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Effects of a multi route (oral and nasal) application of *Lasunadya Ghrita* (An ayurvedic formulation) in cases of primary depression: Inferences from a non randomized open label clinical trial

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Mental diseases are rising globally. Depression is one among the most common mental disorders with an alarmingly high incidence in India. Mental health care in general is suboptimal in India on account of inadequate resources and lack of awareness. Pluralistic health care delivery model of India including its traditional health care services is less explored in case of mental health for its possibility of adding value to the net mental health care delivery. The objective of the study was to explore the efficacy of an ayurvedic formulation *Lasunadya Ghrita* (LG) in a multimodal application form in cases of depression and to compare its efficacy with conventional care composed of Escitalopram, Etizolam and Zolpidem (EEZ) provided in an allopathic psychiatric health care setting. Total 52 patients of depression allocated non randomly to Ayurveda LG group and to Allopathy EEZ group were followed up for 4 weeks and evaluated on the basis of HAM-D and SF-36 mean score changes of the participants on a pre and post basis and also for their intergroup comparisons. Statistically significant changes in mean HAM-D and SF-36 Score were observed in a pre-post comparison in both the groups. An intergroup comparison was non- significant for majority of HAM-D domains, barring a few showing the comparable effects of two treatment approaches. Ayurvedic treatment was effective in work and energy domain and gastrointestinal symptoms.

Pre and post mean changes in HAM-D and SF-36 Score in two groups have shown significant changes in both the groups suggestive of their individual efficacy. Insignificant difference in most domain scores of HAM-D and SF-36 in an inter group comparison was suggestive of comparable efficacy of LG multi route application with EEZ allopathy care.

Keywords: Ayurveda, Depression, Mental health, Traditional health care

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Mental diseases are the cause of a global concern for their impact upon more than 1 billion people globally. Estimated global burden of mental disorders accounts for 32.4% of all years lived with disability (YLD) and 13% of disability adjusted life years (DALY)[1]. These figures place mental illness very high in global burden of diseases in terms of years lived with disease (YLD) and at par with cardiovascular diseases in terms of DALY.

Despite their high burden, unfortunately mental healthcare in general is found disproportionate, inequitable, inaccessible and inadequate across the world with more pronounced impacts upon lower and middle income countries including India[2,3]. Recent estimates suggest India having 150 million people suffering with some kind of mental illness with a meager strength of ~4000 psychiatrists to deal with this burgeoning burden of mental diseases[4].

Mental diseases in contrast to physical illnesses are unique for their ethno-cultural hues and ethos and hence also require a contextual management. From Indian perspective, owing to its diverse culture and pluralistic health care opportunities, utilizing traditional health care for mental diseases seems to be a plausible proposition[5]. Indian National mental health care policy 2017 was a right step in this direction for its identification of Ayurveda as an integral component of composite mental health care delivery in India[6].

Among all mental diseases, depression shares the maximum brunt of DALY. Depression is emerging as a global epidemic accounting for its huge implications

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in various spheres of life including social, personal and economical[7]. Seeing the phenomenal increase of depression incidence and its impact on society, WHO took an initiative to start a dialogue for depression by assigning 'Depression: let's talk' as a theme for year 2017[8].

Depression as a disease has many peculiarities. Having an early incidence, it may arise through life style, workplace or family issues and may result in huge personal, interpersonal, social and economic losses including lives lost due to suicide[9]. India currently has about 5.6 crore people amounting to 4.5% of its population suffering with depression[10]. The prevalence of depression is increased by 18% worldwide in past 10 years and is projected to rise further in next 10 years[11]. With this alarming hike in depression incidence, an urgent recount of our strength for meeting the emerging demands of mental health care is direly needed.

Pharmacotherapy of depression care has not been very promising so far[12]. It has limitations related to delayed onset of action, side effects, dependency and longer treatment requirements. Clinical trials related to depression have continuously failed to distinctly differentiate the effects of placebo and active interventions. Depression is still a stigma in India. Because of the ignorance about psychiatric illnesses and overriding preoccupations to the axiom that "psychiatrists are the doctors of mad people" visiting a psychiatrist is still a taboo in most parts of the country[13].

For its ethno cultural rooting in India, in mental health care, Ayurveda emerges as a serious player to bridge the gaps. For its cultural contextuality, Ayurveda has a higher acceptability in the area of mental health care. The benefits of appropriating Ayurveda for optimizing mental health in India can be many, most immediate of which is easing out the disease burden by sharing the care with existing facilities and by providing more accessible care to a larger niche area. Looking optimistic however, this proposition requires a robust scientific exploration to move further. The first step here could be the screening of Ayurvedic interventions for their therapeutic potentials in depression[14].

