



REVIEW ON INSOMNIA AND ITS TREATMENT (A CHALLENGING TASK)

***M.V.N.L.Chaitanya.**

*Department of Phytopharmacy and Phytomedicine(TIFAC CORE., HD)
J.S.S.College of Pharmacy,Rocklands, Ooty-643001

ABSTRACT

In Simple terminology Insomnia is described as sleeping problem wherein no matter how you want to rest and sleep, you can't do it because of anxiety and frequent awakenings. Even though it is not a dreadful disease that you should be scared of, as this will cause several potent complications in insomniac Human beings. Insomnia is very common especially to people that have disturbed minds and have emotional problems. It is common in people suffering from psychological health issues. Sometimes in sleep literature it is described as a disorder demonstrated by polysomnographic evidence of disturbed sleep. Even though there are lot of Allopathic medicine and Phytomedicine available in this market, in one way all these Medicines are failed to treat Insomniac patient safely. As the available Allopathic medications will cause additional side effects on insomniac patients and coming to Phytomedicine especially in this case, there also a failure except in two or three medications as the clinical data of these medicines is not well established. So the Insomnia is a major prominent symptom or disease or problem in this restless society and it is a challenging one for researchers to cure it fulfil and safely.

Key Words: Insomnia, Allopathic Medicine and Phytomedicine.

INTRODUCTION

Insomnia is most often can be thought of as both a sign and a symptom that can accompany several sleep, medical and psychiatric disorders, characterized by persistent difficulty falling asleep and/or staying asleep or sleep of poor quality. Insomnia is typically followed by functional impairment while awake. One definition of insomnia is "difficulties initiating and/or maintaining sleep, or no restorative sleep, associated with impairments of daytime functioning or marked distress for more than 1 month"[1].

Classification of Insomnia

Insomnia is categorised mainly into 3 types there are primary, secondary and territory or comorbid. Based on the longevity of Insomnia, the insomnia further categorised as follows:

1. Transient Insomnia: Lasts for less than a week, consequences – sleepiness and impaired psychomotor performance are similar to those of sleep deprivation.

2. Acute Insomnia: The inability to consistently sleep well for a period of less than a month.

3. Chronic Insomnia: Lasts for longer than a month. It can be caused by another disorder, or it can be a primary disorder. Its effects can vary according to its causes including disorders like muscular fatigue, hallucinations, and/or mental fatigue [2].

Causes of Insomnia

Insomnia can be caused by or can be co-morbid with:

A) Use of psychoactive drugs or stimulants: Including certain medications, herbs, caffeine, nicotine, cocaine, amphetamines, methylphenidate, MDMA and modafinil.

B) Use of fluoroquinolone antibiotic drugs:

Fluoroquinolone toxicity, associated with more severe and chronic types of insomnia [3].

C) Restless Legs Syndrome: which can cause sleep onset insomnia due to the discomfoting sensations felt and the need to move the legs or other body parts to relieve these sensations?

*Corresponding Author M.v.n.l.Chaitanya E mail: lalipop_1@yahoo.com

D) Periodic limb movement disorder (PLMD): This occurs during sleep and can cause arousals which the sleeper is unaware of.

E) Pain: An injury or condition that causes pain can preclude an individual from finding a comfortable position in which to fall asleep, and can in addition cause awakening [4].

F) Hormone shifts: Such as those that precede menstruation and those during menopause.

G) Life events: such as fear, stress, anxiety, emotional or mental tension, work problems, financial stress, birth of a child and bereavement.

H) Mental disorders: Such as bipolar disorder, clinical depression, generalized anxiety disorder, post traumatic stress disorder, schizophrenia, obsessive compulsive disorder, Dementia or Excessive Alcohol intake.

I) Disturbances of the circadian rhythm: Such as shift work and jet lag, can cause an inability to sleep at some times of the day and excessive sleepiness at other times of the day. Chronic circadian rhythm disorders are characterized by similar symptoms,

J) Certain neurological disorders: Such as brain lesions, or a history of traumatic brain injury,

K) Medical conditions: Such as hyperthyroidism and rheumatoid arthritis [5].

L) Parasomnias: which include such disruptive sleep events as nightmares, sleepwalking, night terrors, violent behaviour while sleeping, and REM behaviour disorder, in which the physical body moves in response to events within dreams.

M) A rare genetic condition: Cause a prion-based, permanent and eventually fatal form of insomnia called fatal familial insomnia and

O) Physical exercise: Exercise-induced insomnia is common in athletes, causing prolonged sleep onset latency [6].

