI-EI. In WHOQOL-Bref, control group showed no improvements in any of the time points. However Ayurveda group showed improvements (p < 0.001) at all the time points. Improvements in both groups in CGI-S were from 30th day onwards. In CGI-GI, control group showed improvements from 45th day onwards but Ayurveda group showed improvements from 30th day onwards. (Table 3).

Effect size showed large effect in WHOQOL-Bref. And was of medium effect in HARS, PSQI and UKU side effect scale. Effect size was small in BPRS, CGI-EI and minimal in weight, BMI, CGI-GI.

UKU side effect assessment showed significant difference between the groups (p = 0.02) and medium effect size. Mild adverse effects noted in 5 patients of Control group. UKU side effect scale assessment showed autonomic side effects 2 (giddiness), psychic side effects 2 (lethargy), other effects 4 (heaviness of head and nausea). UKU global assessment showed physician assessment scores as 2 and patient assessment scores as 2 in autonomic and psychic side effects. UKU global assessment showed physician assessment was 1 and patient assessment was 2 on other side effects. Adverse events were mild, recurrently occurring during course of the intervention, did not affect the functioning of the patients and subsided without any additional intervention. No adverse events were observed in Ayurveda group.

Remission, responders, partial responders, non responders in control group were 0, 2, 8 and 13 respectively. In Ayurveda group were 0, 6, 13 and 5. Group comparison showed significant difference favoring improvements in Ayurveda group (p = 0.03).

Table 1
Patient profile: Expressed in Mean, standard deviations (S.D.) and percentage.

S. No	Clinical Profile	Control Group	Ayurveda group	Total	p value
		No	No		
1	Age (yrs)	43.64 ± 13.53	42.92 ± 14.02	43.28 ± 13.64	0.85
2	Sex Male	12	10	22	0.56
	Female	13	15	28	
3	Socio Economic Status- Lower	4	1	5	0.30
	Middle class	16	20	36	
	Upper class	5	4	9	
4	Educational Status- Illiterate	4	3	7	0.75
	Primary	1	3	4	
	Secondary	7	7	14	
	Graduate	13	12	25	
5	Prakurti (Body constitution)- Vata	2	0	2	0.07
	Pitta	4	8	12	
	Kapha	4	2	6	
	Pitta kapha	3	4	7	
	Vata pitta	7	11	18	
	Vata kapha	5	0	5	
6	Marital Status - Married	18	19	37	0.83
	Unmarried	5	5	10	
	Widow	2	1	3	
7	Agni- Manda	8	6	14	0.21
	Sama	10	6	16	
	vishama	7	13	20	
8	Sleep disturbance- Yes				
10	Duration of illness (In Years)	4.7 ± 3.92	4.35 ± 4.07	4.52 ± 3.96	0.75
11	Weight (Kgs)	62.48 ± 11.72	60.76 ± 9.91	61.61 ± 9.91	0.58
12	BMI	24.33 ± 5.09	24.58 ± 3.11	24.40 ± 3.82	0.83
13	Depression -Severe (HDRS>24)	25	25	50	
14	Anxiety Moderate (HARS>18)	0	2	2	
15	Severe (HARS>24)	25	23	10	
16	Drop outs	2	124	3	
17	Study completed	23		47	
	Total	25	25	50	

Table 2
Base line characteristics of the Clinical assessment scales in two groups - HDRS Hamilton Anxiety Rating scale. Expressed in Mean and standard deviations (S.D.).

S. no	Parameter	Control group (Mean and Sd)	Ayurveda group (Mean and Sd)	p
1.	HDRS	33.91 ± 4.35	33.63 ± 5.35	0.84
2.	HARS	35.35 ± 7.08	35.33 ± 6.68	0.99
3.	BPRS	49.96 ± 9.02	45.92 ± 6.10	0.07
4.	PSQI	17.39 ± 5.87	18 ± 5.42	0.71
5.	WHOQOL-Bref	79.60 ± 8.27	76.45 ± 7.66	0.18
6.	CGI-S	5 ± 0.85	4.75 ± 0.60	0.25

Table 3
Effect of Interventions on Clinical assessment scales- HDRS Hamilton Anxiety Rating scale. Expressed in Mean and standard deviations (S.D.). Gp C-Control group, Gp A-Ayurveda group.

