

Study Protocol

Comparative Study of Efficacy of *Jatamansi* (*Nardostachys jatamansi* DC) and Imipramine in Generalized Anxiety Disorder (G.A.D.): A Randomized Controlled Double Blind Clinical Trial

Abstract -

Background- Onset of G.A.D. is related with bigger excessiveness and uncontrolled worry, along with more chronic course and more severe life mutilation. Individuals suffering from G.A.D. are at high risk of bothered mental health, social functioning, and overall physical & mental well being. Limited long-term efficacy of anxiolytic drugs has shown by clinical trials but drowsiness, dependency, impaired cognition and memory and sexual dysfunction like loss of libido are common adverse side effects of these drugs. *Nardostachys jatamansi* is a reputed Ayurvedic herb useful for treatment of various disorders mainly central nervous disorders. Various preclinical and clinical studies had proven anxiolytic activity of Jatamansi. Hence present study is planned to assess effects of Jatamansi in Generalized Anxiety Disorder.

Materials and methods- Present double-blind randomized control clinical study involves two groups with 38 subjects each. Group A (Study Group) will be treated with administration of Tab. Jatamansi in the dose of 1000 mg B.D. orally with water. Group B (Control Group) will be treated with administration of Tab. Imipramine 75 mg H.S. orally for 60 days. Assessment parameter will be anxiety score based on symptoms of Generalized Anxiety Disorder. H.A.M.-A. Scale, G.A.D. – 7 Scale, Manas Bhava and Oxidative Stress. Primary outcome of study is improvement in the sign and symptoms of anxiety with reduction in anxiety scale score.

Key words- anxiety, Generalized anxiety disorder, G.A.D, Jatamansi,

Introduction

“India needs to talk about mental illness¹” this was the media headline after the release of report of the National Mental Health Survey (NMHS). Worldwide, prevalence of mental and neurological disorders is high; i. e. 13 % of total disability adjusted life years vanished due to all diseases and injuries across the globe. As per estimation of World Health Organization, 450 million persons are affected due to mental illness. Anxiety is extensive, with lifetime prevalence rates oscillating from 13.60 % to 28.80 % in Western nations. Individuals aged between 10 to 25 years are at peak risk for developing an anxiety like ailment.²

Generalized anxiety disorder (G. A.D.) ranked as one of the most common mental illnesses. Each year up to 20% of adults are affected by anxiety disorders. Generalized anxiety disorder results into worry, fear, along with continuous sense of being overwhelmed. It is characterized by tenacious, unnecessary, and unnecessary worry about day-to-day issues such as health, finance, family, and future. It is very difficult to control, because it is frequently accompanied by various non-specific physical and psychological symptoms. Excessive worry is the focal feature of generalized anxiety disorder. Drugs and psychological therapies are useful strategies for the treatment of GAD. Antidepressants, anticonvulsant pregabalin, and benzodiazepines are commonly effective drugs, while psychological

therapies like behavioral therapy, cognitive behavioral therapy (CBT), relaxation response, and mindfulness meditation training³ shown positive response.

In Ayurveda various treatment modalities are explained for diseases related to central nervous system. Various herbs mentioned in the Ayurveda proved its potential to work on anxiety. Various researches validated of Bramhi (*Bacopa monniera*)⁴, Vacha (*Acorus calamus*)^{5,6,7}, Jatamansi (*Nardostachys jatamansi*)⁸, Mandukparni (*Centella asiatica*)⁹, Tagar (*Velerial velchii*), Kawa (*Piper methystium*), Ashwagandha (*Withenia somnifera*), Shunthi (*Zinziber officinale*)¹⁰, Kaitarya (*Myricanagi*)¹¹, Chorak (*Angelica glauca*), Hingu (*Ferula narthex*)¹², Yashtimadhu (*Glycerriza glabra*)¹³ are effective CNS acting herbs with the anxiolytic activities.