Due to sleeplessness or Insomnia, there are several potent complications in insomniac human beings which is represented in the form of a diagram [7].

Diagnosis of Insomnia

Specialists in sleep medicine are qualified to diagnose the many different sleep disorders. Patients with various disorders including delayed sleep phase syndrome are often mis-diagnosed with primary insomnia. When a person has trouble getting to sleep, but has a normal sleep pattern once asleep, a circadian rhythm disorder is a likely cause.

In many cases, insomnia is co-morbid with another disease, side effects from medications, or a psychological problem. Approximately half of all diagnosed insomnia is related to psychiatric disorders.

In depression in many cases "insomnia should be regarded as a co-morbid condition, rather than as a secondary one;" insomnia typically predates psychiatric symptoms."In fact, it is possible that insomnia represents a significant risk for the development of a subsequent

psychiatric disorder."Knowledge of causation is not necessary for a diagnosis [8].

Treatment of Insomnia

Insomnia may be treated in two ways they are Non Pharmacological or Pharmacological

Non Pharmacological Treatment

Non-pharmacological strategies are superior to hypnotic medication for insomnia because tolerance develops to the hypnotic effects. In addition, dependence can develop with rebound withdrawal effects developing upon discontinuation. Hypnotic medication is therefore only recommended for short term use, especially in acute or chronic insomnia [9]. Non pharmacological strategies however, have long lasting improvements to insomnia and are recommended as a first line and long term strategy of managing insomnia. The strategies include attention to sleep hygiene, stimulus control, behavioural interventions, sleep-restriction therapy, paradoxical intention, patient education and relaxation therapy [10].

Pharmacological Treatment

The Pharmacological treatment can be done either by Allopathic Medication or by Herbal Medication. However there are several allopathic medications are available in treatment of insomnia, but however in one way all these available medications are failure in sense of their side effects and habitual forming. So in order to compensate these disadvantages or side effects, many herbal medications or dietary supplements came into existence, however lot of research have to be done still on this herbal remedies which are available in market and assumed to be the safest when compare to allopathic medications. But the scientific evidence and safety profile data of these herbal medications is not up to the mark. In one way the present research focusing on treatment of Insomnia is not up to the mark. Still potent research have to be carried out, as many Pharmaceutical Companies are investing crores of rupees on this major disorder, Definitely one day a novel molecule or medication will be launched soon into market which is potent and Safe without habitual formation.

a) Allopathic Medications for treatment of Insomnia

Many insomniacs rely on sleeping tablets and other sedatives to get rest, with research showing that medications are prescribed to over 95% of insomniac cases [11]. Certain classes of sedatives such as benzodiazepines and newer nonbenzodiazepine drugs can also cause physical dependence which manifests in withdrawal symptoms if the drug is not carefully tapered down. The benzodiazepine and nonbenzodiazepine hypnotic medications also have a number of side effects such as day time fatigue, motor vehicle crashes, cognitive impairments and falls and fractures. Elderly people are more sensitive to these side effects [12]. The non-benzodiazepines zolpidem and zaleplon have not adequately demonstrated effectiveness in sleep maintenance.

Some benzodiazepines have demonstrated effectiveness in sleep maintenance in the short term but in the longer term is associated with tolerance and dependence. Drugs are in development which may prove more effective and safer than existing drugs for insomnia [13].

In comparing the options, a systematic review found that benzodiazepines and nonbenzodiazepines have similar efficacy which was not significantly more than for antidepressants. Benzodiazepines did not have a significant tendency for more adverse drug reactions [14].

Chronic users of hypnotic medications for insomnia do not have better sleep than chronic insomniacs who do not take medications. In fact, chronic users of hypnotic medications actually have more regular nighttime awakenings than insomniacs who do not take hypnotic medications. A further review of the literature regarding benzodiazepine hypnotic as well as the nonbenzodiazepines concluded that these drugs caused an unjustifiable risk to the individual and to public health and lack evidence of long term effectiveness [15].

b) Herbal Medications for treatment of Insomnia:

Many people choose herbal and dietary supplement remedies. (Valerian and melatonin are among

