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Review Article

MANAGEMENT OF SLEEP DISTURBANCE THROUGH BOTANICALS: A REVIEW

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ABSTRACT
Sleep loss can lead to various alterations at physiological and psychological levels such as EEG changes, metabolic changes, irritation, blurred vision, memory lapses, hallucinations, psychosis and can even lead to death. There are several neurotransmitters which are involved in sleep and arousal and disturbance in the levels of these usually involves several behavioral changes and generation of free radicals which further causes oxidative damage. From last few decades antidepressants have been widely used at much lower doses for the treatment of insomnia than for depression and generally recommended to be in combination with cognitive-behavioral therapy. But the treatment with these compounds still remains a challenge as majority of antidepressants and hypnotics are associated with side effects. Herbal medicines as the major remedy in traditional medical system have been used in medical practice for thousands of years and have made a great contribution to maintaining human health. Currently polyherbal preparations are being sold in the market with multiple indications and their exact therapeutic role in the management of sleep disorder is still questionable.

INTRODUCTION

Sleep is normally a period of relaxation and repair, important for the maintenance of physiological homeostasis and psychological balance (Sharma and Kavuru, 2010). Quality of sleep is a vital physiological process for the maintenance of good health. Problems of sleep deprivation are being increased in today's modern society (Kumar and Singh, 2009). Depression is often associated with poor quality of sleep, which represents an important criterion in diagnosis. The different stages used to characterize sleep are stage 1 to stage 4 known as Non-REM sleep and stage 5 refers to as REM sleep (Table 1) (Chokroverty, 2010).

Table 1: Characteristic features of different stages of sleep

Stage of sleep	Characteristic features	Electrophysiology characteristics
1. Non-REM sleep		
a) Stage 1	light sleep, eyes move slowly, muscle activity slows	Slow in frequency and moderately high amplitude
b) Stage 2	No eye movements, Slow brain activity	More synchronized EEG, Occasional bursts of rapid waves (sleep spindles)
c) Stage 3	extremely slow brain waves	prominent δ (delta) activity is slow frequency, greatest amplitude
d) Stage 4	Deep sleep, No eye movement, No muscle activity	δ (delta) activity is prominent slowest in frequency, greatest in amplitude
2. REM sleep	Characteristic traits from both sleep and wakefulness	Desynchronized EEG

Sleep Deprivation (insomnia)

Complaints of poor quality of sleep are very common and remain untreated most of the time. Approximately 65 million adults (36% of the American population) complain of poor sleep and of this group 25% have insomnia on a chronic basis. The National Heart, Lung And Blood Institute (NHLBI) visit working group on insomnia defines insomnia as an experience of inadequate or poor quality of sleep characterized by one or more of the following: difficulty in falling asleep, difficulty in maintaining sleep, waking up to early in the morning or unfreshing sleep (Roth, 2000). The symptoms of insomnia include daytime consequences such as tiredness, lack of energy, and difficulty in concentrating or irritability, which results in poor performance. In human beings, sleep occupies about a third of adult life. Sleep is essential; the precise physiological reasons for this are unknown, but even subtle changes in duration and quality of sleep can impinge greatly on health (Carkadon *et al.,* 2000). Consequences of insomnia include an increased likelihood of accidents and diminished performance, impaired judgment, polydrug abuse (including alcoholism), increased use of health care resources, decline in quality of life, and disturbance in interpersonal relationships. It is crucial that short-term sleep disturbance be promptly recognized and appropriately treated before learned habits, attitudes, and coping mechanisms incongruous with sleep become established and perpetuate the sleep disturbance. Therapy has to address the predisposing, precipitating, and perpetuating factors of insomnia. In the clinical setting, one fifth of patients attending general practitioners have been reported to be suffering from insomnia (Kales *et al*, 1987). Patients with insomnia report difficulty in initiating sleep, difficulty in maintaining sleep, (i.e. waking intermittently during the night), or early morning wakening (i.e. waking in the early morning and being unable to fall asleep again) (Ohayon *et al.,* 1997b). Insomnia lasting only a few days is often a result of acute and transient stress and is usually regarded as a normal phenomenon. Insomnia lasting more than a few weeks, however, is considered significant. According to the "International Classification of Sleep Disorders", persistent insomnia of more than four-week duration is regarded as significant insomnia (WHO, 1994). The causes of insomnia include psychiatric disorders, physical problems such as cardiopulmonary failure and chronic pain, drugs and foods such as caffeine, nicotine, alcohol, and amphetamines, and an irregular sleep-wake cycle.