The plant *Nardostachys jatamansi* is a reputed Ayurvedic herb and it is the major ingredient in Ayurvedic formulations for treatment of various disorders mainly central nervous disorders. It is mentioned as Vednasthapan (analgesics), Sangyasthapan (which restoring the consciousness or alertness of mind), Medhya (brain tonic), Balya (strengthen body), Hrudya (cardio-protective), Jwaraghana (anti-pyretic), Kusthaghna (prevent skin diseases), Keshva (promote hair growth)¹⁴. It is effective in primary insomnia through external application also¹⁵. *Nardostachys jatamansi* possess many activities like Antidepressant activity, Anticonvulsant activity, Antiarrhythmic activity, CNS activity, Neurotropic activity, Antiparkinson activity, Antioxidant activity, Antidiabetic activity, Cardioprotective and hepatoprotective activity useful in Alzheimer & Cerebral ischemia, Anxiolytic & Hypolipidemic activity.¹⁶ Various preclinical and clinical studies had proven anxiolytic activity of Jatamansi. Till now, no research work is published regarding the effect of Jatamansi in Generalized Anxiety Disorder on different parameters like HAM-A, GAD-7, Charakokta Manas Bhava Scale and oxidative stress. Hence this study is designed to assess the effect of Jatamansi on generalized anxiety disorder in comparison with imipramine.

Objectives of the study are to -

- Evaluate and compare efficacy of Jatamansi (*Nardostachys jatamansi* DC) and Imipramine on Generalized Anxiety Disorder (G.A.D.)
- Assess the effect of both drugs on HAM-A, GAD-7 scale and oxidative stress.
- Assess the effectivity of both drugs on Manas Bhavas mentioned in Charak Samhita.
- Analyze effects of both drugs in the context of Prakruti
- Study the complications/side effects of both drugs if any during the course of treatment.

Material and methods –

Source of Data:

Present study is double blind randomized control clinical trial in which sample will be collected with computer generated Simple Random method after approval of I.E.C. Mahatma Gandhi Ayurved Collge, Hospital and R.C. Salod. Participants will be enrolled from Department of Kayachikitsa, Mahatma Gandhi Ayurved College, Hospital and Research Centre, Salod (H) and Department of Psychiatry, Acharya Vinoba Bhave Rural Hospital Sawangi

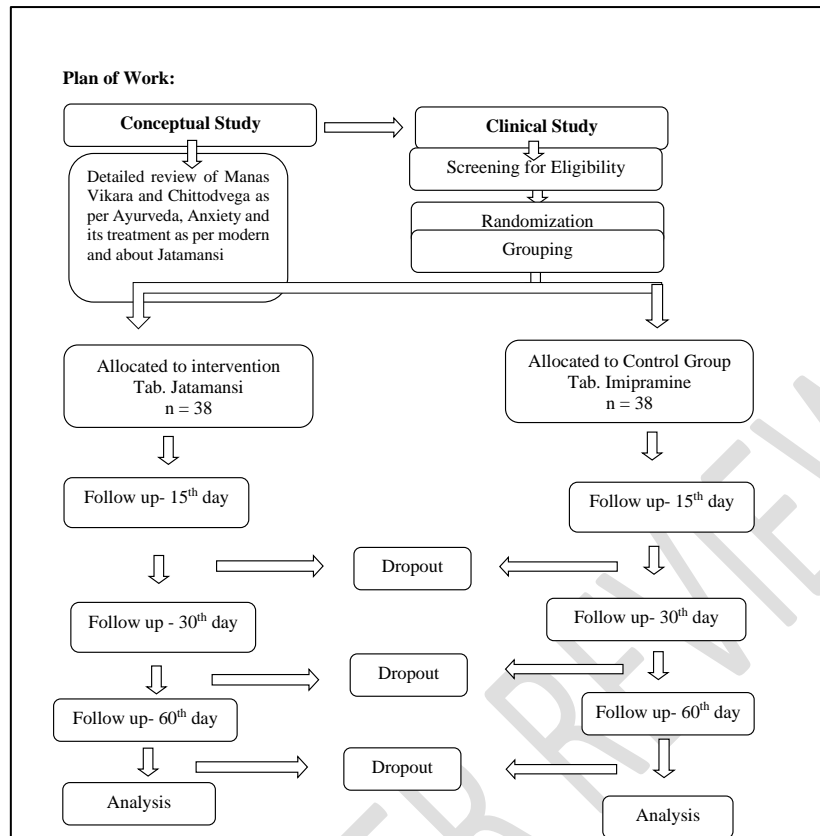


Fig 1: Plan for work

Study design:

Present study is double blind randomized control clinical trial in which sample will be collected with computer generated Simple Random method. Study involves two groups with 38male and female patients of age group 20 – 50 years in each group. Group A (Study Group) will be treated with Tab. Jatamansi orally and Group B (Control Group) will be Treated with Tab. Imipramine.

