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Short Communication

Efficacy of Manasamitra Vataka (Ayurveda Preparation) Over Clonazepam to Establish Normal Sleep Architecture in Patients with Generalized Anxiety Disorder and Co Morbid Generalized Social Phobia

Basavaraj R. Tubaki[1], S. Sulekha[2], CR Chandrashekar[3], D. Sudhakar[4], Sathyaprabha TN[2], Lavekar GS[5] and Bindu Kutty[2]*

[1]*Department of Kayachikitsa, KLEU's Shri BMK Ayurveda Mahavidhyalaya KLE University, India*
[2]*Department of Neurophysiology, NIMHANS, India*
[3]*Department of Psychiatry, NIMHANS, India*
[4]*Advanced Centre for Ayurveda in Mental Health and Neuro-Sciences, NIMHANS, India*
[5]*Central Council for Research in Ayurvedic Sciences (CCRAS), New Delhi, India*

***Corresponding author**
Bindu Kutty, Department of Neurophysiology, NIMHANS Deemed University, Hosur Road. Bangalore, India -56002, Tel: 09449789375; Fax: 08026564830; Email: bindu.nimhans@gmail.com

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- 3. Abbreviations: GAD: Generalized Anxiety Disorder
- SP: Generalized Social Phobia

Abstract

The efficacy of anxiolytic drugs on sleep organization in Generalized Anxiety Disorder (GAD) is poorly studied although sleep disturbances are common manifestations of the disorder. In the present study, we compared the efficacy of Manasamitravataka (Ayurveda preparation) or Clonazepam on macro sleep architecture in patients diagnosed with GAD with co morbid generalized social phobia(SP) using an open label, randomized controlled, parallel group study with 72 GAD patients (of either sex, aged between 20-55 years).Patients were randomly divided into three treatment groups: Group I (n=24) received Manasamitravataka (100mg twice daily for 30 days); Group II, in addition to Manasamitravataka (100mg twice daily for 30 days),received Shirodhara (therapy involving dripping of medicated oil over forehead) treatment for first 7 days; and Group III (n=24) received Clonazepam (0.25 mg in morning and 0.50 mg at night for 30 days). Whole night polysomnographic evaluation of sleep architecture was carried out before and after treatment. Patients from all three groups reported having had good sleep following treatment but showed distinct changes in sleep architecture. Groups I & II showed sleep architecture with proper slow wave sleep and REM sleep states. Additionally, the ayurveda treatment helped to reduce NREM S1 sleep ($p=0.001$) and nocturnal intermittent awakenings ($p=0.005$). Whereas, patients treated with Clonazepam showed increase in lighter sleep states such as NREM S2 ($p<0.001$) but significantly reduced slow wave sleep states($p<0.001$).The study demonstrated the effectiveness of Ayurveda treatment over Clonazepamin preserving the restorative sleep though both drugs and Manasamitra vataka and Clonazepam were found to have anxiolytic properties.

INTRODUCTION

Generalized Anxiety Disorder (GAD) is a common disabling chronic disorder characterized by excessive worry accompanied with wide range of physical symptoms like sweating, palpitation etc. Social phobia (SP) is one of the most frequent co-morbidity of GAD [1-3] and is a chronic disorder characterized by irrational fear of public humiliation or embarrassment.

Sleep disturbances are common manifestations of major depressive and anxiety disorders [4-10]. Relatively little research has been focused on sleep disturbances in anxiety disorders compared to affective disorders [11]. Disturbances in sleep such as trouble in falling sleep or staying asleep, increased day time fatigue, decreased sleep efficiency, increased sleep latencies, intermittent awakenings , reduced slow wave sleep and REM sleep states etc., [4,12,13] have been reported in patients with Generalized Anxiety Disorder (GAD) [14].Though sleep disturbances have been reported in patients with social phobias [15], no subjective or polysomnographic reports on sleep architecture of GAD with comorbid social phobia are available. Additionally, conventional anxiolytic agents such as Clonazepam have been reported to affect sleep quality. It is shown that short term use of benzodiazepines help to improve the sleep quality, sleep duration and efficiency but alters the sleep architecture [16] and long term treatment has been shown to have deleterious effect on sleep [17]. SNRIs (Serotonin-Nor

epinephrine Reuptake Inhibitors) [18] and SSRIs (Selective Serotonin Reuptake Inhibitors) on the other hand, suppress REM (Rapid eye movement) sleep and increase nocturnal arousals [19]. Considering such side effects of these agents on sleep, newer studies are encouraged in the management of anxiety disorders. An alternative system of medicine such as Ayurveda is one such possibility and anxiety was found to be the strongest predictors (odds ratio 3:1; 95% confidence interval, 1.6-6.0) for patients to use this system of medicine [20]. Manasamitravataka [21] and Shirodhara therapy (dripping of medicated oil over forehead) are widely used ayurveda treatments for generalized anxiety. We have demonstrated the clinical effectiveness of such treatment approaches in the management of GAD with co-morbid generalized social phobia [22] and showed better treatment outcome for Manasamitra vataka and Shirodhara therapy over Clonazepam. The present study investigates the effectiveness of these treatments on sleep architecture in GAD patients with co-morbid generalized social phobia.