Neurotransmitters affected by sleep deprivation

Gamma-amino butyric acid (GABA) - GABA is the major inhibitory neurotransmitter in the central nervous system (CNS) (Parades and Agmo, 1992). GABAergic cells induce sleep by inhibiting cells that are involved in arousal function. Cholinergic neurons in the basal forebrain are directly inhibited by GABAergic sleep–active neurons and since the cholinergic system is one of the main forebrain arousal systems of the brain, the inhibition produced by this activity deactivate the cortex. Sleep deprivation induced stress has been reported to alter the content of GABA neurotransmitter in animals suggesting the role of GABAergic mechanism in the sleep deprivation induced behavioral alterations and oxidative damage (Kumar and Kalonia, 2007).

Serotonin - Serotonin, histamine and norepinephrine may have a role in maintaining the arousal and regulating muscle tone and some of the phasic events of REM sleep (Roman et al., 2005). GABA applied to serotonin and norepinephrine cell groups triggers REM sleep (Nitz and Siegel, 1996), demonstrating that cessation of activity in these brain stem cells is important in controlling REM sleep.

Histamine - The histaminergic cells, which are located in posterior hypothalamus, are involved in maintenance of wakefulness (Thakkar, 2011). Further, histaminergic cells are strongly and directly inhibited by the GABAergic neurons (Jhon et al., 2004). Normal cessation of activity of histamine cells during sleep may be directly related to the loss of consciousness during sleep. Thus, accumulating evidence suggests that there is increase in histamine levels as a consequence of total sleep deprivation.

Norepinephrine - Norepinephrine cells are inactive during REM sleep. Several studies suggest that normal cessation of activity of norepinephrine cells during sleep may be related to loss of muscle tone during sleep (Ranjan et al., 2010). Previous studies suggest that sleep deprivation leads to the increase in

the level of catecholamines (norepinephrine, dopamine and acetylcholine), which in turn leads to behavioral alterations and various neurological disorders (Andersen et al., 2005).

Sleep deprivation induced behavioral alterations and oxidative stress

An extensive literature has documented the substantial behavioral effects in animal models of sleep deprivation. These effects include decrease in locomotor activity (Kumar and Kalonia, 2007), genital reflexes (Andersen and Tufik, 2006), stereotyped and aggressive behavior (Tufik et al., 1978), anxiogenic behavior (Kumar and Kalonia, 2007), impaired cognitive performance (Everson, 1995), and changes in body temperature (Blanque et al., 1996). These behavioral changes are attributed to changes in several neurotransmitter pathways, including dopaminergic and noradrenergic neurotransmission (Andersen et al., 2005). Sleep deprivation has also been reported to induce free radical production and decreased antioxidative defense (Gopalakrishnan et al., 2004). Further, free radicals initiate a cascade producing lipid peroxidation, DNA damage and cell death (Singh and Kumar, 2008). Thus, free radicals contribute towards pathogenesis of various neurological disorders (Singh and Kumar, 2008).

Treatment and Management

Treatment of insomnia depends upon on the accurate diagnosis and nature, duration and severity of the problem. Primary goal of the therapy is to remove the cause of the problem and further prevention of its progression. Success of the effective management not only requires appropriate drug intervention but also other effective non-pharmacological treatment measures such as educational, behaviours (Morin *et al.,* 1994) and cognitive, are also required for a successful therapy. Adequate assessment including a detailed history of psychiatric, physical, and sleep aspects is essential. Various hypnotics have been developed over the years for the symptomatic treatment of insomnia. The dependence potential of benzodiazepine has aroused much concern, leading to guidelines and regulations for the restriction of benzodiazepine use to time limited symptomatic treatment of insomnia (Kupfer, 1997). Other pharmacological compounds, such as tricyclic antidepressants and neuroleptics, have also been used to treat insomnia (Kupfer, 1997). Inconclusive evidence, combined with their poor tolerability and sometimes irreversible adverse effects (e.g. anticholinergic effects of tricyclic antidepressants, tardive dyskinesia related to neuroleptics), however, have limited their use (Kupfer, 1999). Although newly developed hypnotics, including zolpidem and zopiclone, have proven safer with lesser psychomotor impairment and memory deficit, the long-term safety of these agents remains a concern (Kupfer, 1997). Thus, the continuing search for newer, better, and safer hypnotic agents for the treatment of insomnia is needed.