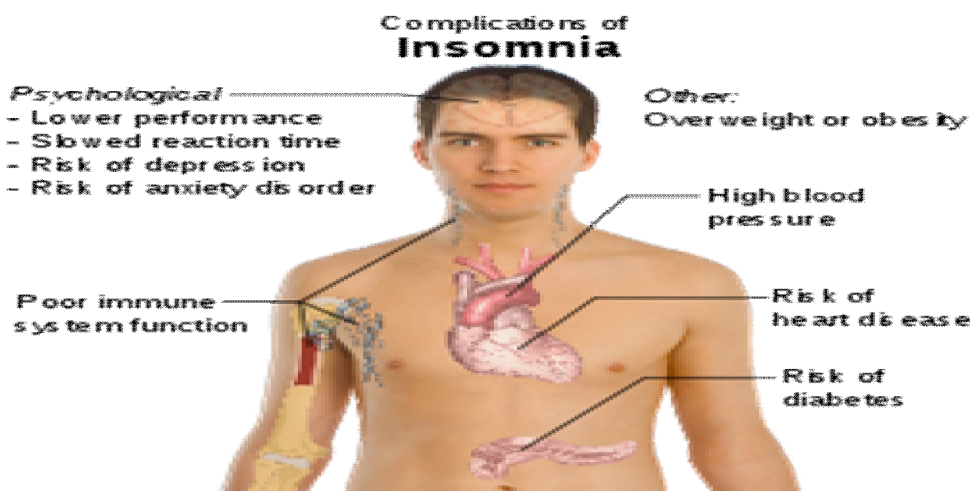
the most popular alternative remedies for insomnia.) Some, such as chamomile tea or lemon balm, are generally harmless for most people. Others have more serious side effects and interactions.

The American Academy of Sleep Medicine (AASM) states that there is only limited scientific evidence to show that herbal and dietary supplements are effective sleep aids. The AASM recommends that these products should be taken only if approved by a doctor. Be sure to talk to your doctor if you are considering taking any herbal or dietary supplement. Some of these products can interact with prescription medications.

Generally, manufacturers of herbal remedies and dietary supplements do not need FDA approval to sell their products. Just like a drug, herbs and supplements can affect the body's chemistry, and therefore have the potential to produce side effects that may be harmful. There have been a number of reported cases of serious and even lethal side effects from herbal products. Patients should always check with their doctors before using any herbal remedies or dietary supplements [16].

The possible allopathic medications and Herbal Medications are used in the treatment of Insomnia is given in the **tabular column** along with their Side effects.

Fig.1.Potent Complications due to Insomnia



S.No	Generic Name and Normal Therapeutic Dose	Brand Names or Trade Names(World Wide)®	Major Side effects
1.	Benzodiazepines (The most commonly used class of hypnotics prescribed for insomnia are the benzodiazepines. Benzodiazepines bind unselectively to the GABAA receptor)	-	-
a)	Temazepam (10mg to 30mg)	Euhypnos, Normison, Norkotral, Nortem, Remestan, Restoril, Temaze, Temtabs and Tenox	Abdominal or stomach cramps or pain; blurred vision or other changes in vision and constipation [17, 22].

b)	Flunitrazepam (1mg to 2mg)	Rohypnol,Hypnodorm,Narcozep, Ruffies and Roofies	Dehydration, diarrhoea, pancreatic atrophy, pancreatic insufficiency [18].
c)	Triazolam (0.125 mg to 0.25 mg)	Halcion,Apo-triazolam,Gen-Triazolam, and Dylan-Triazolam	Drowsiness, Headache Nausea and Hyper sensitivity [19].
d)	Flurazepam (30 mg)	Dalmane,Apo-Flurazepam and Sompam	Dizziness, drowsiness, light-headedness, and ataxia [20,21].
e)	Midazolam(Injection , 1.5 mg to 2.5 mg)	Dormicum; Hypnovel	Localized swelling or irritation at the injection site, nausea with or without vomiting, hiccups, amnesia, sexual disinhibition, anger and aggressive behaviour [23].
f)	Nitrazepam (5 mg to 10 mg)	Alodorm,Apo-nitrazepam tablets,BP,Apodorm,Atempol,Benzal in,Calsamin,,Dumolid,Eatan and Epinelbon	Somnolence, dizziness, depressed mood, rage, violence, fatigue, ataxia, headache and vertigo [24].
g)	Quazepam(7.5 mg to 30 mg)	Doral and Dormalin	Clumsiness or unsteadiness; daytime drowsiness; dizziness; dry mouth; fatigue; headache; light headedness; sluggishness; stomach upset[25].
2.	Non – Benzodiazepines (sedative-hypnotic drugs, are a newer classification of hypnotic medications. They work on the benzodiazepine site on the GABAA receptor complex similarly to the benzodiazepine class of drug.) .	-	-
a)	Zolpidem(5 mg to 10 mg)	Ambien, Ambien CR, Zolpimist, Edluar	Drowsiness, dizziness, and a "drugged" feeling, which probably reflect the action of the drug. Other side effects include confusion, insomnia, euphoria, ataxia (balance problems) [26].
b)	Zaleplon(5 mg to 20 mg)	Sonata,Starnoc	Abnormal skin sensations; decreased sensitivity to touch; dizziness; drowsiness; in coordination; light-headedness; muscle pain; short-term memory loss [27].
c)	Zopiclone(3.75 mg to 7.5 mg)	Somnal , Rhovane, Zopicon , Zimovane	Drowsiness; slow, shallow breathing; sudden onset of sweating; pale skin; blurred vision; and loss of consciousness [28].
d)	Eszopiclone(1 mg to 2 mg)	Lunesta	Headache,pain,daytime drowsiness,lightheadedness,dizziness,loss of coordination,nausea,vomiting,heartburn,unpleasant taste, dry mouth, unusual dreams[29].
3)	Opioids(used for insomnia which is associated with pain due to their analgesic properties and hypnotic effects)	-	-
a)	Hydrocodone(5 mg to 10 mg)	Vicodin, Vicodin ES, Anexsia, Lorcet, Lorcet Plus, Norco	Headache, dry mouth, anxiousness, dizziness and drowsiness, mild to severe nausea, loose motions and emesis [30].
b)	Oxycodone(5 mg to 30 mg)	OxyContin, Roxicodone, OxyIR, Oxyfast	Euphoria, memory loss, constipation, fatigue, dizziness, nausea, lightheadedness, headache, dry mouth,

