Review Article

A Systematic Review on Natural Sedative and Hypnotics

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ABSTRACT

Sedatives manage anxiety and nervous tension as they cause sedation, and sometimes a degree of analgesia, numbed consciousness with sedation, have a tendency to get sleep even at regular therapeutic doses, which distinguishes sedatives from tranquilizers. Herbs are widely used as an alternative medicine in sleep disorders. Currently insomnia is mostly managed by synthetic sedatives-hypnotics, but safety in prolonged use of synthetic sedatives and hypnotics has been raised. Over the past few years, there has been a growing propensity for herbal medicines around the world to prevent insomnia. This paper highlights the need of a natural medicine to treat insomnia and sleep disorder.

Keywords: Natural sedatives, hypnotics, insomnia, psychotic drugs, synthetic drugs.

INTRODUCTION

10 to 20 percent of adults around the world suffer from chronic insomnia, leading to functional impairment following the poor quality of sleep while awake. Under other conditions, insomnia is secondary with, psychological disorders, pain, hormone shift, and alcohol addiction.

Synthetic medicines can treat insomnia but have number of problems in use, following clinical progress. In addition to daytime fatigue and cognitive impairment as side effects of these sedatives, physical dependency may be established. On the other hand, herbal remedies can treat insomnia. Due to the low risk of side effects, many insomniacs are inclined to take medicinal plants.[1]

Insomnia is a common health concern that might induce significant mental and physical disorders. In the field of mental health disorders, depression, anxiety and insomnia are common medical conditions. Impairment of the immune and cardiovascular systems is the association between major depression, insomnia and anxiety disorders.[2]

SAFETY CONCERNS OF SYNTHETIC SEDATIVES AND HYPNOTICS

Pharmacological treatments are successful, only short-term consolation should be accomplished by behavioral treatments. Sedative hypnotics are commonly used in the management of insomnia, which can also impair the vigilance of the psycho motor, but raise safety concerns. Chronic use of sedative hypnotics can result in cognitive impairment, mortality risk, addiction liability, dementia.[3] Side effects include drowsiness, headache, muscle aches, constipation, dry mouth, concentration difficulty, dizziness, instability, and insomnia rebound. Other dangers of sleeping pills include alcohol resistance, drug dependence, signs of withdrawal, drug interactions, relapse insomnia, masking actual problem.

Many of these drugs have a dose dependent effect and disrupting the central nervous system. They are distinguished by opiates by not having action on mood. Traditionally only opium and alcohol was the available choice of drugs. Liquid solution of bromide salt was the first introduced sedatives and hypnotics. Phenobarbital became available in 1912 and a long series of other barbiturates followed over the next 20 years. New types of sedative-hypnotic drugs were synthesized in the mid-20th century, including benzodiazepines (so-called minor tranquilizers) chief among them.[4]

In 1921 first barbiturate derivate phenobarbital was introduced. Barbiturates can produce a deep unconsciousness when taken in high doses, which makes them useful as general anesthetics. The central nervous and respiratory systems are depressed to the point of coma, respiratory failure and death in even higher doses. In addition, prolonged use of barbiturates for insomnia relief leads to tolerance and addiction, where denial of the drug precipitates symptoms of withdrawal, as indicated by symptoms such as restlessness, anxiety, weakness, insomnia, nausea, and convulsions.

Benzodiazepines were introduced in the 1950s, there after barbiturate use declined. BDZ are more effective in relieving depression than in sleep, but they are preferable to barbiturates due to the reduced risks of sensitivity and dependence and because they are much less likely to harm the central nervous system when used at high doses. To achieve their effects, they also require a much smaller dose than barbiturates. Chlordiazepoxide, diazepam, alprazolam, oxazepam and triazolam are the benzodiazepines. However, they are only intended for short-or medium-term use, as the body develops tolerance

to them and symptoms of withdrawal (anxiety, restlessness, and so on) even with four to six weeks. Benzodiazepines not have barbiturate side effects, but produces drowsiness, confusion, dizziness, trembling, impaired coordination, problems with vision, grogginess, depression, headache. Benzodiazepine withdrawal symptoms include sleeping problems, feelings of depression, and sweating.[5]