Pitfalls and Lacunae in the current drug management

Despite its ubiquity the problem of insomnia is often either untreated or inadequately treated. Currently short acting benzodiazepines are kept reserved and widely used for managing transient and short-term insomnia. These agents are comparatively safe and have fewer side effects compared to other categories of drugs such as barbiturates, antidepressants and other OTC preparations etc. However, these drugs also suffer from a number of side effects such as hangover, development of dependence and tolerance, rebound insomnia as a withdrawal symptom, muscular atonia resulting in falling down and bone fracture, inhibition of respiratory system, interaction with alcohol, cognitive disorder including amnesia, and increased anxiety during daytime

Herbal treatment of insomnia

Herbal medicines as the major remedy in traditional medical system have been used in medical practice for thousands of years and have made a great contribution to maintaining human health. Prolonged and apparently uneventful use of an herbal medicine may offer testimony of its safety and efficacy. WHO has also recognized it as a valuable and readily available resource for primary health care, and WHO has endorsed their safe and effective use. Recently herbal drugs have also been used in the management of the sleep and sleep related disorders (Wing, 2001). Currently polyherbal preparations are being sold in the market with multiple indications and their exact therapeutic role in the management of sleep disorders.

Commonly available herbs in the treatment of insomnia

St John's wort: The most popular and well-studied herbal treatment for psychiatric problems in the west in recent years is St John's wort (*Hypericum perforatum*). It has long been used as a remedy for wound healing, mild sedation, and pain relief (Wong *et al.,* 1998). A meta-analysis reviewing randomised trials involving 1757 patients concluded that it was more effective than placebo and had similar efficacy to conventional antidepressants for treating mild-to-moderate depression (Linde *et al.,* 1996). In general, St John's wort is well tolerated with minimal side effects, including sedation, dry mouth, dizziness, gastrointestinal upset, restlessness, and hypersensitivity (Woelk, 2000). It would be interesting to see whether the Asian hypericum share similar psychotropic properties with those reported for St John's wort.

Valerian: Valerian (*Valeriana officinalis*), from the plant family *Valerianaceae*, has been widely used in the west as a folk remedy for its hypnotic properties. A limited number of human studies with double-blind, cross-over design, suggest that valerian could be used as a mild hypnotic with minimal psychomotor impairment or residual side-effects (Beaubrun, 2000). Objective sleep measurements using polysomnographic recordings have suggested improvements in sleep efficiency and slow wave sleep as well as reductions in stage 1 sleep, with repeated rather than single-dose administration (Donath *et al*., 2000).

Hops: Hops (*Humulus lupulus*) are traditionally used to brew beer and to date there have been few studies of their use, usually in combination with valerian. Improvements in subjective sleep quality and quality of life equivalent to that with benzodiazepine use, but with fewer side effects and without a withdrawal reaction, have been reported (Schmitz and Jackel, 1998). The exact biochemical substance is unknown but a volatile oil, such as 2-methyl-3-butene- 2-ol, may be a likely candidate. It is now widely used as a constituent in Chinese combination therapies for treatment of insomnia.

Ashwagandha: Medicinal value of ashwagandha (*Withania somnifera*) as an immunomodulatory, antioxidant, antistress, rasayna and rejuvenator is now well established (Bhattacharya *et al.,* 1997). Recently, hypnotic and sedative property of ashwagandha received a considerable attention but their exact role in sleep is remains to be investigated. Studies have also demonstrated the involvement of various neurotransmitters and their receptors systems such as GABAergic, cholinergic and serotonergic pathways in producing various effect of aswagandha (Bhattacharya, 2002).