Sample size: Sample size was calculated by software n Master 2.0 by which total 76 subjects will be enrolled considering 10% drop out rate and distributed evenly into two groups by random sampling. The groups will be as follows.

1. Study group: 38 patients – treated with Tab. Jatamansi
2. Control group: 38 patients – treated with Tab. Imipramine

Inclusion criteria

1. Patients having confirmed diagnosis of GAD as per DSM 5
2. Freshly diagnosed patients.
3. Male and female patients of age group 20 - 40 years
4. Patients with no previous history of taking medicines for Psychiatric disorders.
5. Patients ready to cooperate, giving written consent.

Exclusion criteria

1. Patient with psychiatric disorders other than GAD.
2. Patients with no history of medications for any psychiatric disorder including GAD

3. Patients suffering from any major medical illness requiring significant care.
4. Patients with risk of serious suicidal & Homicidal tendencies, substance or alcohol dependence, any thyroid pathology.
5. Patients unwilling to participate in study.
6. Pregnant and lactating females will be excluded
7. Having any known history of allergy to treatment component.

Screening Parameters:

1. Assessment will be done on the basis of signs and symptoms of GAD
2. Hamilton Anxiety Rating Scale, Generalized Anxiety Disorder -7 (GAD-7) scale will be used for mental health evaluation of patients.
3. Standard Ayurvedic parameters will be used to assess the impact of psychological factor interfering in the disease process.

Table 1: Details of method and experimental design:

Heading	Group A (Study Group)	Group B (Control Group)
Sample size	38	38
Intervention	Tab. Jatamansi	Tab. Imipramine
Dose	1 gm BD	75 mg HS
Anupan	With water after meal	With Water at bed time
Duration of Treatment	60 days	60 days
Follow up	Day- 15	Day- 15
	Day- 30	Day- 30
	Day- 60	Day- 60
P.T. Follow up	After 30 days of completion of trials	After 30 days of completion of trials
Total duration	90 Days	90 Days

Plan of Work- Material –

Trial Drug - Jatamansi (*Nardostachysjatamansi* DC)

1. Collection and Identification-

- I) Collection of Material (Procurement of drug) :-
 - A) Plant Material – Crude dried rhizome and roots of Jatamansi (*Nardostachysjatamansi* DC) will be collected from Manas Ayurved Nagpur.
 - B) Control drug- Imipramine of standard company (WHO GMP Certified) will be purchased from the market.
- II) Identification and Authentication: -

Identification and Authentication of Jatamansi (*Nardostachysjatamansi* DC) will be done at Department of Dravyaguna, M. G. A. C. Salod

2. Preparation of Tablet Jatamansi

- a) Trial drug i.e. Tab. Jatamansi will be prepared in the Dattatraya Rasashala of M. G. A. C. Salod, Wardha.
- b) Fine powder of dried roots and rhizome of Jatamansi will be made and further converted in to tablet form. Each prepared tablet will contain 500 mg Jaramansi powder (Churna).
- c) Tablets of Jatamansi Churna- 500 mg will be packed in the jars of 30 and 60 tablets.

3. Phytochemical Evaluation: -

A) Macroscopic Study- Evaluation of physical appearance.

B) Organoleptic Study –

- 1) Color
- 2) Odor
- 3) Taste
- 4) Consistency

C) **Microscopy and Histochemistry** – Microscopic cellular structure of tissues

D) **Physicochemical (physical evaluation)-**

i) Foreign Matter ii) Loss on Drying iii) pHiv) Ash Value– Total ash, Acid insoluble and Water soluble ash v) Extractive values - Aqueous extractive and Alcoholic extractive values

E) **Phytochemical Screening: -**

a) **Qualitative evaluation: -** Qualitative evaluation for Tannins, Phloba-tannins, Saponin, Steroid, Terpenoids, Flavonoids, Alkaloid, Glycoside will be carried out in approved laboratory.

b) **Total Phenolic content**

c) **T.L.C.**

d) **H. P. T. L. C.**

F) **Pharmaceutical Standardization of Tablet Jatamansi -**

1. Uniformity of Weight Test
2. Friability Test
3. Hardness Test
4. Disintegration Test

Control Drug-

Tablet Imipramine - 75 mg of reputed brand will be dispensed on prescription of the psychiatric consultant.

Parameters-

Subjective - Anxiety score based on symptoms of Generalized Anxiety Disorder.

H.A.M.-A. Scale, G.A.D. – 7 Scale and Manas Bhava Parikshana.