S. No	Parameters	Gp	Baseline (Mean & Sd)	15th day (Mean & Sd)	30th day (Mean & Sd)	45th day (Mean & Sd)	60th day (Mean & Sd)	Difference of pre & post	p value 2 way rmANOVA	P Diff Ind *t*-test	Effect Size (0–60 days)
1.	Weight	C	61.26 ± 10.31	61.19 ± 10.29	60.98 ± 10.40	60.99 ± 10.40	61.01 ± 10.42	0.27 ± 0.84	0.80	0.52	0.19
		A	60.22 ± 9.98	60.25 ± 10.05	60.07 ± 9.94	60.10 ± 9.94	60.13 ± 9.96	0.13 ± 0.59			
2	BMI	C	24.30 ± 4.55	24.27 ± 4.55	24.22 ± 4.48	24.21 ± 4.48	24.13 ± 4.61	0.19 ± 0.38	0.98	0.51	0.19
		A	24.34 ± 3.10	24.34 ± 3.11	24.20 ± 3.09	24.19 ± 3.09	24.21 ± 3.10	0.12 ± 0.35			
3	HDRS	C	33.72 ± 4.36	31.50 ± 4.42	28.90 ± 4.55	26.31 ± 5.08	24.27 ± 5.24	9.47 ± 5.64	0.11	0.01	0.73
		A	33.54 ± 5.42	30.5 ± 4.54	26.54 ± 3.90	23.13 ± 4.15	19.45 ± 3.26	13.5 ± 5.67			
4.	HARS	C	35.36 ± 7.24	31.81 ± 5.31	28.36 ± 5.24	24.68 ± 6.12	22.04 ± 6.29	13.65 ± 6.69	0.057	0.03	0.66
		A	36 ± 6.55	30.86 ± 5.69	25.86 ± 5.64	21.5 ± 5.03	18.81 ± 6.27	17.95 ± 6.74			
5	BPRS	C	49.22 ± 8.51	45.95 ± 8.12	41.36 ± 7.12	36.31 ± 7.51	31.54 ± 7.15	17.91 ± 6.66	0.01	0.22	0.49
		A	46 ± 6.11	40.68 ± 7.77	35.27 ± 5.47	29 ± 6.21	24.36 ± 6.93	20.83 ± 9.28			
6	PSQI	C	17.36 ± 6.01	15.50 ± 5.19	13.18 ± 4.88	11.31 ± 4.87	10 ± 4.72	7.60 ± 5.06	0.14	0.03	0.61
		A	17.54 ± 4.84	14.40 ± 4.36	11.45 ± 4.04	9.40 ± 2.78	7.36 ± 2.78	10.79 ± 5.06			
7	WHOQOL-Bref	C	79.18 ± 8.20	80.63 ± 7.42	82.86 ± 9.18	83.40 ± 12.31	84.86 ± 15.11	5.73 ± 15.66	0.04	<0.001	1.19
		A	77.13 ± 7.64	81.72 ± 7.61	87 ± 8.75	93 ± 8.61	98 ± 10.36	22.12 ± 11.79			
8	CGI-S	C	5 ± 0.87	4.72 ± 0.82	4.22 ± 0.75	3.72 ± 0.70	3.63 ± 0.90	1.39 ± 0.65	0.06	0.77	0
		A	4.68 ± 0.56	4.36 ± 0.49	3.86 ± 0.77	3.50 ± 0.74	3.31 ± 0.77	1.33 ± 0.70			
9	CGI-GI	C	–	3.95 ± 0.72	3.59 ± 1	3.22 ± 1.10	2.90 ± 0.97	1.08 ± 0.73	0.16	0.69	0.03
		A	–	3.81 ± 0.66	3.40 ± 0.73	2.90 ± 0.75	2.59 ± 0.73	1.16 ± 0.63			
10	CGI-EI	C	–	9.90 ± 1.54	8.50 ± 1.22	6.95 ± 1.32	6.45 ± 1.50	3.56 ± 1.99	0.058	0.28	0.31
		A	–	9.09 ± 2.42	7.63 ± 2.12	6.81 ± 1.46	6.09 ± 1.57	2.91 ± 2.14			
11	UKU	C	–					0.33 ± 0.70		0.02	0.66
		A	–					0			

4. Discussion

The study showed that the effect of whole system Ayurveda management protocol (WSAP) for MDD was better compared to escitalopram. WSAP showed significant outcome improvements in depression, anxiety, night sleep quality, quality of life and side effect profile. Both interventions showed significant improvement in depression, anxiety, night sleep profile, severity of disease, global improvement, and efficacy index. Only WSAP group showed improvements in WHOQOL-Bref. Mild adverse events were noted in 5 patients of Escitalopram group and none in WSAP group.