It is in this intriguing background of high burden of depression in India along with its suboptimal care, potential of Ayurvedic medicine to handle such conditions deem highly desired. This study aimed to explore the role of an ayurvedic formulation *Lasunadya Ghrita* (LG) used in a multi route mode (oral and nasal instillation) in cases of primary depression through a non random open label clinical trial. It has compared the benefits of LG to conventional care of primary depression composed of Escitalopram, Etizolam and Zolpidem (EEZ)[15]. One recently published review article has suggested the connections between gut dysregulation and major depressive disorders, and points out the importance of gut health in restoration of mental functions[16]. The intervention drug from Ayurveda selected for the trial has a high affinity for re-correction of gut dysregulation and hence seems appropriate for this clinical trial.

Done upon 52 patients (26 participants in each group) allocated in a non random way, the study was able to demonstrate the benefits of LG multi route applications comparable to conventional EEZ care (comprised of Escitalopram 10 mg , Etizolam 0.25 mg, and Zolpidem 10 mg every day in single dose). On clinical domains related to work-activity-energy, early and middle insomnia and somatic symptoms pertaining to gastrointestinal functions, effects of LG were found superior to EEZ. The observations made in the study are serious enough to consider Ayurveda as a plausible partner in a comprehensive and holistic management plan for depression.

Materials and Methods

Setting of the study

The study was conducted at State Ayurvedic College and Hospital, Lucknow in collaboration with the Department of Psychiatry, King George's Medical University, Lucknow. Patients were recruited from both the places and were given the treatment as per the place of their recruitment.

Necessary permissions and ethical clearance

Necessary permissions and ethical clearance were duly obtained from the Institutional Ethics Committee (IEC/AYM/066-2017 Dt.25.08.2018). The study was also registered with Clinical Trial Registry of India (CTRI2019/08/020756). All the participants in the study have been informed well about the study and an informed consent was obtained following the due process.

Study design

This was a non random two arm open label study where one arm (Group A) of the study was given LG

(through oral and nasal route) and the other arm (Group B) was given EEZ for one month. This period was selected on the assumption that for any anti-depressant drug to act, it takes around 4 weeks to give the observable results.

Study sample and participants recruitment

Depression patients diagnosed on the basis of WHO-ICD 10, DCR criteria for mild to moderate depression[17] and fulfilling the essential inclusion and exclusion criteria were recruited from State Ayurvedic College, Lucknow (place of recruitment for group A patients) and Department of Psychiatry, King George Medical University, Lucknow (Place of recruitment for group B patients), respectively. Informed consent was obtained from prospectively suitable participants and those willing to participate were allocated the group as per their primary recruitment place (This was a non random study and the patients were enrolled from ayurvedic and allopathic hospital, respectively and given the treatment as per the specific hospitals). Patients having other psychiatric co-morbidities and severe depression with attempted suicides have been excluded from the study.

Sample size

Considering the 5% margin of error and 95% confidence interval and 4.5% disease prevalence, the study sample was determined to be 385. However, considering the pilot nature of study, the study sample was limited to 60 with a proportionate distribution of 1:1 in two groups. Considering 20% drop outs, total sample is 72 with approximate 36 participants in each group.

Trial drug and active comparator

Lasunadya Ghrita (LG) originally cited in Charak Samhita for the treatment of *Unmada* (a psychiatric condition described in Ayurveda resembling with mood disorders) was selected as the trial drug on the basis of its textual praise in depression like symptoms[18]. The drug was prepared at a local GMP certified ayurvedic pharmacy and was packed in the dose form suitable for oral consumption for 28 days. It was given orally in 2.5 g dose two times every day before meal for 4 weeks. For nasal instillation (*nasya*), 6 drops (~0.3 mL) of the drug were instilled in each nostril following strict SOP of *nasya* as recommended in Ayurveda. Nasal instillation on each patient each time was done by the investigator (VT) herself in the hospital setting in the morning hours. Total 20 nasal instillations dispersed in 4 weeks were given to each patient in Group A (approximately 5 sittings in a week). The Group B patients were given Escitalopram 10 mg, Etizolam 0.25 mg, and Zolpidem 10 mg once in a day for 4 weeks. These drugs were purchased by the patients from the local market. For the oral drug intake compliance in both the groups, a compliance diary was recommended to be made by every registered patient and was checked from time to time by the investigator (VT).

Conduction of the study

The study has begun in April 2018 and completed in July 2019. Total 68 patients of depression (38 from group A i.e., recruited from ayurvedic hospital and 30 from group B i.e., recruited from allopathic hospital) were screened for their eligibility in the study and subsequently asked for their willingness to participate in the study through an informed consent process. Total 32 eligible patients in Group A and 30 in Group B have given their consent to participate in the study. The data was finally analyzed on 52 patients, comprising of 26 patients in each group. Data pertaining to 10 patients was incomplete due to the lost follow ups and therefore was not included in the final analysis (study flow chart).

