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EDITORIAL

Insomnia

Insomnia is a complaint about inadequate sleep. Symptoms are usually referable to either loss of normal physical ability, or to some unpleasant change of mood. Some people who complain of insomnia, are found after study in the sleep laboratory to have no sleep disturbance, while others may show sleep disorders without a complaint. When the complaint has existed for three months or more, insomnia is said to be chronic.

The functions of sleep are unknown. Sleep may have originated as an instinctual process for conserving energy, and affording security. It seems to be clearly linked to the circadian biological rhythm. The consequences of sleep loss are known to everyone; day time drowziness, a lack of motivation, and a feeling of dysphoria are common experiences after one or two nights of poor sleep. Until fairly recently, sleep was thought to be homogenous. For practical purposes, sleep can now be classified as either rapid eye movement (REM), or non-REM sleep, the latter being divided into four stages based on EEG patterns. The different stages of sleep are distinguished by different recordings of muscle tone as measured by the Electromyograph (EMG) and eye movements as measured by the Electrooculogram (EOG), and the Electro Encephalogram (EEG). The awake state is characterized by sporadic eye movements, high muscle tone, and low voltage, fast EEG activity. Slow eye movements mark the onset of stage I NREM sleep, which is often associated with hypnagogic hallucinations. Stage II NREM sleep is characterized by sleep spindles in the EEG, as well as a considerable decrease in muscle tone. In stage III & IV NREM sleep, the EEG becomes progressively slower in frequency and higher

in amplitude. Stage IV NREM sleep is characterized by very slow frequency, high amplitude waves in the EEG (slow wave or delta wave sleep).

These definitions are somewhat arbitrary and pure. Such nice divisions are not observed in actual practice.

Sleep is not a uniform passive state, but a repetitive cycling from one state of the CNS to another. During NREM sleep, heart rate and respiration are slowed, blood pressure falls, and body temperature and metabolic activity are decreased. During REM sleep, on the other hand, heart and respiratory rates become variable and accelerated, oxygen saturation of blood decreases, along with an increase in oxygen utilization, and penile erection is typical. With so many resemblances to the awake state, REM sleep has been termed Paradoxical sleep.

Wakefulness is mediated by the ascending reticular activating system. High activity in this system prevents sleep. Sleep itself (stages 1 to IV) requires the participation of hypnagogic system, which may be located in either the serotonergic nuclei of the pontine raphe system, or the median forebrain area.

The REM state requires active involvement of the locus cereuleus, and the Giganto-cellular Tegmental field located in the Pons. The relationship between various neurotransmitters and sleep is still being explored, and the picture is not at all clear. When the synthesis of Serotonin is blocked by the Tryptophon Hydroxylase Inhibitor, insomnia and loss of REM sleep ensue. Administration of 5Ht, a precursor of serotonin, countered this effect. Again levo-dopa, a precursor of Dopamine, has been reported to both increase and decrease REM sleep. Cholinergic influences are now being studied. In small doses, increasing the brain concentration of Acetyl choline by choline Estrase inhibitor with drugs such as Physostigmine, increases REM sleep. Atropine blocks the transition from NREM to REM

sleep, suggesting that a cholinergic mechanism may trigger the nor-adrenergic system of the Locus Cereuleus. The whole system of discharges in the mechanism of sleep is known as Pontine-Geniculate, Occipital Spikes (P.G.O.), which are the hallmark electrophysiologically of the initiation of the REM period.

SLEEP DISORDERS

Four major categories have been designated :

1. **Disorders of initiating and maintaining sleep (Insomnias) :**

These include disturbances due to psychophysiological factors, painful conditions, and those associated with psychiatric disorders like anxiety, depression, or schizophrenia, use of drugs and alcohol, sleep-induced respiratory impairment, sleep related myoclonus, or with other disorders, as well as childhood onset insomnia.

2. **Disorders of excessive somnolence :**

This includes disturbances due to many of the same factors listed above, as well as narcolepsy, or idiopathic hyper-somnolence.

3. **Disorders of the sleep-wake cycle :**

This may be transient or persistent, as in a person in trouble, or through several time zones a day, e.g. intercontinental flight or night shifts which may alter their biological rhythm.

4. **Dysfunctions associated with sleep, sleep stage, or partial arousals (Parasomnias) :**

These include sleep walking, sleep terrors, enuresis or other dysfunctions.