Patient profile in the study showed that majority were of middle age (43.28 yrs), female, middle socio economic status, graduate level of education, vata pitta prakurti, married, vishama agni (type of metabolic derangement), mean duration of illness was 4.5 yrs, weight (61.6 kgs), BMI (24.4), severe depression (total score of HDRS was 33.7), severe anxiety (total score of HARS was 35.3), sleep was disturbed (PSQI was 17.7) and were moderately ill (CGI –S was 4.87).

Whole system research (WSR) approach is in sync with the philosophy, principles and practices of complementary and alternative systems of medicines including Ayurveda science [30]. WSR is model congruent to these systems. Ayurveda integrates the physical, mental, emotional, social, and spiritual components of the individual in diagnostic and treatment strategies. Treatment is multi modal, complex, synergistic, integrative and dynamic in nature. A WSR study on weight management with Ayurveda and yoga has shown positive outcomes [31]. Another study has evaluated the effect of whole system ayurveda management protocol on Irritable Bowel Syndrome [32] and showed beneficial effects.

4.1. Whole system ayurveda diagnostic protocol

WSAP was developed with the help of 8 physicians. WSAP group had two components based on *dosha* (KT and VRKT), *srotas* involved (8) and subcomponent of srotas (10) involved (Annexure 1). VRKT (n = 27, 54 %) was predominant compared to KT (n = 23, 46 %) diagnosis. Diagnostic components distribution among groups (Control group: KT-12, VRKT-13; Ayurveda group: KT-11,VRKT-14) was comparable ($p = 0.23$). Weight and BMI were significantly ($p < 0.001$) less in VRKT group. Other parameters like depression ($p = 0.22$), anxiety ($p = 0.98$), sleep disturbance ($p = 0.33$), quality of life ($p = 0.59$), severity of disease ($p = 0.05$), anxiety severity ($p = 0.52$), depression severity ($p = 0.32$) were comparable between the KT and VRKT diagnostic groups. *Srotas* (systems) involved in our patient were *manavaha*, *rasavaha*, *purishavaha*, *medoavaha*, and *arthavaha*. Multiple *srotas* were involved in each patient (Table 4).

4.2. Whole system ayurveda therapeutic protocol

Drugs were listed according to the diagnostic components. Number of drugs listed were 43, drug used were 24. Ayurveda psychological counselling techniques [20] were used in all the patients with severe depression (HDRS>24) in Ayurveda group. *Rajasika* or *tamsika* protocol was decided on the basis of grades of anxiety or depression and

Table 4
Comparison of profiles among two Ayurveda sub groups (VRKT & KT) in patients (n = 50).

S. no	Parameter	Group VRKT (Mean and Sd) (n = 27)	Group KT (Mean and Sd) (n = 23)	p
1.	Weight	55.35 ± 8.48	68.97 ± 8.3	<0.001
2.	BMI	22 ± 3.02	27.34 ± 3.45	<0.001
3.	HDRS	35.32 ± 4.58	33.9 ± 4.5	0.22
4.	HARS	35.32 ± 6.96	35.36 ± 6.77	0.98
5.	BPRS	48.60 ± 7.70	47.09 ± 8.13	0.51
6.	PSQI	16.96 ± 5.06	18.55 ± 6.15	0.33
7.	WHOQOL-Bref	77.40 ± 8.23	78.68 ± 7.95	0.59
8.	CGI-S	4.68 ± 0.69	5.09 ± 0.75	0.05
9.	Anxiety severity	3.12 ± 0.66	3 ± 0.61	0.52
10.	Depression Severity	3.24 ± 0.77	3.45 ± 0.67	0.32

predominant mood in the patient. Total counselling sessions were 35. Music or mantra (spiritual practice of chanting in hindu religion), exercise and yoga were advised in all the patients of WSAP group.