Evaluation parameters

Primary evaluation of the changes in the clinical status of depression following the active Ayurveda treatment or the Allopathic care was done on the basis of mean changes in the HAM-D score[19]. A secondary outcome was also evaluated through finding the changes in mean SF-36 scores[20] in both the groups. The groups were initially compared at their base line to see the similarity of their demographic and clinical profiles. Subsequently, a pre and post comparison was done to see any statistically valid difference between the HAM-D baseline and 4 week scores obtained after the treatment in each group. An intergroup comparison was also done for HAM-D and SF-36 mean score changes obtained in two groups at various time intervals. Safety of the interventions was also evaluated through pre and post liver and kidney function tests and lipid profile in both the groups.

Results

The final evaluation was done on 52 patients comprising of 26 participants in each group. Mean age of the patients registered and finally analyzed in the study was 36 years with a mean of 38.38 year in Group A and 33.7 years in group B (Inter group

x^2=1.622 and p=0.805). Maximum number of patients in both the groups was 20-39 years of age. A male predominance was observed among the registered participants. A high literacy level was obtained in both the groups under study (100% in group A, 92% in group B). The study has shown the marital conflicts as an important predisposing factor for depression. Financial issues also emerged as a large precipitant to depression in the study.

HAM-D and SF-36 were important evaluation parameters utilized in this study. These parameters were statistically evaluated for any difference in their scores in two groups at the time of registration, during the follow-up and on completion of the study. No significant differences were elicitable in baseline total HAM-D and SF 36 scores in two groups showing the comparability of two groups. Out of 21 domains scores enquired in HAM-D, 16 were found statistically indifferent in group A and B at the time of registration. Significant differences however were observed in Group A and Group B in domains like Insomnia (early, middle and late), Anxiety (psychological) and Hypochondrias is at the time of registration showing their different intensities in two groups before the start of therapy.

Pre and post treatment comparison

In group A significant difference was found in mean HAM-D score from Day 0 to Week 4 (46.29%, p<0.001). Similar difference in mean HAM-D score was also observed in group B from Day 0 to Week 4 (61.66%, p<0.001). (Table 1).

Pre and post treatment comparison of individual domain scores in HAM-D

A pre and post treatment comparison was further done for all the domains of HAM-D to see if there are any domain specific differences in responses of the two groups (Table 2). This has shown that after 4 weeks of the treatment, in group A, significant

Table 1 — Pre and post treatment changes in HAM-D Score in Group A and Group B

Time	Group A					Group B				
	Mean Difference	SD (Difference)	% Improvement	z-Value	p-Value	Mean Difference	SD (Difference)	% Improvement	z-Value	p-Value
Day 0-Week 2	2.77	1.31	12.72	-4.48	<0.001	7.08	2.46	28.22	-4.47	<0.001
Day 0-Week4	10.08	2.17	46.29	-4.47	<0.001	15.46	3.84	61.66	-4.46	<0.001

Table 2 — Pre and post treatment comparison of HAM-D domain scores between Day 0 and 4th week in Group A and B

Domain	Group A			Group B		
	% Improvement	z-value	p-value	% Improvement	z-value	p-value
Depressed mood	79.37	-4.59	**<.001**	69.70	-4.65	**<.001**
Feeling of Guilt	2.63	-1.00	.317	48.65	-2.97	**.003**
Suicide	50.00	-2.46	**.014**	27.78	-2.24	**.025**
Insomnia Early	41.18	-3.30	**.001**	89.13	-4.54	**<.001**
Insomnia Middle	53.33	-2.83	**.005**	93.94	-4.24	**<.001**
Insomnia Late	62.96	0.00	1.000	93.18	-4.46	**<.001**
Work & Activities	65.79	-4.62	**<.001**	56.79	-4.72	**<.001**
Psychomotor Retardation	84.62	-3.32	**.001**	72.73	-2.53	**.011**
Agitation	22.22	-2.12	**.034**	60.61	-3.54	**<.001**
Anxiety (Psychological)	65.00	-4.06	**<.001**	59.68	-4.40	**<.001**
Anxiety (Somatic)	54.76	-4.07	**<.001**	52.08	-4.63	**<.001**
Somatic Symptoms (Gastrointestinal)	90.32	-4.18	**<.001**	41.38	-3.46	**<.001**
Somatic Symptoms (General	50.00	-4.30	**<.001**	64.10	-4.46	**<.001**
Genital Symptoms	0.00	0.00	1.000	23.81	-2.24	**.025**
Hypochondriasis	5.56	-1.00	.317	33.33	-1.41	.157
Loss of Weight	9.52	-1.00	.317	5.26	-0.27	.785
Insight	0.00	0.00	1.000	100.00	-1.00	.317
Diurnal Variation	21.74	-1.89	.059	95.00	-3.07	**.002**
Depersonalization & Derealization	25.00	-1.00	.317	0.00	0.00	1.000
Paranoid Symptoms	0.00	0.00	1.000	0.00	0.00	1.000
Obsessional & Compulsive Symptoms	0.00	0.00	1.000	21.43	-1.73	.083