HERBAL SEDATIVES-HYPNOTICS

There are various herbal sedatives, and the material responsible for the sedative effect can be categorized according to the chemical structure as follows:

1. **Essential oil or oleoresins**: hop, lavender, valeriana, chamomile, lemon balm, Perforate St John's-wort
2. **Alkaloids**: passiflora, ashwagandha
3. **Glucosides, bitter substances or resins**: motherwort
4. **Lactones:** kava kava

Hop (*Humulus lupulus*)

Humulus lupulus (common hop or hops) is a species of flowering plant in the hemp family (Cannabaceae), native to Europe, western Asia and North America. It is a dioecious, perennial, herbaceous climbing plant which sends up new shoots in early spring and dies back to a cold-hardy rhizome in autumn. The chemical compounds found in *H. lupulus* are main components in flavoring and bittering beer. Some other compounds help with creating foam in beer. Chemicals such as linalool and aldehydes contribute to the flavor of beer. It contains oleoresin in which the resin fraction contains bitter substances (humulone and lupulone); its volatile or oily fraction is rich in methylbutenol which has experimental sedative effects. It is commonly used in the treatment of insomnia in phytotherapy.[6]

The experiment was conducted with healthy female nurses (n = 17) working rotating and/or night shifts the sedative effect of hop, a component of beer, on the activity/rest rhythm. The doses administered, close to the content of non-alcoholic beer, were 1, 2 and 11 mg extract of hop as one capsule per day, at 18:00 h for one week. A control group received capsules only with a methylcellulose excipient and a basal group received no treatment. dose of 2 mg, similar to the concentration in beer, was more effective in reducing nocturnal activity than the other doses of 1 and 11 mg, as well as preserving the circadian activity/rest rhythm. Conclusion: The concentration of 2 mg of hop extract effectively decreased nocturnal activity in the circadian activity rhythm. On the basis of this investigation, administration of non-alcoholic beer would be recommended due to its hop content and consequent sedative action, which would be an aid to nocturnal sleep.[7]

Lavender (*Lavandula angustifolia*)

Mediterranean bush, whose flowers are rich in essential oil of linalyl acetate and linalool. Lavender (*Lavandula angustifolia*) has a long history of use in aromatherapy to promote sleep and relaxation and to relieve anxiety. Oral doses of lavender (diluted 1:60 in olive oil) had marked sedative effects on mice and enhanced barbiturate sleep time. Such products have been shown to inhibit the stimulation of caffeine by up to 50 %, mostly through olfactory receptors. It is used in phytotherapy, particularly in geriatric patients, to treat neuroleptic and benzodiazepine dependency.[8]

Valerian (*Valeriana officinalis*)

Euro Siberian herbaceous plant with 0.3-0.8 % essential oil in its roots. The characteristic scent of the plant "sweaty feet" is due to its high content of essential oil isovalerianic and ace toxic valerenic acids. It also contains valepotriates of 1 percent. It has an effect of sedation and anti-seizure. In vitro, valerenic acid inhibits 3H-GABA absorption and promotes its release in synaptosomes, irrespective of the function and membrane potential of Na-KATIasa. Isovaleric acid enhances GABA's affinity to its receptors, resulting in greater receptor binding and a more intense effect. All this contributes to a decline in excitability of nerve cells. Pharmacodynamic trials have shown that the sedative effect of liquid valerian extract (1200 mg) is equivalent to that of diazepam (10 mg). Valerian is commonly used mainly in the treatment of depression and in patients with nervous disorders as an alternative to hypnotic sedative agents such as benzodiazepines and/or Z-drugs.[9]

Chamomile (*Chamomilla recutita*)

Chamomile preparations such as tea and essential oil aromatherapy have historically been used to treat insomnia and sedation (calming effects). Chamomile is widely considered to be a mild sleep-inducer and tranquilizer. Chamomile is widely regarded as a mild tranquillizer and sleep-inducer. Sedative effects may be due to the flavonoid, apigenin that binds to benzodiazepine receptors in the brain. Sedative symptoms can be caused by flavonoid, an apigenin that binds in the brain to benzodiazepine receptors.[10]

Lemon balm (*Melissa officinalis*)

The officinal or lemon balm of Melissa belongs to the family of Labiacae. Melissa Officinal is growing in the Mediterranean, Iran, Central and Minor Asia. *Melissa officinalis* is used for its anxiolytic, hypnotic, sedative, and spasmolytic effects by people practicing traditional medicine This herbaceous aromatic plant is soothing, sleepy and perfect for pressure. Lemon balm is one of the two main herbal medicinal plants Valeric, Neurogol Fort and Neurogol, prescribed for depression, insomnia and nervous stress.