METHODOLOGY

The study was an open label, randomized controlled, parallel group study. Patients attending the outpatient department of psychiatry, NIMHANS (National Institute for Mental Health and Neuro Sciences), Bangalore, India were recruited for the study. The CONSORT statement recommendations were used to ensure the quality of the study [23]. Methodology of the study is described in our previous publication [22], however, important components are described in the present paper.

PATIENTS

Right handed patients (n=72), between the age 20-55 years, diagnosed as GAD with co-morbid generalized social phobia as per DSM-IV-TR criteria by a psychiatrist and meeting Hamilton Anxiety Rating Scale (HARS) >18, [24] were recruited for the study. Patients with significant depression (Beck Depression Inventory scores >17), any other AXIS I and medical disorders, or on any psychotropic drugs within four weeks prior to the study were excluded. Patients with substance abuse, pregnant and lactating females were also excluded. Patients were explained about the nature and design of the study and informed consent was obtained. The study was approved by Institute ethics committee.

METHODS

Patients were randomized (blocked randomization) into one of the 3 groups

Group I: Patients (n=24) received tablet Manasamitravataka 100 mg, twice daily, for 30 days.

Dose was selected as per available literature [21].Group II: Patients (n=24) received Shirodhara [22]with Brahmi tailam (oil based extract of Bacopamonneira) in the morning [25] for first 7 days in addition to Manasamitravataka as mentioned above. Group III*:* Patients (n=24) received tablet Clonazepam (0.25 mg in morning and 0.50 mg at night) for 30 days. Medications were administered in the morning and 1 hour prior to the habitual sleep time.

ASSESSMENTS

Assessment of Sleep Architecture through Whole night Polysomnography

Subjects were asked to maintain a sleep diary and abstain from alcohol, caffeine and naps for a period of 2 weeks prior to the study and during the study. Patients were asked to enter data immediately after getting up from bed. In addition, whole night polysomnographic (PSG) recordings were accomplished in a semi soundproof recording chamber (sleep cabin) under video monitored supervision in the standard sleep laboratory setting at the patients' habitual sleep timings. A minimum of two consecutive whole night recordings were carried out before and after the interventions. First night was for habituation to the lab settings and second night recordings were used for the assessments. The PSGs were recorded according to the method described by the Rechtshaffen and Kales [26].

EEG were recorded from disc electrodes placed bilaterally in frontal (F3, F4), central (CZ), and occipital (O1, O2) positions based on the 10-20 system recording of EEG introduced by Jasper [27]. Monopolar EOG electrodes were placed on both canthi and Bipolar EMG recording was obtained from the chin. The EEG and EOG were recorded with a time constant of 0.3s and a sensitivity of 5μV/mm and low pass of 70Hz, while the EMG had a time constant of1.0s and a sensitivity of 5μV/mm and low pass of 70 Hz respectively using a 32-channel digital Neurofax EEG instrument (Neurofax EEG 2110, Nihan Kohden – Japan). The electrical impedance was kept below 3 KOhms. The monopolar derivation was used for the assessment of the sleep stages using Polysmith software. Epoch by epoch visual scoring was done manually by a trained scorer blind to the study.

Statistical Methods

Statistical analysis was carried out using SPSS Version 15.0. Homogeneity of the data across the groups was evaluated by χ^2test. Comparison of groups across different time points was done using Repeated measures ANOVA with Bonferronis post-hoc test. Values are reported as mean±1 standard deviation. All tests were considered statistically significant at $p<0.05$.By considering the 16 variables of polysomnography, adjustment to multiple corrections was done. $P<0.003$ was considered to be significant.

RESULTS

Patient profile

A total of 72 patients recruited, 7 patients (Group I=2, Group II=2 and Group III=3) dropped out from the study due to various personal problems unrelated to the study and nobody discontinued due to adverse effects of the treatment. Mild adverse and side effects reported by the patients during interventions include: four patients (2 patients each from Groups I & II) reported mild abdominal colic which subsided without any intervention, six patients in Group III reported day time sleepiness (but it did not affect their day time functioning) during the first week of medication.

The mean age, gender, height, weight, body mass index, duration, severity of illness and history of sleep disturbance of

the patients were comparable in all the 3 groups [22] (Table 1). Base line values of sleep architecture (Table 3) were comparable between groups.

Sleep Quality Assessment

The details of sleep quality especially the time of waking, time of getting out of bed, waking up refreshed or tired, time of going to bed, time of falling asleep, number of awakenings, duration of awakenings and factors affecting sleep etc were obtained from the sleep diary maintained by the patients. Sleep disturbances ascertained from the sleep diary are provided in Table 1. All interventions showed significant improvement in sleep quality. Effect of intervention was comparable between groups except duration of night awakenings, where improvement was better in Group III (p=0.006) and Group II (p=0.005) compared to Group I. Group II and group III were comparable in all the parameters (Table 2).