Comparison of outcomes showed better improvement in WSAP compared to Escitalopram in primary out come criteria (HDRS) and in few of secondary out come criterias like HARS, PSQI, WHOQOL-Bref and UKU side effect scale. Both the interventions were comparable in BPRS, CGI-S, CGI-GI and CGI-EI. Both the interventions showed significant improvement in HDRS, HARS, BPRS, PSQI, CGI-S,CGI-GI, CGI-EI. Effect size was large in quality of life and moderate in depression, anxiety, sleep disturbance and side effect profile. BPRS is used to measure for medication titration and dosing questions, treatment response and to note emergence of other psychiatric manifestations like psychotic symptoms [33]. No psychotic symptoms emerged during the interventions in any of the groups. Improvements with interventions were similar in BPRS and CGI -GI.

Depression severity was assessed through HDRS scores (no depression (0–7), mild depression (8–16), moderate depression (17–23) and severe depression (≥24) [34]. In control group, depression severity before treatment was of sever grade (n = 25) and after intervention depression reduced to severe (n = 16), moderate (n = 5) and mild (n = 2). In Ayurveda group, depression was severe (n = 23), moderate (n = 2) before intervention and post intervention it reduced to severe (n = 7), moderate (n = 12) and mild (n = 5). Depression severity reduced significantly in Ayurveda group (p = 0.02). Anxiety severity was assessed through HARS scores (mild anxiety (8–14), moderate (15–23), severe ≥24, scores ≤7 (no/minimal anxiety) [35]. In control group, anxiety severity before treatment was sever grade (n = 25) and after intervention anxiety reduced to sever (n = 16), moderate (n = 5) and mild (n = 2). In Ayurveda group, anxiety was sever (n = 25) before intervention and post intervention it reduced to sever (n = 7), moderate (n = 12) and mild (n = 5). Anxiety severity reduced significantly in Ayurveda group (p = 0.04). Reduction of depression in both the groups was from severe to moderate depression. Reduction in anxiety in control group was from severe to moderate but in gAyurveda group was from severe to mild ranges.

WSAP showed better improvements in depression, anxiety, sleep disturbance, quality of life and had safer side effect profile. These could be due to integrative and synergic effects of drugs, counselling, music therapy, exercise and yoga practices. Drugs used were *Brahmi vati*, *Sarpagandha ghana vati*, *Manasmitravataka*, *Smrutisagar rasa, Ashwagandharishta*, *Saraswatarishta*, *Dashmoolarishta, draksharishta*, *anandbhairavrasa*, *ashokarishta*, *trikatu*, *kshirabala taila, ashwagandha powder* etc. Drugs like Brahmi vati, Aswagandharishta, draksharista etc have predominant action on *vata* and *raja*. *Sarpagandha ghana vati*, *smrutisagara rasa*, *Manasamitra vataka* etc have predominant action on kapha and tama. Study has shown that Brahmi vati and *Manasamitra vataka* produced reduction of worry, depression, daytime sleepiness, sleep profile, quality of life, disease severity, global improvement and efficacy index in patients of Generalized anxiety disorder [36,37]. *Sarpagandha ghana vati* has shown anxiolytic and improved sleep profiles in patients of essential hypertension [38]. Extracts of W*ithania somnifera* (WSE) (Ashwagandha) administered in patients of schizophrenia or schizoaffective disorder produced reduction in anxiety and depression symptoms [39]. Many herbs have shown antidepressant activities in behavioural models of depression like immobility time in the forced swimming test (FST), learned helplessness test (LHT) and tail suspending test (TST). Aqueous ethanol extract of Crocus sativus L [40] (saffron) showed antidepressant like activity in dose dependant manners in FST and TST models. Aqueous ethanolic root extracts of Withania somnifera [41] showed antidepressant activity in FST and LHT models and had adaptogenic activity. Chloroform fraction of the total ethanolic extract of Convolvulus pluricaulis Choisy [42] (*shankapushpi*) showed antidepressant activity in FST and TST models. Aqueous extract of Glycyrrhiza glabra L [43] (*Yasthimadhu*) showed antidepressant activity in FST and TST through increase of brain norepinephrine, dopamine and Monoamine oxidase inhibition.

