SLEEP DISORDERS

I. EPIDEMIOLOGY OF SLEEP DISORDERS

A. Depending on the severity criterion and phraseology of the question, perhaps 20% of American females and 10% of American males have insomnia. About half take a sleeping pill within a given year. Both insomnia and sleeping pill use increase markedly with age.

B. On average, insomniacs report about an hour's less sleep than uncomplaining subjects, but many insomniacs report more than 7 hours sleep and many people who report less than 5 hours sleep a night deny insomnia. On average, insomniacs greatly exaggerate their sleep latencies and they underestimate their sleep durations. About 1/3 of patients who use sleeping pills (or receive them from physicians) deny insomnia. What's going on? Many have conditions different from short sleep.

C. There are no studies of the prevalence of specific sleep disorders among representative population samples. The case series of sleep disorders clinics are rich in the following conditions:

depression

drug misuse

nocturnal myoclonus (leg jerks)

secondary to medical conditions

sleep apnea

body clock disturbance including shiftwork

pseudo-insomnia (nothing wrong physiologically)

It may be seen that few of these conditions would be expected to respond to hypnotics. Most conditions require more specific treatment.

II. SLEEP APNEA

A. Obstructive and Central Apnea

1. Obstructive apnea is characterized by cessation of air flow despite respiratory effort. Usually, the obstruction is in the lower pharynx between the base of the tongue and the larynx.
2. Central apnea is caused by cessation of diaphragmatic and intercostal respiratory effort, presumably due to failure of the pontine respiratory center.
3. Many patients have mixed apnea, a mixture of central and obstructive processes.

B. Causes of obstructive apnea

1. Newborn? Aging?
2. Obesity and bull neck
3. Hypnognathia, jaw deformities
4. Large tonsils or other tumors
5. Neurologic deficits (central or peripheral), eg, polio, pharyngeal nerve injuries
6. Myasthenia and myopathies
7. Hypothyroidism, goiter, acromegaly

C. Symptoms of sleep apnea

1. Insomnia (especially central apnea) and/or excessive daytime sleepiness (especially obstructive apnea)

2. Loud snoring, gasping, or choking during sleep
3. Thrashing and kicking during sleep and falling out of bed
4. Bedwetting
5. Morning headache
6. Nocturnal hypertension and arrhythmias
7. Nocturnal confusion or wandering

D. Physiologic consequences

1. Hypertension
2. Bradycardia, asystole, ventricular irritability
3. Nocturnal sudden death
4. Right heart failure, pulmonary fibrosis

E. Epidemiology

1. Perhaps 10% of all insomniacs and 1% of population or more
2. More common in newborns (1 month to 1 year) or older males
3. Associated with snoring
4. Mortality from all causes rises 30% during the hours of sleep

III. BODY CLOCK DISTURBANCES

A. Nightwork almost always causes insomnia

1. Nightworkers sleep at night on nights off, so they are constantly shifting their sleep times.
2. Shifting sleep times, whether from shift work or air travel (jet lag) almost always causes sleep disturbance,

often characterized by rapid sleep onset and early awakening.

3. Artificial light, social problems, dietary abnormalities, and noise may exacerbate these problems.
4. The best solutions are extremely rapid shifts (only 1-2 nights of work at a time) or very constant day-sleep schedules, even on days off.

B. Even very small shifts in sleep times, ie, going to bed 1-2 hours late or 1-2 hours early, cause impairments of mood and performance equivalent to sleep loss.

C. Delayed sleep phase syndrome

1. Patient has trouble falling asleep, eg, lies in bed awake for 1-5 hours, but once asleep, can easily sleep late, eg, until noon.
2. Patient likes to stay up late on weekends and to sleep late on weekend days, but finds himself unable to go to bed earlier.
3. Often becomes associated with abuse of alcohol or hypnotic drugs or results in irregular sleep habits and sleep anxiety.
4. First solution: patient must gradually establish an extremely regular bedtime by always going to bed at a regular hour and arising at a regular hour (even if there was trouble falling asleep). No napping allowed.
5. If solution #4 is unsuccessful, patient can go to bed 2-3 hours later each day (eg, 4 AM, 7 AM, 10 AM, 1 PM,

4 PM, 7 PM, 10 PM) until he wraps around to a more suitable bedtime. Then he must rigidly maintain this bedtime and the corresponding time of awakening.

IV. ANXIETY DISTURBANCES AND COMBINED HABIT DISTURBANCES

A. If patient experiences tension upon going to bed, he may try the following:

1. Relaxation training, eg, deep muscle relaxation, autogenic training, transcendental meditation, self-hypnosis, EMG biofeedback.
2. Allow for a 15-30 min. period of relaxation before bedtime, eg, a quiet period for thinking and ruminating, reading, or listening to music.
3. A little warm milk (skim milk is OK) before bedtime may be useful.
4. Regular exercise in the day or evening, but not just before sleep, is helpful.
5. Avoid caffeinated beverages after 6 PM.
6. Regular bedtimes are a must. Avoid napping and sleeping very late on weekends.

B. If patient becomes frightened of going to bed because he fears insomnia (cue: patient sleeps <u>better</u> in strange beds), this fear can be extinguished if the patient will go to bed only when sleepy. He should not go to bed until sleepy, no matter how late, and should get out of bed if not asleep in 10-15 minutes, not returning until sleepy again. After 2-3 nights of very poor sleep, the patient becomes accustomed

to falling to sleep once in bed.