			anxiety, pruritus, and diaphoresis [31].
c)	Morphine(5 mg to 30 mg)	MS Contin, Kadian, Morphine Sulfate ER, Avinza	Many side effects, Major is Respiratory depression [32].
4)	Antidepressants (can often have a very strong sedative effect, and are prescribed off label to treat insomnia).	-	-
a)	Amitriptyline(40 mg to 150 mg)	Elavil, Tryptizol, Laroxyl, Sarotex, Lentizol	Due to its anticholinergic activity, including: weight gain, dry mouth, changes in appetite, drowsiness, muscle stiffness and, nausea [33].
b)	Doxepin(10 mg to 25 mg)	Sinequan, Adapin	Blurred vision, urinary retention (difficulty urinating), dry mouth, constipation, weight gain or loss, and low blood pressure [34].
c)	Mirtazapine(15 mg to 45 mg)	Alodorm; Apo-nitrazepam tablets BP; Apodorm; Atempol; Benzalin; Calsamin; Calsmin; Cerson; Dormicum .	Dizziness, blurred vision, sedation, somnolence, malaise/lassitude, increased appetite and subsequent weight gain [35].
d)	Trazodone(150 mg to 200 mg)	Apo-Trazodone D®; Apo-Trazodone®; Desyrel®; Dom-Trazodone; Mylan-Trazodone; Novo-Trazodone; Nu-Trazodone; PHL-Trazodone	Less prominent anticholinergic (dry mouth, constipation, tachycardia) and sexual side effects [36].
5)	Melatonin (Has demonstrated effectiveness equivalent to the prescription sleeping tablet zopiclone in inducing sleep and regulating the sleep/waking cycle)49(3 mg to 120 mg)	Melatonin Tablets, capsules	Orthostatic intolerance and grogginess [37].
6)	Melatonin agonists (a drug has a relatively mild side effect profile and low likelihood of causing morning sedation. While these drugs show good effect for the treatment of insomnia due to jet lag)	-	-
a)	Ramelteon(5 mg to 8 mg)	Rathmelton, Rath Mealtain	Abnormal behaviour, blood creatine phosphokinase increased, blood creatinine increased [38].
b)	Tasimelteon	Unable to find full information	Unable to find full information (in clinical trials)
7)	Antihistamines		
a)	Diphenhydramine(25 mg to 50 mg)	Allerdryl®; Allernix; Benadryl®; Nytol®; Nytol® Extra Strength; PMS-Diphenhydramine; Simply Sleep® ..	Dizziness, difficulties with coordination, confusion, restlessness, nervousness, difficulty sleeping, blurry or double vision, ringing in the ears,headache[39].
b)	Doxylamine (50 mg to 100 mg)	Aldex® ANEquate® Sleep AidNitetime™Unisom® SleepTabs™	Dry mouth, ataxia and urinary retention [40].
c)	Cyproheptadine(2 mg to 8 mg)	Cyproheptadine; Cyproheptadiene, Periactin	Blurred vision, Constipation,Dry mouth, throat, or nose,Excitability,Nausea,,Nervousness and Restlessness or akathisia[41].
8)	Atypical Antipsychotics(prescribed for their sedative effect but the danger of neurological, metabolic and cognitive side effects make	-	-