Objective - Oxidative Stress – MDA and SOD

Assessment will be done before and after treatment

Subjective parameters

1. Scoring Adopted for the symptoms of Generalized Anxiety Disorder¹⁷

(On the scale of 0 – 4)

1. Worry
2. Restlessness
3. Irritability
4. Insomnia
5. Concentration

6. Muscle tension
7. Fatigue

Table 2. Hamilton Anxiety Rating Scale (HAM-A)¹⁸

No	Class	Symptoms	Rating				
			0	1	2	3	4
1	Anxious Mood	Worries, anticipation of the worst, fearful anticipation, irritability	0	1	2	3	4
2	Tension	Feelings of tension, fatigability, startle response, moved to tears easily, trembling, feeling of restlessness, inability to relax	0	1	2	3	4
3	Fears	Of dark, of strangers, of being left alone of animals, of traffic, of crowds	0	1	2	3	4
4	Insomnia	Difficulty in falling asleep, broken sleep, unsatisfying sleep and fatigue on walking, dreams, nightmares, night-terrors	0	1	2	3	4
5	Intellectual	(Cognitive) Difficulty in concentration, poor memory	0	1	2	3	4
6	Depressed Mood	Loss of interest, lack of pleasure in hobbies, depression, early waking, diurnal swing	0	1	2	3	4
7	Somatic (Muscular)	Pains and aches, twitching, stiffness, myoclonic jerks, grinding of teeth, unsteady voice, increased muscular tone	0	1	2	3	4
8	Somatic (Sensory)	Tinnitus, blurring of vision, hot and cold flushes, feeling of weakness, picking sensation	0	1	2	3	4
9	Cardiovascular Symptoms	Tachycardia, palpitations, pain in chest, throbbing of vessels, fainting feelings, missing beat	0	1	2	3	4
10	Respiratory Symptoms	Pressure of constriction in chest, choking feelings, sighing, dyspnea	0	1	2	3	4
11	Gastrointestinal Symptoms	Difficulty in swallowing, wind, abdominal pain, burning sensations, abdominal fullness, nausea, vomiting, looseness to bowels, loss of weight, constipation	0	1	2	3	4
12	Genitourinary Symptoms	Frequency of micturition, urgency of micturition, amenorrhea, menorrhagia, development of frigidity premature ejaculation, loss of libido, impotence.	0	1	2	3	4
13	Autonomic Symptoms	Dry mouth, flushing, pallor, tendency to sweat, giddiness, tension headache, raising of hair	0	1	2	3	4
14	Behavior at Interview	Restlessness or pacing, tremor of hands, furrowed brow, strained face. Sighing or rapid respiration, facial pallor, swallowing, belching, brisk tendon jerks, dilated pupils,	0	1	2	3	4

		exophthalmos					
--	--	--------------	--	--	--	--	--

Table 3. Generalized Anxiety Disorder 7-item (GAD-7) scale¹⁹ -

Generalized Anxiety Disorder 7-item (GAD-7) scale					
	Over the last 2 weeks, how often have you been bothered by the following problems?	Not at all sure	Several days	Over half the days	Nearly every day
1	Feeling nervous, anxious, or on edge	0	1	2	3
2	Not being able to stop or control worrying	0	1	2	3
3	Worrying too much about different things	0	1	2	3
4	Trouble relaxing	0	1	2	3
5	Being so restless that it's hard to sit still	0	1	2	3
6	Becoming easily annoyed or irritable	0	1	2	3
7	Feeling afraid as if something awful might happen	0	1	2	3
	Add the score for each column	+ + +			
	Total Score =				

4. Gradation of Manas Bhava Pariksha¹⁷ (On scale of 0 – 3)

I) Negative Emotions-

1. Krodha–Abhidrohenai.e.ParapidarthaPravrittih
2. Bhayam- Vishadena
3. Shoka Dainyenai.e.Rodanadi
4. Dvesha–Pratishedhenai.e.Vyavrutya
5. Rajah-Sangenai.e.NaryadisangenaTatkaranamRajoanumiyate
6. Moha–Avijnanena

II) Positive Emotions-

1. Dhairyam-Avishhadenai.e.ManasoAdeinyam
2. Harsha –Amodenai.e.Nrityagitavaditradutsavakaranama
3. Priti–Tosenai.e.Mukhanayanprasadadih
4. Viryam–Utthanenai.e.Kriyarambhena
5. Shraddha –Abhiprayenai.e.Abhyarthanena
6. Medha–Grahanenai.e.Granthadidharanena