improvements were seen in the domains like depressed mood, suicide, insomnia early, insomnia middle, work & activities, psychomotor retardation, agitation, anxiety (psychological), anxiety (somatic), somatic symptoms (gastrointestinal) and somatic symptoms (general). In Group B, after 4 weeks, significant improvements were found in all the domains except hypochondriasis, loss of weight, insight, depersonalization & de-realization, paranoid symptoms and obsessive and compulsive symptoms.

Pre and post treatment comparison of changes in SF-36 score in two groups

In group A significant difference in mean SF-36 score was found from Day 0 to Week 4 (44.19%, $p<0.001$). Similar difference was also observed in Group B in mean SF -36 score from Day 0 to 4th week (59.29%, $p<0.001$) (Table 3).

Intergroup comparison of changes in HAM-D score in two groups

No significant intergroup difference was observed at Day 0, 2nd week and 4th week mean HAM-D scores obtained in two groups.

On comparing the difference in HAM-D mean score between Day 0 and 4th week, the mean HAM-D score difference of group A was 10.08±2.17, whereas the mean HAM-D score difference of group B was 15.46±3.84. This intergroup difference in mean change of HAM-D score from day 0 to week 4 was significantly different ($p<0.001$), favoring more reduction in mean HAM-D score in Group B comparing to group A (Table 4).

Intergroup comparison of changes in SF-36 score in two groups

No significant differences in mean SF-36 score at Day 0, 2nd week and 4th week was observed in an intergroup comparison of Group A and B. On comparing the difference in SF-36 score between Day 0 and 4th week, the mean SF-36 score difference of group A was found to be 515.38±143.19, whereas the mean SF-36 score difference of group B was 604.23±133.94. No significant difference was found in mean SF-36 scores changes from day 0 to week 4 in two groups ($p=0.117$) (Table 5).

Intergroup comparison of changes in domain scores in HAM-D

After 4 weeks, significant differences between the groups were found for the domains like feeling of guilt ($p=0.010$), insomnia early ($p=0.001$), insomnia late ($p<0.001$), work & activities ($p=0.020$), anxiety (psychological) ($p=0.007$), somatic symptoms (gastrointestinal) ($p<0.001$), somatic symptoms (general) ($p=0.017$), hypochondrias is ($p=0.012$) and diurnal variation ($p=0.001$) (Table 6).

More pronounced intergroup differences favoring Group A were found in domains like work & activities ($p=0.020$) and somatic symptoms (gastrointestinal) ($p<0.001$),

Intergroup differences favoring Group B were found in domains like feeling of guilt ($p=0.010$), insomnia early ($p=0.001$), insomnia late ($p<0.001$), anxiety (psychological) ($p=0.007$), somatic

Table 5 — Intergroup Comparison of SF-36 QL Scores between the Groups

SF-36 Score	Group A		Group B		Mann Whitney Test	
	Mean	SD	Mean	SD	U-value	p-value
Day 0	1166.35	±256.67	1019.04	±170.89	232.0	0.052
2nd Week	1301.35	±240.27	1281.35	±150.81	336.0	0.971
4th Week	1681.73	±186.79	1623.27	±131.54	262.5	0.167
Diff Day 0 to 4th Week	515.38	±143.19	604.23	±133.94	2.5	0.117

Table 3 — Pre and post treatment changes in SF-36 Score in Group A and Group B

Time	Group A					Group B				
	Mean Difference	SD (Difference)	% Improvement	z-Value	p-Value	Mean Difference	SD (Difference)	% Improvement	z-Value	p-Value
Day 0-Week 2	-135.00	77.97	11.57	-4.46	<0.001	-262.31	62.15	25.74	-4.46	<0.001
Day 0-Week4	-515.38	143.19	44.19	-4.46	<0.001	-604.23	133.94	59.29	-4.46	<0.001

Table 4 — Intergroup Comparison of HAM-D Scores between the Groups

HAMD Score	Group A		Group B		Mann Whitney Test	
	Mean	SD	Mean	SD	U-value	p-value
Day 0	21.77	±5.87	25.08	±4.63	231.0	0.050
2nd Week	19.00	±5.51	18.00	±3.45	291.5	0.393
4th Week	11.69	±4.43	9.62	±2.28	246.0	0.090
Diff Day 0 to 4th Week	10.08	±2.17	15.46	±3.84	23.3	<0.001

symptoms (general) (p=0.017), hypochondriasis (p=0.012), and diurnal variation (p=0.001).