Sleep architecture Assessment of Sleep variables

The Sleep efficiency index, sleep duration, REM duration, sleep onset latency, REM onset latency, total wake duration, micro arousal index, sleep cycles were comparable between groups (Table 3).NREM Stage 1 (%) (F (1, 62) =38.063, p<0.001) and NREM Stage 1(mins) (F (1, 62) =32.088, p<0.001) showed significant changes among groups with time as within group factor, however Group III showed significant reduction compared to Group I (Table 3) (Figures1,4).

NREM Stage 2 (%)

Repeated measures ANOVA with Time as within subject factor and Groups as between subject factor showed a significant effect of Time F(1,62)=24.994, p<0.001.There was significant effect of Group F (2, 62) = 11.857, p<0.001Post hoc tests revealed significant increase in Group III compared to Group I (p=0.016) & II (p<0.001)after treatment. Group X Time interaction was significant F (2, 62) = 20.972, p<0.001.Post hoc analysis showed that post treatment NREM S2% in Group III was significantly increased compared to Group I and Group II (P<0.001)(Table 3) (Figures 1,3).

NREM SWS (%)

Repeated measure ANOVA with time as within subject factor and groups as between subject factor showed a significant effect of time F(1,62)=17.710, p<0.001.There was significant effect of group F (2, 62) = 6.368, p=0.003.Post hoc showed that group III showed significant decrease compared to group I (p=0.004) and group II (p=0.020). Group X time interaction was significant F (2, 62) = 31.138, p<0.001. Post hoc analysis showed that post treatment SWS in Group III was significantly decreased compared to group I & II (p<0.001). (Table 3) (Figures 2,3).

Between groups major significant changes were observed in NREM S2% and NREM SWS. Post treatment significant increase of NREM S2 % (p<0.001) and decrease in NREM SWS (p<0.001) in Group III compared to Group II and Group I. The REM sleep states were not altered in patients and remained same following treatment in all three groups. The representative hypnograms to highlight the changes brought by interventions are depicted in (Figure 4).

DISCUSSION

The study comprehensively evaluated the distinct changes

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

Sl. No	Clinical profiles	Group-I (n=24)	Group- II(n=24)	Group-III(n=24)	p value
1	Age (years)	27.46±4.45	26.84±5.02	30.25±6.90	0.126
2	Gender Male	20	21	18	0.518
	Female	4	3	6	
3	Height (Centimeters)	166.97±5.95	166.84±5.71	165.38±8.78	0.674
4	Weight (Kilograms)	62.59±9.07	61.08±10.34	63.46±12.46	0.730
5	Body Mass Index	22.43±2.84	21.91±3.35	23.22±4.23	0.435
6	Severity of anxiety (Moderate)	0	0	1	2.03
	(Severe)	24	24	23	
7	Hamilton Anxiety Rating scale (HARS)	31.58±3.23	32.63±3.31	31.85±4.28	0.732
8	Becks Anxiety Inventory(BAI)	26.50±5.13	30.63±5.32	26.57±7.92	0.055
9	Becks Depression Inventory(BDI)	13.66±4.70	14.41±2.31	12.52±3.74	0.286
10	Epworth Sleepiness Scale(ESS)	6.22±3.43	6.35±4.10	6.28±5.26	0.968
11	Duration of illness (Years)	6.44±4.87	7.35±3.75	7.48±6.33	0.735
12	Age of onset (Years)	21.01± 5.71	19.49±6.08	23.76±6.86	0.102
13	H/O sleep disturbance Yes	12	14	13	0.336
	No	12	10	11	
14	Total patients Recruited	24	24	24	
	Drop outs	2	2	3	0.316
	Completed study	22	22	21	

Table 2: Comparison of sleep diary variables in three groups of patients -Before and after the Interventions. Expressed in Mean ± Standard Deviation.*p<0.05, **p<0.01, ***p<0.001.

Qualitative sleep parameters from sleep Diary

S.N	Intervention	Group I (n=22)	Group II (n=21)	Group III (n=21)	P Value			
					Comparison between groups			
					Group I-II-III	Group I-II	Group I-III	Group II-III
1	a.	Wake up Refreshed						
	Pre	12	9	8	0.367			
	post	16	15	15				
	b.	Wake up Tired						
	Pre	10	13	13	0.138			
	post	6	7	6				
2	Duration of sleep onset (minutes)							
	Pre	11.36±4.41	11.36±4.92	13.09±5.11	0.599			
	Post	8.40±3.89	6.81±2.46	7.14±2.53				
	P	0.001**	<0.001***	<0.001***				
3	Number of Night awakenings							
	Pre	2.18±1.43	2.54±1.18	2.80±1.36	0.545			
	Post	1.36±1.09	1.40±0.59	1.42±1.20				
	P	0.001**	<0.001***	<0.001***				
4	Duration of Night awakenings (minutes)							
	Pre	3.36±1.52	2.63±1.52	2.57±1.43	0.015	0.005**	0.006**	1
	Post	2.77±1.30	1.81±0.90	1.80±0.51				
	P	0.032*	0.003**	0.007**				
5	Number of days of stress affecting sleep in a week							
	Pre	3.09±0.92	2.86±0.88	3.04±0.86	0.919			
	Post	1.50±0.51	1.59±0.50	1.42±0.50				
	P	<0.001***	<0.001***	<0.001***				
6	Time of getting out of bed (minutes)							
	Pre	9.18±6.31	9.63±4.68	9.52±3.84	0.828			
	Post	7.72±4.34	8.04±2.71	6.66±2.88				
	P	0.046*	0.029*	<0.001***				

Table 3: Comparison of Sleep architecture variables in three groups of patients -Before and after the Interventions. Expressed in Mean ± Standard Deviation.*p<0.05, **p<0.01, ***p<0.001.