It has been estimated that a third of the American adults say that they have trouble sleeping during a given year, but only about 2% characterize the problem as insomnia. About 4% of the American adult population have used prescription hypnotics.

Diagnosis of sleep disorders relies mainly on the history, including medical, psychiatric and drug histories. Histories should also be obtained from a bed partner.

Physical examination will provide only confirmation of disorders that may be painful during the night as rheumatoid arthritis or peptic ulcer.

A less frequent type of disorder is sleep apnoea, which is a universal occurrence in young infants, and is possibly related to some cases of sudden infant death syndrome (SIDS). During periods of sleep apnoea, respiration ceases totally, this is either due to a central mechanism of diminished sensitivity of the respiratory center; a peripheral mechanism of upper airway obstruction, or both. When upper airway obstruction occurs, the patient may resume breathing with snorting or gasping sounds, so that the diagnosis may be suggested clinically if such sounds were heard by another who shares the same room or bed with the patient.

Sleep myoclonus is an abnormality in which the patient has severe myoclonic movements specially of the lower extremities. Use of Hypnotic drugs which often have anticonvulsant action such as Clonazepam (Rivotril), seems reasonable and is reported to be effective.

Sleep walking and enuresis, both occur during slow wave sleep. Enuresis responds well to tricyclic antidepressants. Drugs that reduce or eliminate stage IV NREM sleep such as Florazepam (Dalmane), might be worth trying for sleep walking.

HYPNOTICS

A hypnotic is any drug needed to facilitate sleep. **Chloral Hydrate** is probably the oldest hypnotic drug of the modern era. Its popularity disappeared after the introduction of Barbiturates, but interest was

revived when Barbiturates were recognized to cause physical dependence. **Paraldehyde** was introduced at the same time as **Chloral Hydrate**. Being a liquid, it is rapidly absorbed so it induces a rapid and satisfactory hypnosis. It is an unpleasant substance, but curiously is favoured by alcoholics. **Barbiturates** were introduced as hypnotics early in the Twentieth century, they were certainly the wonder drugs of psychopharmacology of their time. But because of dependence, withdrawal symptoms, effects on the respiratory centre, and many suicides, they were replaced first by the non-Barbiturate hypnotics as **Glutethimide,** and then in the (1960,s) by the **Benzodiazepines.** The number of benzodiazepines has increased substantially in the past few years, and now has reached up to about twenty types. It is better to classify them according to their Half-Life plasma level, and to the length of elimination of the drug :

1. **Very short;** like Triazolam (Halcione)
2. **Short;** like Lorazepam (Ativan)
   Oxazepam (Serepax)
   Temazepam (Normison)
   Alprazolam (Xanax)
3. **Intermediate;** Chordiazepoxide (Librium)
   Diazepam (Valium)
4. **Long;** Chlorazepate (Tranxene)
   Prazepam (Demetrin)
5. **Very long;** Flurazepam (**Dalm**ane)

One should have two goals in mind when prescribing hypnotic drugs :

1. Drugs should be used occasionally and not habitually.
2. The least amount that will provide symptomatic relief should be used.

Ideally, a hypnotic will alter sleep in the following manner :

1. Sleep would come about rapidly.
2. The normal pattern of sleep would not be changed.
3. Duration of sleep would cover that whole night, with no early morning awakening.
4. After effects will not last into the day-time.
5. The drug would have little or no tendency to become habituating, and tolerance will not develop.
6. An over-dose will not be fatal.

Although none of the drugs currently available meets all those requirements some come closer than others.

The drug may act faster if it is given in liquid form, but most hypnotics are available only in tablet and capsule forms. Remaining active or upright for a short time after taking the medication may increase the drug effect sooner. This can be accomplished to some degree by taking the dose about an hour before bed time.

The issue facing the clinicians is : What are the factors that are useful to know in prefering one benzodiazepine over the other ? There are really two major factors :

1. Half-Life of the benzodiazepine.
2. Route of metabolism.

For example, Librium, Valium, Dalmane, are all metabolized in the liver, and have markedly increased half-lives specially in people who have liver impairment, whether it is from medical disease, or through normal aging. So for all these patients, it is important to use benzodiazepines that have a short half-life, and aren't metabolized in the liver. For example; Ativan, Normison, or Haleione.