Safety, adversity and toxicity observations

No drug related adversity has been reported during the study period in either group. No significant differences were observed in their pre and post treatment values in any biochemical or hematological parameters including Liver function, Kidney function and lipid profile in either of the groups. (Table 7 & 8)

Discussion

Depression for its huge impacts upon individual and societal health and for its increasing global incidence, requires an urgent attention. A limitation of current therapeutic approaches linked to the resource deficit or intervention related undesired effects,

Table 6 — Intergroup Comparison of Depression Domain Scores between the Groups

Domains	Time period	Group A		Group B		Mann Whitney Test	
		Mean	SD	Mean	SD	U-value	p-value
Depressed mood	Day 0	2.42	0.90	2.54	0.71	303.5	0.494
	4th Week	0.50	0.65	0.77	0.51	247.5	0.061
Feeling of Guilt	Day 0	1.46	0.90	1.42	0.90	334.5	0.939
	4th Week	1.42	0.86	0.73	0.96	213.0	**0.010**
Suicide	Day 0	0.69	0.97	0.69	0.55	294.0	0.369
	4th Week	0.35	0.56	0.50	0.51	279.5	0.211
Insomnia Early	Day 0	1.31	0.79	1.77	0.51	228.0	**0.017**
	4th Week	0.77	0.71	0.19	0.40	185.0	**0.001**
Insomnia Middle	Day 0	0.58	0.58	1.27	0.67	162.5	**<.001**
	4th Week	0.27	0.45	0.08	0.27	273.0	0.070
Insomnia Late	Day 0	1.04	1.00	1.69	0.74	223.0	**0.010**
	4th Week	1.69	4.05	0.12	0.33	178.5	**<.001**
Work & Activities	Day 0	2.92	0.80	3.12	0.91	288.5	0.296
	4th Week	1.00	0.63	1.35	0.56	231.5	**0.020**
Psychomotor	Day 0	0.50	0.71	0.42	0.76	305.5	0.482
Retardation	4th Week	0.08	0.39	0.12	0.33	313.5	0.332
Agitation	Day 0	1.04	1.11	1.27	1.00	286.0	0.312
	4th Week	0.81	1.02	0.50	0.51	299.0	0.426
Anxiety	Day 0	1.54	0.95	2.38	0.85	157.5	**<.001**
(PSYCHOLOGICAL)	4th Week	0.54	0.51	0.96	0.53	213.0	**0.007**
Anxiety	Day 0	1.62	0.80	1.85	0.67	290.0	0.260
(SOMATIC)	4th Week	0.73	0.45	0.88	0.33	286.0	0.163
Somatic Symptoms	Day 0	1.19	0.75	1.12	0.77	319.5	0.716
(GASTROINTESTINAL)	4th Week	0.12	0.33	0.65	0.49	156.0	**<.001**
Somatic Symptoms	Day 0	1.69	0.55	1.50	0.65	284.5	0.241
(GENERAL)	4th Week	0.85	0.37	0.54	0.51	234.0	**0.017**
Genital Symptoms	Day 0	0.77	0.91	0.81	0.80	322.0	0.753
	4th Week	0.77	0.91	0.62	0.70	318.0	0.689
Hypochondriasis	Day 0	0.69	0.97	0.23	0.82	243.0	**0.018**
	4th Week	0.65	0.94	0.15	0.54	237.0	**0.012**
Loss of Weight	Day 0	0.81	1.13	0.73	0.83	330.0	0.871
	4th Week	0.73	1.12	0.69	0.84	323.0	0.756
Insight	Day 0	0.08	0.39	0.08	0.39	338.0	1.000
	4th Week	0.08	0.39	0.00	0.00	325.0	0.317
Diurnal Variation	Day 0	0.88	0.91	0.77	0.91	314.0	0.631
	4th Week	0.69	0.88	0.04	0.20	204.5	**0.001**
Depersonalization	Day 0	0.15	0.46	0.04	0.20	311.5	0.294
& Derealization	4th Week	0.12	0.33	0.04	0.20	312.0	0.303
Paranoid Symptoms	Day 0	0.12	0.33	0.08	0.27	311.0	0.609
	4th Week	0.12	0.33	0.08	0.27	311.0	0.609
Obsessional	Day 0	0.28	0.61	0.54	0.58	238.0	0.051
& Compulsive Symptoms	4th Week	0.28	0.61	0.42	0.50	263.5	0.153