Objective parameters-

Table 4 Oxidative Stress Study²⁰-

Sr No	Marker	B.T.	A.T.
1.	MDA – Malondialdehyde		
2.	SOD- Dismutase	Superoxide	

Table

5 Assessment of Total Effect of the Therapy:

1	Complete Remission	100% relief in signs and symptoms
2	Markedly Improved	Patients showing improvement between 75% –99%
3	Moderately Improved	Improvement between 50% – 74% in the patients.
4	Improved	Improvement between 25% – 49%
5	Not Improved	No relief or symptoms relieved up to 24%

Analysis plan (Statistical test):

1. Interim analysis will be done.
2. I.T.T. (Intention to Treat analysis)
3. Statistical assessment will be done through paired t test and unpaired t test.

Discussion -

Jatamansi is useful in various CNS related problems. It is widely used in the management of stress, insomnia, hypertension, Unmada, Apasmar, memory loss, hair fall and various other CVS, GIT problems. Its efficacy is validated through various clinical studies. *Nardostachys Jatamansi* is natural antianxiety drug. It is effective to control the anxiety and related symptoms, gives a relaxing state of mind without disturbing normal physical or mental functions. Various pre-clinical studies proven its anxiolytic activities in the dose of 100 – 300 mg/kg^{21,22,23}, Some toxicity studies also established its safety as no toxicity is reported even at the dose of 5000mg/kg²⁴. Considering complex chemical compositions of Jatamansi like volatile essential oil and other biological active compounds, powdered Jatamansi may prove more effective than Kwatha or Ghana Vati. The use of Jatamansi in form of tablet can prove promising potential to treat the anxiety and stress related problems. The use of herbal drug may be helpful in resolving issues related to the adverse effect and challenges monitoring safety. One case report reviewed²⁵. Besides that, social effect will develop that use of herbal medicine is helpful to recovered disease and promote healthier living. Few of the related studies were reviewed^{26,27}.

Conclusion:

Conclusion will be drawn on the basis of statistical analysis with expected primary outcome—Improvement in the sign and symptoms of anxiety with reduction in anxiety scale score and secondary outcome—Prakruti wise variations in the results.

NOTE:

The study highlights the efficacy of "Ayurveda" which is an ancient tradition, used in some parts of India. This ancient concept should be carefully evaluated in the light of modern medical science and can be utilized partially if found suitable.

References:

1. Afshan, Y. India needs to talk about mental illness, The Hindu, 23 October, 2016.
2. National Mental Health Survey of India, 2015-2016 Prevalence, Patterns and Outcomes, Supported by Ministry of Health and Family Welfare, Government of India, and Implemented by National Institute of Mental Health and Neurosciences (NIMHANS). Bengaluru: In Collaboration with Partner Institutions; 2015-2016.
3. Alkhader, 2018;2(2):65–69. <https://doi.org/10.24911/IJMDC.51-1518966687>
4. Sawarkar G, Sawarkar P. Role of Ayurveda in the management of Apasmara: A case study. *Journal of Indian System of Medicine*. 2019 Oct 1;7(4):245.
5. Gupta K, Ashok BK, Ravishankar B, Thakar AB. Anti-anxiety and anti-depressant activities of Sarasvatachoorna in experimental animals. *Ayu*. 2011;32(4):590–593. doi:10.4103/0974-8520.96139
6. Bhattacharyya ID, A clinical study on the management of generalized anxiety disorder with *Vaca (Acorus calamus)*, *Indian Journal of Traditional Knowledge* 10 (4), 2011, 668-671
7. Evaluation of the Efficacy and Safety of Ayurvedic Drug (*Vacha Bramhi Ghana*) in the Management of *Manodwega* (Anxiety Neurosis), Anil Mangal, *J. Res. Educ. Indian Med* 2012; XVIII (3-4): 143-48
8. Jadhav V .M ., Herbal anxiolyte : *Nardostachys jatamansi* , *Journal of Pharmacy Research* 2009, 2)8(,1208-1211
9. U Jana et al, A clinical study on the management of generalized anxiety disorder with *Centella asiatica*, *Nepal Med Coll J* 2010; 12(1): 8-11
10. Thakur Priyanka, Anxiolytic potential of Medicinal Plant, *Int. Journal of Nutrition Pharmacology, Neurological diseases*, 3 (4), 2013
11. Md .Yaseen Khan, H .Sagrawat, N .Upmanyu & S .Siddique Anxiolytic Properties of *Myrica nagi* Bark Extract, *Pharmaceutical Biology*, 2008, 46:10-11, 757-761, DOI: 10.1080/13880200802315436
12. Prashant Saxena, Kalyani Divakar, Anxiolytic and Antiepileptic effects of asafoetida oleo gum resin, *World Journal of Pharmaceutical Research*, 3(6), 793-805
13. Sheshagiri S, Patel KS, Rajagopala S. Randomized placebo-controlled clinical study on enhancement of Medha (intelligence quotient) in school going children with Yahstimadhu granules. *Ayu*. 2015 Jan;36(1):56.
14. Talmale Sanjay, *Dravyagunavigyan*, Dhanwantari Book Publishers, Nagpur, 1st Edition, 2017, Page 574
15. Mhaiskar B, Parwe S. Evaluation Of Efficacy Of Jatamansi Tail Shirodhara In Anidra (Primary Insomnia). *Journal Of Critical Reviews*, 2019;6(6); 930-935
16. Mohammed Abdul Aleem, Ibrahim M *et al*. Phytochemical, antioxidant and neurobehavioral study of hydroalcoholic extract of *N. jatamansi* in reversing metoclopramide-induced catalepsy in rats. *International Journal of Indigenous Medicinal Plant*. 2013; 46(3):1338-1347.