Vacha: Vacha (*Acorus calamus*) is an important bitter-tasting remedy in Ayurvedic medicine, used in much the same way as it is in the west, as a bitter stomachic and carminative. A sedative action and a potentiation of barbiturate effect (increased sleeping time, reduced body temperature) was observed in small animals (mice, rats, rabbits and cats) following the intraperitoneal administration of the aqueous and ethanolic extracts of both European and Asian varieties of *Acorus calamus* (Opdyke, 1977). A monoamine oxidase inhibiting activity has been observed in the oil of the Asian species of *Acorus, calamus* (Opdyke, 1977). However, their therapeutic role in sleep management still remains to be answered.

Jatamansi: Jatamansi (*Nardostachy jatamansi*) is a medically important herb of Indian origin used for centuries in Ayurvedic and Unani systems of medicine for the treatment of various ailments. Several studies have reported that Jatamansi caused an overall increase in the levels of central monoamine and inhibitory neurotransmitters (Prabhu, 1994). However, the entire mechanism of its action still remains to be elucidated in order to establish its therapeutic role in sleep and related disorders.

Passiflora: *Passiflora incarnata* Linneaus have been used for curing various ailments, the most important because of possessing significant CNS modulatory properties (Dhawan *et al.,* 2004). Extracts and fluid extracts from the aerial parts from *Passiflora incarnata* L. are widely used as components of herbal sedatives (Krenn, 2002). As Passionflower is mainly used in combinations, clinical studies of the single drug are not available. Based on pharmacological data, the experiences of traditional use and the use in combinations passiflora extracts are an important factor in the phytotherapy of tenseness, restlessness and irritability with difficulty in falling asleep.

Lavender oil: Essential oils distilled from members of the genus Lavandula have been used both cosmetically and therapeutically for centuries as a antibacterial, antifungal, carminative (smooth muscle relaxing), sedative, antidepressive and effective for burns and insect bites (Cavanagh, 2002). The most commonly used species being L. angustifolia, L. latifolia, L. stoechas and L. xintermedia. Essential lavender oil has a long tradition as a mild sedative in herbal medicine. Although there is considerable anecdotal information about the biological activity of these oils much of this has not been substantiated by scientific or clinical evidence.

Skullcap: The leaves and blue flowers of the skullcap (*Scutellaria laterifolia*) are used as an ingredient in many over the counter (OTC) sleep remedies in the west. Some related species are common ingredients in some Chinese herbal formulas for inflammation and hepatitis (Newall *et al.,* 1996) Clinical studies of their use are currently lacking.

Future directions in the herbal treatment of insomnia

Problems of insomnia and its prevalence in modern world are increasing day by day. Many adults with insomnia do not seek treatment from physician and instead, may self-treat with over the counter medicines including herbals medicine products with an intention that they are totally safe. Therefore present research on herbs traditionally used to aid sleep has focused mainly on the effects of valerian (*Valerian officianlis, V. Wallichi, V. edulis*), passion flower (*Passiflora incarnata*), lemon balm (*Melissa officinalis* L.), lavender (*Lavender angustifolia* Mill) and Jamaica dogwood (*Piscidia erythrima* L.) are reputed to have hypnotic effects, but have been subject to little scientific investigations (Barnes *et al.,* 2002). These herbs are also reputed to have sedative effects and have been used particularly for "nervous sleeping disorder" Other herbs which have their effect on nervous system are given in table 4. These herbs have a role in helping to re-establish a regular pattern of sleep. However these herbs are also recommended not to be taken indefinitely because of lack of adequate safety profile. Besides fewer more studies are still needed to explore their effects on long-term usage.

Conclusion

In conclusion, sleep loss related problems are prevalent in our society because of the changing life style and it's the need of an hour to develop an effective therapy to minimize the damage and to deal with all the alterations associated with it. Recently it has been noticed that people have started choosing herbal preparation for treating insomnia. This may be due to least or no side effects of these remedies. Therefore a lot many herbal formulations are being developed in which a single herb or a mixture of different herbs is employed to maximize the therapeutic efficacy along with eliminating the undesirable side effects.

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