Table 7 — Effect of Treatment on biochemical and hematological parameters in Group A

Laboratory Parameter	Time	Group A				
		Mean	SD	% change	t-value	p-value
Hemoglobin (g%)	BT	13.23	1.45			
	AT	13.04	1.59	1.42	1.13	0.269
Total Leucocyte Count	BT	7692.31	1081.45			
	AT	7692.31	1043.43	0.00	0.00	1.000
Neutrophil	BT	59.19	5.59			
	AT	59.04	5.50	0.26	0.55	0.589
Lymphocyte	BT	30.81	5.18			
	AT	31.73	6.29	3.00	1.58	0.184
Monocyte	BT	4.81	3.29			
	AT	5.31	4.36	10.40	1.98	0.056
Eosinophil	BT	2.65	1.38			
	AT	2.73	1.25	2.90	-0.46	0.646
Basophil	BT	1.19	1.27			
	AT	1.00	1.02	16.13	1.73	0.096
TOTAL CHOLESTEROL (mg/dL)	BT	174.73	12.67			
	AT	175.04	12.61	0.18	-0.82	0.420
L.D.L. (mg/dL)	BT	101.77	18.14			
	AT	101.46	18.12	0.30	0.94	0.356
VLDL (mg/dL)	BT	28.65	4.57			
	AT	29.19	4.89	1.88	1.29	0.246
HDL (mg/dL)	BT	43.42	2.79			
	AT	43.73	3.01	0.71	-1.14	0.266
T.G. (mg/dL)	BT	149.69	11.86			
	AT	150.00	11.85	0.21	-0.89	0.381
S. BILIRUBIN (mg/dL)	BT	0.54	0.23			
	AT	0.55	0.21	1.92	-1.34	0.193
ALKALINE PHOSPHATASE (IU/L)	BT	96.73	11.41			
	AT	97.15	11.20	0.44	-0.90	0.375
SGOT (Units per liter)	BT	27.85	8.99			
	AT	27.88	9.13	0.14	-0.13	0.898
SGPT (Units per liter)	BT	30.46	9.15			
	AT	30.65	9.80	0.63	-0.38	0.705
B. UREA (mg/dL)	BT	29.04	3.03			
	AT	29.46	2.89	1.46	-1.74	0.094
S. CREATININE (mg/dL)	BT	0.89	0.20			
	AT	0.90	0.20	1.17	-0.50	0.624

warrants a search for better alternatives. India having a pluralistic health care model has many alternative health care systems including Ayurveda to help in psychiatric diseases due to their strong cultural and social bearing[21].

Reverse pharmacology has been a tested approach to develop new solutions for old problems on the basis of clues obtained from available traditional references for natural remedies[22]. LG was screened as a potential drug for depression on the basis of its description available in Charaka Samhita (CS), a classical treatise of Ayurveda presumed to be of 200 BC. This drug is composed of *rasona* (*Allium sativum*) as one of its main ingredients besides many other herbal components having *ushna* (hot) *tikshana* (pungent) and *srotoshodhana* (passage cleansing) properties (Table 9). An ayurvedic hypothesis developed to propose the possible mechanism of LG in depression largely favoured its postulated actions in depression. The classical recommendation of LG in CS was to use it through oral and nasal routes and also through external massage. Nasal route of drug

Table 8 — Effect of Treatment on biochemical and hematological parameters in Group B

Laboratory Parameter	Time	Group B				
		Mean	SD	% change	t-value	p-value
Haemoglobin (g %)	BT	12.65	1.60			
	AT	12.69	1.76	0.30	-0.25	0.802
Total Leucocyte Count	BT	7165.38	662.08			
	AT	7173.08	636.59	0.11	-0.32	0.753
Neutrophil	BT	58.77	9.70			
	AT	59.15	9.88	0.65	-1.85	0.076
Lymphocyte	BT	31.00	4.93			
	AT	31.50	4.81	1.61	-1.73	0.097
Monocyte	BT	2.96	1.37			
	AT	3.35	1.52	12.99	-2.61	0.015
Eosinophil	BT	1.27	1.31			
	AT	1.46	1.17	15.15	-1.55	0.134
Basophil	BT	0.54	0.65			
	AT	0.48	0.64	10.86	1.13	0.278
TOTAL CHOLESTEROL (mg/dL)	BT	173.96	9.32			
	AT	174.08	9.13	0.07	-0.33	0.746
L.D.L.(mg/dL)	BT	82.42	8.86			
	AT	83.00	9.08	0.70	-1.81	0.083
VLDL (mg/dL)	BT	31.69	2.71			
	AT	32.08	2.64	1.21	-1.73	0.096
HDL (mg/dL)	BT	44.58	8.42			
	AT	45.85	7.71	2.85	1.87	0.112
T.G. (mg/dL)	BT	144.19	10.36			
	AT	145.54	17.49	0.93	1.94	0.068
S. BILIRUBIN (mg/dl)	BT	0.50	0.42			
	AT	0.52	0.61	3.60	1.88	0.115
ALKALINE PHOSPHATASE (IU/L)	BT	101.00	9.13			
	AT	101.46	9.13	0.46	-0.99	0.334
SGOT(Units per liter)	BT	29.81	2.73			
	AT	29.96	2.75	0.52	-0.58	0.566
SGPT (Units per liter)	BT	32.08	4.46			
	AT	32.62	5.68	1.68	1.65	0.111
B. UREA (mg/dL)	BT	31.15	2.96			
	AT	31.54	2.75	1.23	-1.73	0.096
S. CREATININE (mg/dL)	BT	0.80	0.08			
	AT	0.81	0.09	0.72	-0.53	0.597