Other modalities of WSAP like counselling, music or mantra, exercise and Yoga have also contributed in clinical improvements. Ayurveda counselling techniques work through modulation of thought and information processing mechanisms, behavior, inter personal relationship, coping abilities etc. Pratidwandwa chikitsa is inducing the opposite emotions like in grief (shoka) with joy (harsha), this is done through cognitive restructuring. Ayurveda counselling also includes the behavioural components like adhering to dinacharya (daily regimens and making schedules of the day) and achara rasayan [44]. Achara rasayana has components of positive mental health, social conduct, professional conduct and behavioural practices. Sleep hygiene is an integral part of dinacharya and achara rasayana. There exists a strong causal relationship exists between sleep and depression [45]. Sleep disturbance is commonly seen in depression. Ayurveda counselling techniques may include the components of Cognitive Behavior Therapy (CBT), Behavioural therapy, interpersonal therapy or supportive therapy etc. Among the Psychological counselling techniques CBT, interpersonal therapy or supportive therapy have shown efficacy in MDD [46].

Epidemiological study has showed that increased physical activity decreases depression [47]. Exercise increases important psychological attributes related to depression like self efficacy and self esteem [48]. Exercise moderates pathways like inflammation, oxidative stress, neurotrophins and neurogenesis [49], increases brain derived neurotropic factor (BDNF) [50]. A systemic review [51] showed that Yoga has moderate evidence of beneficial effect compared to usual care in depression and had limited evidence compared to aerobic exercise and relaxation. Meditation has showed biological activities like increase thickness in prefrontal cortex and right anterior insula, increased oxygenated haemoglobin in prefrontal cortex and increase in whole blood serotonin, improvement in negative mood, increased alpha band activity and decreased theta band activity [52]. A systematic review study showed that music listening over a period of time helps in reducing depressive symptoms in adults. All types of music in accordance with preference of listener showed the beneficial effect and the repeated sessions needs to be conducted for more than 3 weeks [53].

CAM studies on MDD showed beneficial effect. A meta analysis study comprising of 29 randomized controlled trials (RCTs) on St John's wort showed that it is superior to placebo and similar to standard antidepressants and had fewer side effects compared to antidepressants [54]. A Cochrane review comprising of 30 RCTs showed no consistent benefit with any form of acupuncture when compared with wait list or sham controls and did not recommend it's use in depression [55]. A Cochrane review [56] on some form of exercise in depression through 37 clinical studies showed exercise was superior to inactive controls, equivalent to psychological and pharmacological interventions. Duration of exercise but not any specific type of exercise showed beneficial effect.

Present study is the first to evaluate WS approach in the management of MDD. Strengths of the study include randomized controlled design,

use of Escitalopram a gold standard control. Study evaluated multi components of MDD like depression, anxiety, sleep disturbance, quality of life, disease severity, global improvements, efficacy index and side effect profiles and forms its merit. WSAP involved medications, counselling, music, exercise and yoga. Few of the limitations included unblinded design, which is difficult in WS studies. Major p*anchakarma* procedures were not part of WSAP and is a major limitation. Active involvement of the patient is needed in complying to interventions like counselling, music, exercise and yoga and it was a challenge. Perseverance and dedication in self directed activities was needed and hence frequent monitoring and motivation were done. Similarly active participation by patients and multi modal treatments in WSAP can lead to placebo effect due to increased expectancies of positive outcome and can be a confounder. Culture, belief related to yoga and mantra can be patient specific and can produce placebo effect apart from treatment specific effects in Indian populations. However patients had an option of music and or mantra, yoga and or exercise and this can lead to bias. Biological assessments like serum cortisol levels, autonomic nervous system dysfunction etc would have thrown more light on the biological effects of interventions.

5. Conclusion

Study demonstrated that WSAP in MDD is beneficial compared to Escitalopram. It showed significant improvements in depression, anxiety, sleep disturbance, quality of life, disease severity, global improvements and efficacy index. It had beneficial effects compared to escitalopram on parameters of depression, anxiety, sleep disturbance, quality of life and side effect profiles. Quality of life improvements were noted in WSAP group only. Both interventions had similar effects on BPRS, disease severity, global improvement and efficacy index.

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Author contribution

AP- Visualization, Data collection, Writing - Reviewing and Editing.

SC- Conceptualization, Methodology, Writing - Original draft preparation, Writing -Reviewing and Editing.

BRT- Conceptualization, Methodology, Writing - Original draft preparation, Writing -Reviewing and Editing, Statistical analysis.

NM- Visualization, Data collection, Writing - Reviewing and Editing.

Declaration on use of generative AI in scientific writing

Nothing to disclose.

Declaration of competing interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jaim.2024.100896.

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