	these drugs a poor choice to treat insomnia)		
a)	Quetiapine(25mg to 300 mg)	Seroquel and Ketipinor	Sluggishness, fatigue, dry mouth, sore throat, and dizziness [42].
b)	Olanzapine(5 mg to 10 mg)	Zyprexa, Zydis and Relprevv	Insomnia, constipation, urinary retention, orthostatic hypotension, weight gain, increased appetite, runny nose and impaired judgment, thinking, and motor skills[43].
c)	Risperidone(0.5 mg to 4 mg)	Apo-Risperidone and Risperdal	Fever, stiff muscles, confusion, sweating, fast or uneven heartbeats; restless muscle movements in your eyes, tongue, jaw, or neck; tremor (uncontrolled shaking); and trouble swallowing[44].
d)	Eplivanserin(5mg)	Ciltiari	Cognitive, hypnotic, anxiolytic and mild antidepressant effects [45].
9)	Herbal Supplements or Phytomedicine or Traditional Chinese Medicine	-	-
a)	St. Johns wort(<i>Hypericum perforatum</i>) (250 mg to 1000 mg)	Jarsin and Jarsin 300, Joymore and Perika	Photosensitisation (no side effects found in dose up to 1000 mg) [46].
b)	Valerian(<i>Valerian officinalis</i>) (250 mg to 1000 mg)	Valerian, Alluna™ SleepOleomed™ and Sleep Sedonium®	Giddiness [47].
c)	Hops(<i>Humulus lupulus</i>) (500 mg to 1000 mg)	Fu Min and Aladin	Seizure, hyperthermia and restlessness only in case of overdosing more than 1000 mg [48].
d)	Passion flower(<i>Passiflora speices</i>) (200mg to 1000mg)	Lipex, Thompsons and clarocet	Side effects not found in normal dosing [49].
e)	Skull Cap(<i>Scutellaria laterifolia</i>)(100 mg to 650 mg)	Actiphyte and Jarrow stress	Confusion, stupor, giddiness, twitching and seizures[50].
f)	Suanzaoren fruit(<i>Semen ziziphi</i>)(10 g to 15 g)	No formulation in Market	No significant clinical data was found [51].
h)	Longyanoru fruit(<i>Arillus longan</i>)	No formulation in Market	No significant clinical data was found [52].
i)	Fuxiaomai(<i>Triticifructus</i>)	No formulation in Market	No significant preclinical and clinical data was found [53].
j)	Hehuanpi(<i>Albiziaae Cortex</i>)	No formulation in Market	No significant clinical data was found [54].
k)	Kava(<i>Piper methysticum</i>)(250 mg to 1000 mg)	ReVia ,Depad and Kavatrol	Dizziness, drowsiness, headache, mouth numbness, or blurred vision and Nausea [55].
l)	Lemon balm (<i>Melissa officinalis</i>)600 mg	SUPTEK, Herbies and Ceti Eureka	Stomach problem and Nervousness [56,57].
m)	Rooibos(<i>Aspalanthus linearis</i>)	No formulation in Market as sleeping aid, available in form of herbal tea	Toxicity rate is very high even used as cytotoxic (European Patent EP0796620) [58].
n)	Chamomile (<i>Chamomilla recutita</i>) (250 mg to 500 mg)	Deep sleep, lights off and herbal tea	Allergy symptoms, Nausea and Vomiting [59].
o)	Oat straw(<i>Avena sativa</i>)(100 mg to 500 mg)	Avena Sativa Oat Complex™	No known side effects

CONCLUSION

Even though many medications are available in the market for the treatment of Insomnia, None of these allopathic medication is free from side effects that's why instead of curing one symptom, with the advent of

allopathic system causes many severe multiple side effects on this insomniac subjects, most of these medications are habitual forming that's why many people are diverting their minds towards the Phytomedications, but most of these phytomedications are without fulfilled clinical

validations. Many plants are available in traditional literature or in folk system but without proper scientific documentation and validation's. Further rapid research has to be carried out on this area of insomnia, in order to bring

out new clinically validated molecules without side effects and habitual formation as a gift to this insomniac society. Thus there is a lot scope of research especially in this Challenging area of insomnia.

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