application is highly acclaimed in Ayurveda for diseases pertaining to the head. Recent researches have supported this opinion of Ayurveda by finding that the drugs given through nasal routes may bypass the blood brain barrier and hence may directly reach to the brain tissue and therefore may assure a site specific delivery[23]. This novel drug routing, yet is less explored in conventional psychiatric care[24]. This study utilizing a multi route application including both oral and nasal routes simultaneously in a presumption to maximize the impact of the drug was also a validity test for Ayurvedic recommendation of nasal route of drug application for mental diseases.

Testing the Ayurvedic drug efficacy for depression against the conventionally used pharmacotherapy was a most feasible plan to check if the drug in question has a comparable efficacy. An intergroup comparison of initial HAM-D and SF-36 QL scores assured no significant statistical differences and hence endorsed the similarity of the samples registered in both the groups.

Table 9 — Ingredients of *Lasunadya Ghrita*

No	Ingredient name	English name	Latin name	Quantity/ proportion
1	*Lasun*	Garlic	*Alium sativum* L.	100 part
2	*Haritaki*	Myrobillon	*Terminalia chebula* Retz.	30 part
3	*Shunthi*	Dried ginger	*Gingiber officinale* Rosc.	1 part
4	*Marich*	Black pepper	*Piper nigrum* L.	1 part
5	*Pippali*	Long pepper	*Piper longum* L.	1 part
6	*Go Dugdha*	Cow milk		64 part
7	*Purana Go Ghrita*	Old Clarified butter		64 part
8	*Go mutra*	Cow urine		16 part
9	*Hingu*	Asafoetida	*Ferula asafoetida* L.	1 part
10	*Madhu*	Honey		8 part

Responses of the treatments were observed in individual groups and were analyzed for their significance on the basis of mean changes in HAM-D and SF-36 QL scores before, during the follow-ups and after completion of the trial. After initial pre and post analysis, an intergroup comparison was also done to see any quantitative difference in the responses obtained in both the groups and to see if this difference refers to certain specific domains in HAM-D scale.

This was observed that both groups were able to give statistically significant improvements in 4 weeks of treatment period in terms of HAM-D mean score changes and SF 36 QL mean score changes. These changes were more pronounced for Group B (EAZ) comparing to Group A (LG) for HAM-D mean score change however no such significant intergroup difference was found for SF-36 mean score changes. This was a landmark observation showing that Ayurvedic trial intervention for depression as is provided to Group A participants has shown comparable results in terms of quality of life improvements when compared to standard modern care given to the Group B patients. This was substantiated further by seeing statistically significant differences in HAM-D mean score in Group A before and after 4 weeks of the treatment. The dichotomy of observations seen through two evaluation parameters also proposes different mode of action of two interventions used in the trial. A better HAM-D scoring through Group B intervention proposes the direct action of these drugs onto symptoms of depression. Group A drug (LG) however seem to act through different pathways by improving the quality of life initially and correcting the depression subsequently.

A domain mean score analysis for HAM-D was also revealing by finding that the interventions given in group A and B had their differential responses to different domain specific variables of HAM-D. For domains like depressed mood, feeling of suicide, psychomotor retardation, somatic anxiety, genital symptoms, loss of weight, insight, depersonalization and de-realization, paranoid symptoms, obsessional and compulsive symptoms, the effects of the treatments were similar in both the groups after 4 weeks of the treatment as is shown by insignificant difference between two groups in these domain areas after the completion of four week of treatment. This may thereby be inferred that in these domain areas of clinical features of depression, symptoms were as effectively cared for by Ayurvedic regime as is done by modern standard care. For few other symptoms there were differences in responses obtained between two groups and here the responses have favored the effect of one treatment over the other. For symptoms like feeling of guilt, late insomnia, psychological anxiety and general somatic symptoms, hypochondriasis and diurnal variation the modern standard care was found significantly more effective comparing to the given Ayurvedic intervention after 4 weeks of therapy. For few other symptoms like work and activities and somatic symptoms pertaining to the gastrointestinal system Ayurvedic treatment was found more effective comparing to the standard modern care and this difference was shown by the significant statistical differences between the score obtained by the two groups after the completion of 4 week of the therapy.