In mice, an aqueous alcoholic extract of lemon balm was reported to produce dose-dependent sedation, inducing sleep and potentiating sub-hypnotic and hypnotic doses of pentobarbital. On the other hand, in the same study the essential oil of lemon balm was reported to have no

sedative effect. With high doses, a peripheral analgesic effect was noted.[11]

Ethanolic extract of lemon balm was tested for affinity to the GABA(A)-benzodiazepine site, and moderate activity was reported sedative activity in mice.[12]

Perforate St John's-wort (*Hypericum perforatum*)

Hypericum perforatum is a member of the family Hypericacea. It's a perennial grass full of essence holes with spoon leaves. The plant species is called Perforatum because of this feature. Hypericum is used in herbal medicinal products such as hypiran, nervoxin, hypifor and perforan, which are used for insomnia, anxiety, nervous headaches and migraines in addition to depression.[13]

hydro alcohol extract of plant aerial organ was dosed 500 mg/kg and 250 mg/kg of extract, 1/2 mg/kg of diazepam and also di-metyl solphoxid with equal volume was injected in wistar rats with equal age and weight conditions, (as plasebo), 15 min before assessing the sedative/sleep inducing effects (induced sleep duration by Ketamin, dose 44 mg/kg), showed meaningful increase in induced sleep duration.

Passiflora (*Passiflora incarnata*)

Flavonoids, including vitexin, orientin, lucenin, coumarin, umbelliferon and maltol is responsible for its myorelaxant effect. The oral and peritoneal administration of passiflora extracts in humans, depending on the dose given, causes a sedative or hypnotic effect. In a related plant study, *Passiflora coerulea*, used ethnopharmacologically as a sedative, has been shown to have an anxiolytic and myorelaxant effect due to its flavonoid content, particularly chrysene (5-and7-hydroxyflavone), which acts as a partial agonist of the central benzodiazepine receptors. The resulting sedative effect appears to be due to the pharmacological interaction and synergy of flavonoids, maltol and indole alkaloids.[14]

Extracts of the plant *Passiflora incarnata* L. (Passifloraceae) were administered intraperitoneally experiments were carried out on chronically implanted male adult wistar rats to obtain cerebral (EEG), ocular (EOG) and muscular (EMG) activities throughout their states of vigilance. Polygraphic recordings were taken during 9 continuous hours before and after the extract administration (500 mg/kg). Passiflora incarnata induced a significant increment in the total sleep time[15]

Ashwagandha (*Withania Somnifera*)

It was considered an excellent rejuvenator, a general health tonic, and a cure for a number of health problems. It is a sedative, diuretic, anti-inflammatory and generally respected agent, strong immunostimulatory and anti-stress agent. Ashwagandha is effective for insomnia, its rejuvenating properties and produces energy that in turn helps the body to settle and sleep. It helps the body cope with a stress-related illness instead of masking it with sedatives. A nervous system rejuvenating plant erases anxiety and relieves stress.[16]

Withania somniferra extract (100 mg/kg) was administered intraperitoneally (i.p.) 30 min before actual recording (EEG and EMG) recording and electrophysiological recordings are further classified as-sleep latency, slow wave sleep, paradoxical sleep, total sleep, wakefulness. Withania root extract induced sleep-promoting effect by involving GABAergic modulation, which was significantly antagonized and potentiated by picrotoxin and muscimol, respectively.[17]

Motherwort (*Leonurus cardiaca*)

Herbaceous plant from Asia, the aerial portion of which produces bitter glucosides with a similar structure to bufadienolides, alkaloids (Leon-urine) and essential oil. It is used in the treatment of nervous disorders as a sedative. *Leonurus cardiaca*, commonly known as motherwort, is a member of the Lamiaceae family. It has a number of interesting biological activities, for example, sedative and hypotensive, antioxidant, anti-inflammatory, and antimicrobial activities.