Sleep variables	Intervention	Group I (n=22)	Group II (n=22)	Group III (n=21)	P value (Comparison between groups)		
					I-II	I-III	II-III
Sleep Efficacy Index (%)	Before	89.87±7.11	90.62±6.23	88.97±6.86	1	1	1
	After	89.06±8.04	92.26±5.42	91.69±5.02	0.294	0.534	1
Sleep Duration	Before	413.68±57.23	416.79±49.94	392.35±41.14	1	0.501	0.343
	After	400.53±60.23	422.61±35.72	415.76±38.79	0.357	0.857	1
NREM Stage 1 (%)	Before	9.11±6.46	8.76±7.02	6.18±3.75	1	0.337	0.482
	After	6.29±4.08	5.77±4.45	3.15±2.66	1	0.027*	0.085
	P value	0.001**	0.001**	0.001**	-		
NREM Stage 2 (%)	Before	48.16±6.72	43.10±10.97	47.68±9.18	0.211	1	0.315
	After	49.08±10.85	43.14±10.36	65.21±12.69	0.260	<0.001***	<0.001***
NREM SWS(%)	Before	18.77±6.06	18.27±7.61	18.29±8.52	1	1	1
	After	20.46±6.79	18.57±7.13	7.21±7.57	1	<0.001***	<0.001***
REM (%)	Before	23.96±4.88	29.85±6.94	27.85±7.79	0.014*	0.177	0.983
	After	24.15±7.62	30.18±8.28	24.41±7.29	0.037*	1	0.053

Wake (min)	Before	46.43±33.09	42.97±32.80	49.59±33.41	1	1	1
	After	49.09±34.19	36.77±27.32	37.95±23.66	0.483	0.629	1
NREM Stage 1 (min)	Before	37.90±25.66	36.02±27.46	24.95±16.44	1	0.237	0.397
	After	25.86±17.15	24.47±18.67	13.28±11.62	1	0.04*	0.08
	P value	0.001**	0.002**	0.002**	-		
NREM Stage 2 (min)	Before	197.36±32.76	179.09±47.53	186.04±35.51	0.381	1	1
	After	195.09±40.88	171.38±61.66	256.26±73.61	0.585	0.004**	<0.001***
NREM Stage 3 (min)	Before	46.47±18.22	41.18±15.68	46.67±17.16	0.921	1	0.885
	After	45.18±17.71	41.90±19.59	20.50±19.30	1	<0.001***	0.001***
NREM Stage 4 (min)	Before	31.77±24.40	34.54±29.28	36.30±61.91	1	1	1
	After	36.86±23.95	40.65±31.22	9.40±18.52	1	0.002**	<0.001***
REM (min)	Before	100.84±29.65	125.97±38.27	110.57±38.77	0.069	1	0.489
	After	94.14±40.58	126.86±38.61	101.47±30.70	0.014*	1	0.084
SOL (min)	Before	10.15±7.61	10.09±8.03	11.09±8.28	1	1	1
	After	10.00±6.78	9.09±12.78	8.97±8.04	1	1	1
ROL (min)	Before	93.36±32.99	97.34±53.85	91.76±37.59	1	1	1
	After	105.63±43.08	99.27±41.97	127.00±75.25	1	0.629	0.315
Micro arousal Index	Before	15.14±6.51	12.89±4.16	13.94±6.35	0.601	1	1
	After	15.36±7.33	12.17±5.60	11.94±4.82	0.251	0.202	1
Sleep cycles	Before	4.18±1.05	4.36±0.95	4.38±1.11	1	1	1
	After	3.72±1.03	4.04±0.89	4.00±1.18	0.945	1	1

Abbreviations: NREM: Non Rapid Eye Movement Sleep; REM: Rapid Eye Movement Sleep; SOL: Sleep Onset Latency; ROL: REM Onset Latency

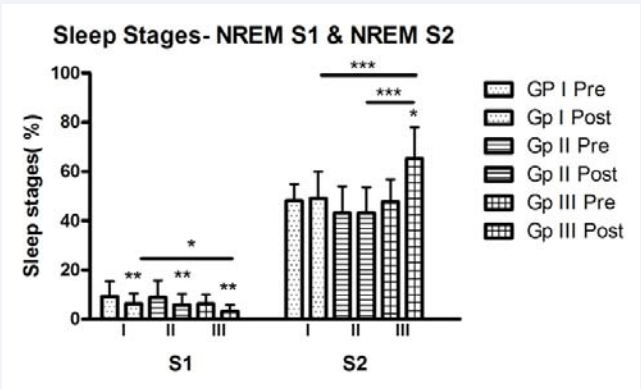

Figure 1 Changes in NREM S1 and NREM S2 stages of Sleep in Group I (n=22), Group II (n=22) and Group III (n=21) assessment pre and post interventions. Results are expressed in Mean ± standard deviation. Level of significance is *p<0.05, **p<0.01, ***p<0.001.

in sleep architecture brought by Manasamitra vataka and Clonazepam interventions in GAD patients with comorbid generalized social phobia. Ayurveda treatments were found to be more effective in promoting and preserving the sleep whereas Clonazepam treatment grossly altered the sleep architecture in GAD patients.