These observations suggest about comparable efficacy of Ayurvedic interventions (LG) through its multi route application with modern standard interventions (EAZ) for depression when compared through changes in HAM-D and SF-36 scores. These effects however were distinct when compared in

individual domain areas of HAM-D. This proposes that a selective treatment strategy for depression may be more productive if the selection is based on the predominating symptoms with evidences of one treatment doing better than the other. A depression patient having predominant symptoms related with late insomnia may better be treated with modern standard care whereas a depression patient having predominant somatic symptoms related to the work, energy and gastrointestinal symptoms may obtain a better response through Ayurvedic interventions. This observation may have a very significant future implication warranting the need of identifying clinical subgroups within a large population of depression where each group may have a different pathogenesis and therefore may need a different approach of treatment. There were no meaningful differences among pre and post treatment values of selected biochemical and hematological parameters to ensure safety and non toxicity of the drug. No significant changes in lipid profile in the patients treated with LG has eliminated the myth of alteration in the lipid levels by ayurvedic drugs composed of *ghrita* (Clarified butter).

This study had its own limitations. It was a non random study which is considered inferior to a random study. Although, the group allocation was seen balanced in the study by finding no significant differences between the clinical profiles of the participants before the trial actually begun, a randomization may have given more strength to the study observations. The study was done for a short period only. For a disease like depression, a long term trial is required to evaluate the effects of a drug and also its safety. A long duration trial therefore is required to verify the observations made in this study.

Despite these limitations, the study was still able to give substantial information about comparative benefits of an Ayurvedic treatment plan involving multi route drug application in cases of depression and suggests about designing a specific treatment strategy to treat the individuals on the basis of their dominating symptoms and not on the basis of their diagnosis alone. This study strongly proposes personalized psychiatry[25], as the future approach in psychiatry. Exploring nasal routes of drug applications in psychiatry is also one promising research avenue in psychiatry which is opened through this study.

Conclusion

Continuously rising mental diseases clubbed with inadequacies of current approaches to handle them across the globe pose a dreadful global challenge. For its obvious differences from physical illness in terms of etiology, clinical features and impacts, a mental disease requires much more to be done in contrast to the physical illnesses. Although, the ideal strategy to meet the emerging challenges of the mental health is to ensure the optimal, accessible and affordable care for each one who is in need of it, this seems a near impossible task in near future.

Optimizing the mental health care by duly utilizing the traditional and alternative health care systems may seem promising approach in India and at other places[26,27] where a pluralistic health care delivery model is officially adopted and where systems like Ayurveda and Yoga enjoy a position of repute for their ethno cultural contexuatilty. Out of a great variety of mental diseases the most prevalent among all is depression. India is recently identified as 6th country in the world having a huge population suffering with depression. Depression is unique in sense of its etiology arriving from a faulty surrounding including home and work place and is also unique for its huge impacts on social and personal life accounting it to be a big cause of YLD and DALY. Seeing the limitations of conventional care of depression, on account of the huge burden of the disease and also on account of limitations associated with resources and drug therapy, this seems appropriate to look at alternative therapies to see if these can be of some help to share the burden of depression in India.

A literature search has identified *Lasunadya Ghrita* as one potential drug from Ayurveda recommended for the treatment of depression-like symptoms. To screen its possible efficacy in treating mild to moderate depression, a non random open clinical study was done where effects of LG through a multi route application were compared with conventional modern care consisted of Escitalopram, Atizolam and Zolpidam through parameters like HAM-D and SF-36. A comparable efficacy of Ayurvedic preparation in improving the depression symptoms found in the study was suggestive of potential of ayurvedic therapies in managing depression symptoms and hence suggests more serious exploration in the area to effectively utilize the traditional health care wisdom of Ayurveda pertinent to India to improve its

mental health care status in general. This may particularly be more relevant to depression for which the trial was actually done.

Conflict of interest

Authors declare that they do not have any conflict of interest related to this manuscript.

Authors' contributions

SR- Study design and protocol, monitoring and analysis; VT- Study execution and analysis; AK- Review of the literature, Monitoring and AN- Study design and protocol, approval of final manuscript.

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