Flurazepam (Dalmane) is not available in Egypt, but is very widely used in USA and Europe. The long half-life (37–289 hours) of its metabolites, allows its ready cummulation on repeated doses. The effects of the long-lived metabolites are clear in producing varying degrees of day-time sedation and probably a sustained hypnotic effect over a period of several weeks of continuous administration. It may also diminish the severity of rebound insomnia observed following discontinuation of shorter acting drugs.

Although **Temazepam's (Normison)** short half-life may be a potential advantage in avoiding accumulation, the slow absorption of the form of the drug available in some countries, whether it is in gelatin or tablet form, make it relatively ineffective for inducing sleep, although probably effective for maintaining sleep. It is known that the gelatin form has better absorption than the tablet one. This slow absorption rate may also allow a significant amount of hangover effect to be present the next day. Finally, like other short half-life drugs, major rebound insomnia may be observed after discontinuation of chronic doses of the drug.

Nitrazepam (Mogadon) has a half-life plasma level of 18 – 36 hours, peak plasma concentration following a single 5mg dose were higher in young volunteers than in old people. The rapid distribution of the drug may be a favourable attribute with use of single doses, but the intermediate half-life of the drug could lead to some cummulative effects with chronic dosage.

Triazolam (Halcione) again is not available in Egypt, but has a domination half-life of 2–3hrs, and it is one of the most short acting Benzodiazepines. Sleep may be initiated very quickly, but probably can not be maintained for a long time. Rapid absorption and rapid elimination make this hypnotic extremely interesting. It should induce little residual day time impairment, while being able to induce and maintain sleep for the desired length of time.

Other benzodiazepine hypnotics include : Flunitrazepam (Rohypnol), which is an intermediate acting drug, Midazolam (Dormicam); a very short acting drug, Clobazam (Frisium), long acting drug, Val-release-15mg which is a slow release Valium.

But it seems unlikely that any of these additional entries will offer any substantial advantage over those Benzodiazepines currently available.

There seems to be little doubt that **L-Tryptophan** has mild sedative hypnotic effects. It was used for treating depression, but in substantial doses it makes sleep come sooner and lasts longer.

Some patients with insomnia require specific treatment for an underlying disorder. Anti-depressants or ECT may be required in the depressed patients who present with insomnia. Schizophrenics are often troubled by insomnia, although it is seldom the presenting complaint, sometimes anti-psychotics are often not adequate, in which case hypnotics like Benzodiazepines may be added. Poor sleep due to anxiety may be treated with same drugs for treating the latter symptom.

NON–PHARMACOLOGIC TREATMENT OF INSOMNIA :

The relaxation that follows a warm bath, massage, or the relief of sexual tension, can promote sleep. Many insomniacs have developed elaborate rituals to induce sleep, and some seem to work. Boring tasks that do not require attention, such as watching the commercials of T.V., often induce sleep. Regular pattern of activities and exercises may facilitate normal sleep.

When hypnotics are mis-used, they have serious adverse effects, such as drug dependence, drug withdrawal insomnia, over-sedation, and day time hangover effects.

Alcohol is commonly self-administered and has lethal interactions

with hypnotics, also Barbiturates may synergise with the respiratory depression caused by alcohol, and may lead to unexpected deaths.

To summarize :

Analysis of insomnia is best done under three headings :

1. **Transient Insomnia:** occurs in those who normally sleep well, and is usually due to an alteration in the conditions which surround sleep, for example; noise, or to an unusual pattern of rest. If treatment is necessary, a hypnotic which is rapidly eliminated is the appropriate drug.

2. **Short-term Insomnia :** which is usually related to an emotional problem, or to a serious medical illness. Good management is needed to avoid long-term problems, and proper attention to sleep hygiene is essential. A hypnotic is likely to be useful, but it should not be given for more than three weeks, preferably for only a week or so. Intermittent use is desirable. A rapidly eliminated drug is usually appropriate.

3. **Chronic Insomnia :** Careful diagnosis is essential, possibly one third to one half of all such patients have an underlying psychiatric disorder, especially depression, and may need specific treatment.

Another group includes those with chronic abuse of drugs or alcohol, and yet others may have specific sleep disorders. The essentials here are exercise, controlled curtailment of sleep, reduction of stress, restriction of caffeine and alcohol, and the intermittent use of a hypnotic for one night in three, for up to a month. A long acting Benzodiazepine is appropriate, but after about a month, if this treatment is unsuccessful, a trail of sedative anti-depressants for four weeks is recommended, even in the absence of manifest depressive symptoms.

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