Insomnia is quite prevalent in GAD [28] and almost 60-70% patients of GAD reported sleep disturbances such as trouble falling sleep and staying asleep, increased daytime fatigue, irritability, and difficulty in coping [4,12]. Patients with Social phobia reported poor sleep quality, longer sleep latency, frequent awakenings and day time dysfunctions [15]. In the present study, almost 56% of patients reported history of disturbed sleep and also reported delayed period of sleep onset, more awakenings per night and non-refreshing sleep. The patients reported improvement in sleep quality and felt refreshed after sleep following interventions. Sleep architecture profiles revealed that the major polysomnographic parameters like sleep efficiency, duration, micro arousals etc, were almost within the normal physiological limits [29]. Previous studies on sleep architecture however revealed inconclusive reports; either increase or decrease in NREM S1, NREM S2 ,NREM S4, changes in NREM S3 and REM Sleep etc.[13].Differences in both

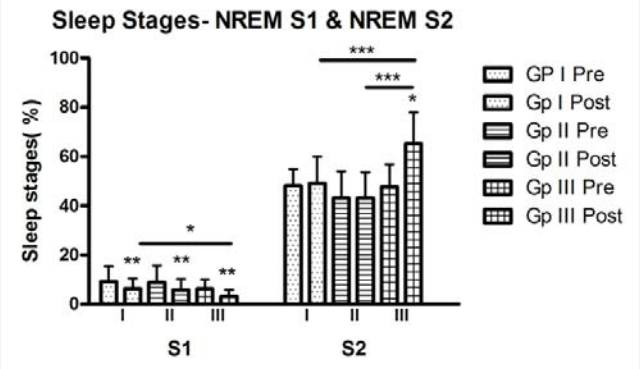

Figure 2 Changes in NREM SWS and REM stages of Sleep in Group I (n=22), Group II (n=22) and Group III (n=21) assessment pre and post interventions. Results are expressed in Mean ± standard deviation. Level of significance is *p<0.05, **p<0.01, ***p<0.001.

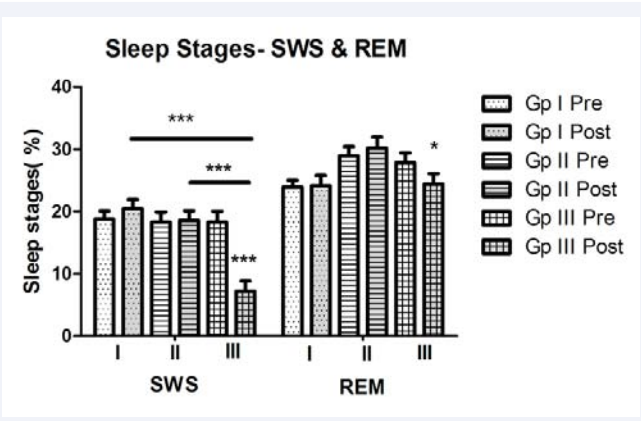

Figure 3 Representative Hypnogram of GAD patient with co morbid Generalized social phobia, before and after clonazepam intervention.

subjective and objective sleep assessments could be due to inconsistent sleep disturbance in the patients. The slow wave sleep states are restorative in nature and Ayurveda interventions preserved the slow wave sleep states. Additionally, Ayurveda treatments (Manasamitravataka treatment/Shirodhara) reduced the NREM S1 sleep, and thus reduced the sleep onset latency, reduced intermittent awakenings and helped in maintaining sleep continuity. Clonazepam however, enhanced NREM S2, REM (%), REM onset latency (ROL) but reduced significantly the slow wave sleep (SWS) which is important component of restoration. Benzodiazepine [30], is shown to grossly alter the architecture of sleep [16] and our study also showed non restorative sleep by Clonazepam. The literature on the effects of Clonazepam on sleep architecture is very scanty and the study contributes towards its role on sleep architecture.

Manasamitravataka is a compound formulation [22] with neurotropic and psychotropic action. The ingredients such as With an iasomnifera has GABA-mimetic activity [31]. Bacopamonneira has been shown to be sleep promoting [32].Up regulation of serotonin receptors[33], GABAergic modulation[34] of Bacopamonneira and Centella asiatica [35] have been reported. However, the effect of external use of Brahmi oil (Bacopamonneira) has not been reported. Shirodhara in healthy individuals showed anxiolytic effect as assessed by State-Trait Anxiety Inventory [36-39] and Shirodhara effect could be through brain targeted transcranial drug delivery [40,41]. Present study showed that Shirodhara with Brahmi tailam considerably reduced the micro arousals and hence helped in sleep continuity. We have also reported earlier about the sleep promoting effects of Shirodhara the treatment significantly reduced daytime sleepiness [22].