17. Ahir Yogita, Evaluation of Clinical Effect of Kushmandadi Ghrita in Generalized Anxiety Disorder, *Indian Journal of Traditional Knowledge*, 2011,10(2), 239-246
18. Hamilton M., The assessment of anxiety states by rating. *Br J Med Psychol* 1959; 32:50–55
19. Spitzer RL, Kroenke K, Williams JBW, Lowe B. A brief measure for assessing generalized anxiety disorder. *Arch Intern Med*. 2006;166:1092-1097.
20. Fındıklı E, Camkurt MA, İzci F, et al. The Diagnostic Value of Malondialdehyde, Superoxide Dismutase and Catalase Activity in Drug Naïve, First Episode, Non-Smoker Generalized Anxiety Disorder Patients. *Clinical Psychopharmacology and Neuroscience: The Official Scientific Journal of the Korean College of Neuropsychopharmacology*. 2018 Feb;16(1):88-94. DOI: 10.9758/cpn.2018.16.1.88.
21. Protective Effect of *Nardostachysjatamansion* Radiation Induced Anxiety and Oxidative Stress. N. Suchetha Kumari, *Biomedicine: 2012*; 32(3): 337- 341
22. Gaurav Mude, Shailesh Pise, Potentiating effect of N. Jatamansi root extract by evaluating anti-depression and anxiolytic activity in rats, *Journal of Pharmacognosy and Phytochemistry*, [http:// www.phytojournal.com](http://www.phytojournal.com)
23. EVALUATION OF ANTIPSYCHOTIC ACTIVITY OF ETHANOLIC EXTRACT OF *NARDOSTACHYSJATAMANSION* WISTAR ALBINO RAT *Jash, IJPSR, 2013*; 4(7): 2730-2736
24. Rasheed A, Evaluation of toxicological and antioxidant potential of *Nardostachysjatamansi* in reversing halopredol induced catalepsy in rats, *Int. Journal of General Medicine* 2010:3
25. Shweta P, Snehal B. ROLE OF HERBAL OIL IN STRESS INDUCED INSOMNIA (ANIDRA) AND ITS MANAGEMENT-A CASE STUDY. *International Journal of Research in Ayurveda and Medical Sciences*.;2:140-7.
26. Ghogare, Ajinkya Sureshrao, and Pradeep Shriram Patil. “A Cross-Sectional Study of Co-Morbid Generalized Anxiety Disorder and Major Depressive Disorder in Patients with Tension-Type Headache Attending Tertiary Health Care Centre in Central Rural India.” *NIGERIAN POSTGRADUATE MEDICAL JOURNAL* 27, no. 3 (September 2020): 224–29. https://doi.org/10.4103/npmj.npmj_23_20.
27. Gupta, Ravi, Sourav Das, Kishore Gujar, K. K. Mishra, Navendu Gaur, and Abdul Majid. “Clinical Practice Guidelines for Sleep Disorders.” *INDIAN JOURNAL OF PSYCHIATRY* 59, no. 5, 1 (January 2017): S116–38. <https://doi.org/10.4103/0019-5545.196978>.