Chromatography determination, as well as their above named isolated, possible active constituents of different chemical nature were tested in several receptor binding assays at rat GABAA receptors using [3H]-SR95 531 and [3H]-Ro-15–1788 (flumazenil)/diazepam control. The *L. cardiaca* and *L. japonicus* extracts as well as Leon-urine inhibited the concentration-dependent binding of [3H]-SR95 531 to the gamma-aminobutyric acid site of the gamma-aminobutyric acid type A receptor with a high binding affinity.[18]

Kava (*Piper methysticum G. Forst*. [Piperaceae])

Kava (also called kava-kava), a psychoactive member of the black pepper family, has long been used as a ceremonial tranquilizing beverage by Pacific Island peoples, both recreationally and ritualistically. The drink is traditionally prepared by grinding or pounding the kava root and then mixed with water or coconut milk before the evening meal. As with valerian, kava has been widely prescribed for anxiety and sleep disorders by complementary medical practitioners. In Europe and the United States, various kava preparations have become popular. In Germany, in doses of 60 to 120 mg of kavalactones for up to 3 months, the herb is approved for "state of nervous anxiety, tension, and agitation." Kavain, a significant chemical constituent of kava, was used in a drug regimen for anxiety-related disorders in Europe.[19]

HERBAL SEDATIVES OVER SYNTHETIC DRUGS

In Germany, a polyherbal combination of valerian, hops and passion flower is licensed and marketed under the name of Kyatta-Sedativum. With this triple herb mixture in Germany, several clinical studies have been carried out. In patients with mild sleep disorders, significant improvement in sleep quality was found with the use of this polyherbal combination relative to benzodiazepines.[20]

Although few clinical studies were conducted with the combination of these three herbal medicines, numerous studies were conducted to check the effectiveness and protection of individual components. A meta-analysis of studies comparing valerian-induced subjective sleep assessment with placebo showed significant superiority over placebo.[21]

Kava is a psychoactive member of the black pepper family which has long been used as a ceremonial tranquilizing drink by Pacific Island cultures, both recreationally and ritualistically. Traditionally, by grinding or pounding the kava root, the drink is prepared, then combined with water or coconut milk to be drunk before the evening meal. As with valerian, kava was frequently recommended for anxiety and sleep disorders by complementary medical practitioners.

Numerous studies have examined the use of kava to treat anxiety disorders and, more recently, sleep disorders. In order to treat depression, 11 randomized, double-blind, placebo-controlled trials involving 645 patients reviewed. A meta-analysis conducted on 6 of the trials using the HAM-A scale indicated a significantly better reduction of anxiety with kava than with placebo. According to these studies, adverse events were transient, rare, and mild. They found kava to be an effective treatment for anxiety and sleep disorders.[22]

Among British psychogeriatric patients, lavender oil inhalation received insomnia relief. Each patient showed increased sleep time and decreased restlessness during sleep; after cessation of aromatherapy, sleep time decreased again, followed by increased lavender treatment after restart. After inhalation of lavender oil, a multiple crossover analysis of 23 female insomnia sufferers showed significant depressive central nervous system activity (via EEG recordings). The subjects were more relaxed after 3 minutes of lavender inhalation and showed increased β energy, indicating somnolence. No toxicity of lavender has been confirmed.[23]

CONCLUSION

Many incidents reported about the side effects and adverse events caused by synthetic sedatives and hypnotics leading to other psychotic problems which raises need for a better herbal sedatives and hypnotics. Herbal drugs are more effectives and safety as compared to synthetic drugs,even though all chemicals in the world has got side effects, herbals drugs benefits stand over its side effects. Patients can use herbal sedatives any time by simply making a tea or a smoke of aroma and it do not required to use entire life time to be effective and also no withdrawal symptoms reported for herbal sedatives and hypnotics.

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