Ayurveda treatments thus shown to be effective over Clonazepam in maintaining proper sleep architecture and helps in preserving slow wave sleep. Slow wave sleep has a significant role in maintaining body homeostasis like cerebral restoration and recovery [42,43].Slow wave sleep is the main time period for secretion of anabolic growth hormone [44], for tissue repair and growth [45],synaptic density [46], learning and synaptic

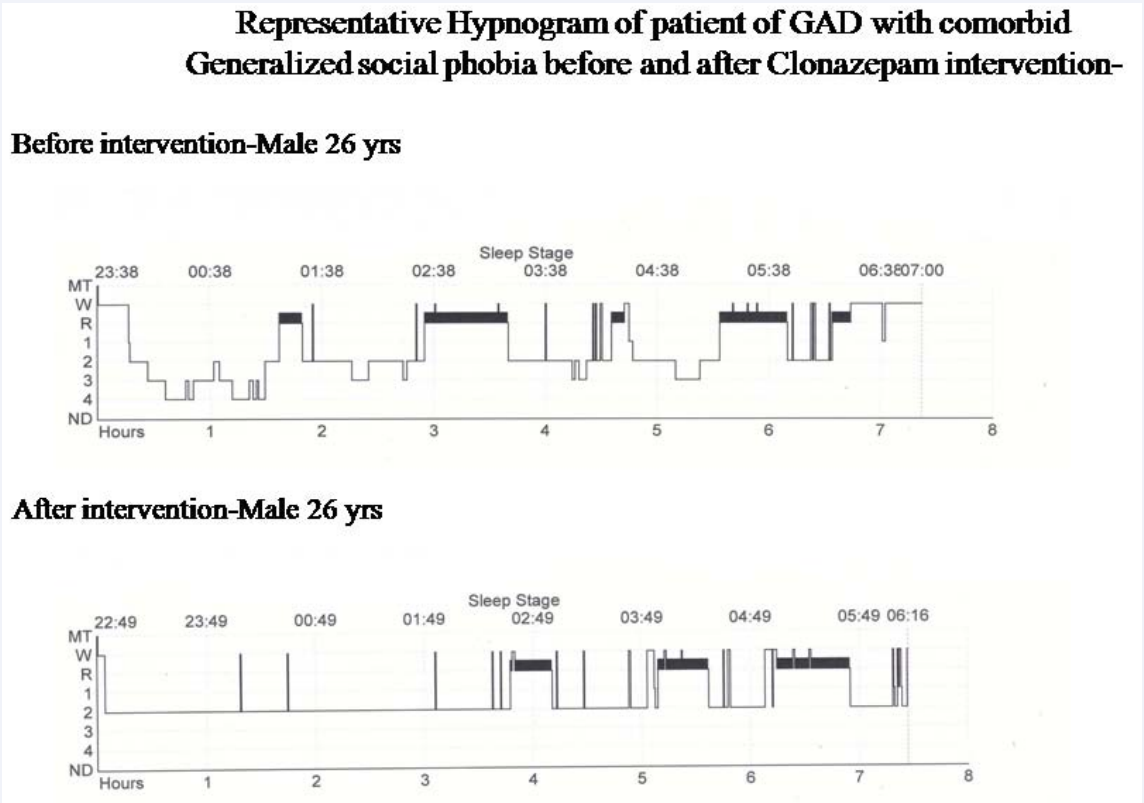

Figure 4 Representative Hypnogram of patient of GAD with co morbid Generalized social phobia before and after intervention with Manasamitravataka and Shirodhara therapy.

plasticity, memory consolidation especially declarative memory [47] and is involved in the maintenance and consolidation of sleep [48].

The present study has several limitations such as it is an open labeled study and not a double blind randomized control study. An additional placebo group would have helped to demonstrate the subsequent changes in sleep after the interventions but would have had ethical implications in the psychiatric population under consideration. Similarly, long term interventions would have thrown more light on the effect of treatments on clinical and sleep profiles. As both Manasamitravataka and Shirodhara are being studied for the first time by us on psychiatric population [22], further studies are required to detail the profile of the medications on other biological parameters as well for additional information.

Overall, the study highlights the sleep promoting and sleep architecture preserving nature of Manasamitravataka and Shirodhara in GAD patients with co-morbid generalized social phobia. Ayurveda treatments were helpful in improving the subjective quality of sleep and to preserve the sleep organization. Ayurveda treatments also were found to be highly effective over Clonazepam in terms of preserving the sleep. Add on effect of Shirodhara on Manasamitra vataka has improved the sleep continuity by reducing the micro arousals and also the day time sleepiness [22]. Clinical variables outcome showed that Ayurveda interventions were effective in ameliorating GAD with comorbid generalized social phobia and were comparable to Clonazepam [22].Hence Ayurveda interventions like Manasamitravataka can be the drug of choice in the comprehensive management of GAD with generalized social phobia. Hence, the current medications are suggestive of an effective comprehensive treatment strategy in GAD with generalized social phobia.

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REFERENCES

1. Brawman-Mintzer O, Lydiard RB, Emmanuel N, Payeur R, Johnson M, Roberts J, et al. Psychiatric comorbidity in patients with generalized anxiety disorder. Am J Psychiatry. 1993; 150: 1216-1218.
2. Coelho HF, Cooper PJ, Murray L. A family study of co-morbidity between generalized social phobia and generalized anxiety disorder in a non-clinic sample. J Affect Disord. 2007; 100: 103-113.
3. Sanderson WC, Barlow DH. A description of patients diagnosed with DSM-III-R generalized anxiety disorder. J Nerv Ment Dis. 1990; 178: 588-591.
4. Benca RM. Sleep in psychiatric disorders. Neurol Clin. 1996; 14: 739-764.
5. Gillin JC. Are sleep disturbances risk factors for anxiety, depressive and addictive disorders? Acta Psychiatr Scand Suppl. 1998; 393: 39-43.
6. Hughes JR. A review of the usefulness of the standard EEG in psychiatry. Clin Electroencephalogr. 1996; 27: 35-39.
7. Leskin GA, Woodward SH, Young HE, Sheikh JI. Effects of comorbid diagnoses on sleep disturbance in PTSD. J.Psychiatr Res. 2002; 36: 449-452.
8. Ohayon MM, Caulet M, Lemoine P. Comorbidity of mental and insomnia disorders in the general population. Compr Psychiatry. 1998; 39: 185-197.
9. Ohayon MM, Shapiro CM. Sleep disturbances and psychiatric disorders associated with posttraumatic stress disorder in the general population. Compr Psychiatry. 2000; 41: 469-478.
10. Ohayon MM, Roth T. Place of chronic insomnia in the course of depressive and anxiety disorders. J Psychiatr Res. 2003; 37: 9-15.
11. Fuller KH, Waters WF, Binks PG, Anderson T. Generalized anxiety and sleep architecture: a polysomnographic investigation. Sleep. 1997; 20: 370-376.
12. Saletu B, Saletu-Zyhlarz G, Anderer P, Brandstatter N, Frey R, Gruber G, et al. Nonorganic insomnia in generalized anxiety disorder. 2. Comparative studies on sleep, awakening, daytime vigilance and anxiety under lorazepam plus diphenhydramine (Somnium) versus lorazepam alone, utilizing clinical, polysomnographic and EEG mapping methods. Neuropsychobiology 1997; 36: 130-152.
13. Monti JM, Monti D. Sleep disturbance in generalized anxiety disorder and its treatment. Sleep Med Rev. 2000; 4: 263-276.
14. Papadimitriou GN, Linkowski P. Sleep disturbance in anxiety disorders. Int Rev Psychiatry. 2005; 17: 229-236.
15. Stein MB, Kroft CD, Walker JR. Sleep impairment in patients with social phobia. Psychiatry Res. 1993; 49: 251-256.
16. Saletu B, Anderer P, Brandstätter N, Frey R, Grünberger J, Klösch G et al. Insomnia in generalized anxiety disorder: polysomnographic, psychometric and clinical investigations before, during and after therapy with a long- versus a short-half-life benzodiazepine (quazepam versus triazolam). Neuropsychobiology 1994; 29: 69-90.
17. Bastien CH, LeBlanc M, Carrier J, Morin CM. Sleep EEG power spectra, insomnia, and chronic use of benzodiazepines. Sleep. 2003; 26: 313-317.
18. Gervasoni D, Panconi E, Henninot V, Boissard R, Barbagli B, Fort P, et al. Effect of chronic treatment with milnacipran on sleep architecture in rats compared with paroxetine and imipramine. Pharmacol Biochem Behav. 2002; 73: 557-563.
19. Jindal RD, Friedman ES, Berman SR, Fasiczka AL, Howland RH, Thase ME. Effects of sertraline on sleep architecture in patients with depression. J Clin Psychopharmacol. 2003; 23: 540-548.
20. Astin JA.Why patients use alternative medicine: results of a national study. JAMA. 1998; 279: 1548-1553.
21. Sahasrayoga. In: Ramnivas Sharama and Surendra Sharama, ed. Sahasrayoga. 3 ed. In New Delhi: Choukamba sanskrut prathisthan, 2002: 253-4.
22. Tubaki BR, Chandrashekar CR, Sudhakar D, Prabha TN, Lavekar GS,

Kutty BM. Clinical Efficacy of Manasamitra Vataka (an Ayurveda Medication) on Generalized Anxiety Disorder with Comorbid Generalized Social Phobia: A Randomized Controlled Study. J Altern. Complement Med. 2012; 18: 612-621.

23. Moher D, Schulz KF, Altman DG. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomized trials. Ann. Intern. Med. 2001;134: 657-662.

24. Hamilton M. The assessment of anxiety states by rating. Br J Med Psychol. 1959; 32: 50-55.

25. Ramanarayan Sharma vaidya. In: Shree Baidyanath Ayurved Bhavan Limited, ed. Ayurveda Sara sangraha. 18 ed. Nagpur. Maharashtra: 1996: 690.

26. Crofts HS, Wilson S, Muggleton NG, Nutt DJ, Scott EA, Pearce PC. Investigation of the sleep electrocorticogram of the common marmoset (Callithrix jacchus) using radiotelemetry. Clin Neurophysiol. 2001; 112: 2265-2273.

27. Jasper HH. The ten-twenty electrode placement system of the International Federation. Electroencephalography & Clinical Neurophysiology.1958; 10: 418-24.

28. Anderson DJ, Noyes R Jr, Crowe RR. A comparison of panic disorder and generalized anxiety disorder. Am J Psychiatry. 1984; 141: 572-575.

29. Carskadon M A, Dement W C. In: Kryger M H, Roth T, Dement W C, eds. Principles and Practice of Sleep Medicine. 4 ed. Philadelphia: Elsevier Saunders, 2005: 13-23.

30. Hindmarch I, Dawson J, Stanley N. A double-blind study in healthy volunteers to assess the effects on sleep of pregabalin compared with alprazolam and placebo. Sleep. 2005; 28: 187-193.

31. Kulkarni SK, Verma AV. GABA receptor mediated anticonvulsant action of Withania somnifera root extract. Indian Drugs. 1993; 30: 305-312.

32. Malhotra CL, Das PK. Pharmacological studies of Herpestis monniera, Linn., (Brahmi). Indian J Med Res. 1959; 47: 294-305.

33. Saraf MK, Prabhakar S, Anand A. Bacopa monniera alleviates N (omega)-nitro-L-arginine arginine-induced but not MK-801-induced amnesia: a mouse Morris watermaze study. Neuroscience 2009; 160: 149-155.

34. Prabhakar S, Saraf MK, Pandhi P, Anand A. Bacopa monniera exerts antiamnesic effect on diazepam-induced anterograde amnesia in mice. Psychopharmacology (Berl). 2008; 200: 27-37.

35. Awad R, Levac D, Cybulska P, Merali Z, Trudeau VL, Arnason JT. Effects of traditionally used anxiolytic botanicals on enzymes of the gamma-aminobutyric acid (GABA) system. Can J Physiol Pharmacol. 2007; 85: 933-942.

36. Uebaba K, Xu FH, Tatsuse T, Hisajima T. Psychological mechanism of Traditional healing technique performed by the healing robot through the life information field. J Int Soc Life Info Sci 2004; 22: 169-178.

37. Uebaba K, Xu FH, Tagawa M, Asakura R, Itou T, Tatsuse T, et al. Using a healing robot for the scientific study of shirodhara. Altered states of consciousness and decreased anxiety through Indian dripping oil treatments. IEEE Eng Med.Biol.Mag. 2005; 24: 69-78.

38. Uebaba K, Xu FH, Ogawa H, Tatsuse T, Wang BH, Hisajima T, et al. Psychoneuroimmunologic effects of Ayurvedic oil-dripping treatment. J Altern Complement Med. 2008; 14: 1189-1198.

39. Xu F, Uebaba K, Ogawa H, Tatsuse T, Wang BH, Hisajima T, et al. Pharmaco-physio-psychologic effect of Ayurvedic oil-dripping treatment using an essential oil from Lavendula angustifolia. J Altern Complement Med. 2008; 14: 947-956.

40. Pathirana W, Abhayawardhana P, Kariyawasam H, Ratnasooriya WD. Transcranial route of brain targeted delivery of methadone in oil. Indian J Pharm Sci. 2009; 71: 264-269.

41. Pathirana W, Gunasekera SM, Constantine GR, Perera S, Perera BM, Kamaladiwela R. Brain targeted transcranial administration of diazepam and shortening of sleep latency in healthy human volunteers. Indian J Pharm.Sci. 2011; 73: 497-503.

42. Benington JH, Heller HC. Restoration of brain energy metabolism as the function of sleep. Prog Neurobiol. 1995; 45: 347-360.

43. Horne J. Human slow wave sleep: a review and appraisal of recent findings, with implications for sleep functions, and psychiatric illness. Experientia. 1992; 48: 941-954.

44. Takahashi Y, Kipnis DM, Daughaday WH. Growth hormone secretion during sleep. J Clin Invest. 1968; 47: 2079-2090.

45. Adam K. Sleep as a restorative process and a theory to explain why. Prog Brain Res. 1980; 53: 289-305.

46. Feinberg I. Schizophrenia: caused by a fault in programmed synaptic elimination during adolescence? J Psychiatr Res. 1982; 17: 319-334.

47. Marshall L, Helgadóttir H, Mölle M, Born J. Boosting slow oscillations during sleep potentiates memory. Nature. 2006; 444: 610-613.

48. Dijk DJ, Groeger J, Deacon S, Stanley N. Association between individual differences in slow wave sleep, slow wave activity and sleep continuity in young, middle-aged and older men and women. Eur Neuropsychopharmacol. 2006; 16: S538.

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