C. Hypnotic drugs are probably not useful for chronic disturbances.

V. HYPNOTIC DRUG MISUSE AND ABUSE

A. Barbiturates, chloral hydrate, glutethimide, methaqualone, etc. must be withdrawn very slowly if the patient has developed tolerance, become accustomed to more than one dose per night, and has developed physical addiction.

B. The patient should be advised that although he may experience several weeks of increased insomnia during withdrawal, ultimately he will sleep better without the drug.

C. Sometimes a benzodiazepine, eg, flurazepam, can be substituted after the problem of physical addiction has been resolved. Withdrawal from flurazepam seems to often go more smoothly, after the substitution has been completed.

D. Although there is little if any recognized indication for chronic (more than 4-week) prescription of hypnotics, one must be sympathetic with the physician and patient who are reluctant to terminate hypnotic use.

VI. NARCOLEPSY

A. Key symptoms

1. Sleep attacks (generally 1-30 minutes), not necessarily sudden or without warning

2. Cataplexy, ie, sudden muscular weakness or paralysis triggered by strong emotion, eg, laughter, anger, surprise, sexual arousal

3. Sleep paralysis--being unable to move when falling asleep

4. Hypnagogic hallucinations--dreamlike sensations while still awake
5. Confusional spells, eg, automatic behaviors, fugue-like states

B. Signs

1. Sleep-onset rapid eye movement periods
2. Short sleep latencies on multiple sleep latency test

C. Treatment

1. Always rule out sleep apnea
2. Education and guidance: the American Narcolepsy Association
3. Imipramine and similar tricyclics or MAOI's are useful for cataplexy, not very helpful for sleepiness, eg, imipramine 50 mg TID.
4. Amphetamines, eg, methylphenidate 5-10 mg TID or QID is useful for sleepiness, not helpful for cataplexy.
5. Employ very regular sleep habits, adequate night sleep, scheduled naps.
6. Use drug holidays.

HYPNOTICS: A CLINICAL UPDATE

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depression

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myoclonus (leg jerks)

sleep apnea

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habit disturbances

pseudo-insomnia (nothing wrong physiologically) secondary to medical conditons

Few of these conditons would be expected to respond to hypnotics. Most conditions require more specific treatment.

II. SLEEPING PILLS

A. Prevalent in inpatient and outpatient practice

1. 27-35,000,000 retail prescriptions yearly, i.e., prescribed on 3% of all office visits to American physicians.
2. Perhaps 50% of all patients hospitalized receive a sleeping pill in the hospital.
3. As many as 92% of patients in skilled nursing facilities receive sleeping pills.
4. The cost is estimated at over $500,000,000 yearly.

B. The lack of knowledge: no long-term studies of benefit and risk, no long-term mortality/morbidity studies, no adequate comparative studies.

C. Considerations in comparing sleeping pills

1. Effectiveness: many compounds extend sleep 20-40 min. on the first night of use by insomniacs, but there is evidence that barbiturates and perhaps other drugs (glutethimide, methaqualone, methyprylon) may develop complete tolerance and be useless within 2 weeks, although still causing withdrawal insomnia. No adequate dose/response comparisons between drugs are available.

2. LD50: animal studies and available case reports and medical examiner data suggest that the overdose risk varies greatly among compounds. The barbiturates kill with 15-20 doses. Glutethimide may be even more dangerous. The lethal dose of flurazepam is about 300 doses, and there are only 1/50th as many reported overdoses per prescription (may be under-reported). Methaqualone, methyprylon and doxepin are problably intermediate in safety, while for chloral hydrate there is conflicting evidence. All hypnotics are far more lethal when combined with even modest doses of alcohol, as they often are.
3. Half-life: Drugs with half-lives beyond 8 hours tend to be quite sedating during the day. The benzodiazepines (flurazepam, diazepam, chlordiazepoxide) impair simulated driving performance without creating anxiety (or awareness of impairment) in the driver. Impairments of psychomotor performance are remarkably potentiated by even one alcoholic drink, even taken 1-2 days after the sleeping pill (in the case of the benzodiazepines). On the other hand, apparently the longer the half-life, the milder the withdrawal syndrome.
4. Addiction: Habituation and phsical addiction to hypnotics is common, but the addiction potential of the compounds seems to vary.

5. Enzymes: The barbiturates induce liver enzymes which increase and disturb metabolism of many other drugs. Flurazepam possibly causes little drug interaction. Chloral hydrate is a mild enzyme inducer but also displaces drugs from plasma protein binding sites, sometimes potentiating physiologic activity. Triclofos and betachlor are soluble (and better tolerated) administration forms which like chloral hydrate, become trichloroethanol in plasma (this is the active form).
6. REM suppression: Although REM suppression in itself lacks demonstrated liability, most REM-suppressing drugs produce rebound nightmares.
7. Slow-wave (stages 3-4) suppression: The benzodiazepines (flurazepam, chlordiazepoxide, diazepam) may almost eliminate slow waves, but no consequences directly attributable have been demonstrated.

DRUG	MILLIONS Rx/YEAR	OVERDOSES*	EFFECTIVENESS (2 WEEK +)	LD50 DOSES	HALF-LIFE (HOURS)	ADDICTIVE RISK	ENZYME INDUC.	REM	ST.3-4
Barbiturates									
Pentobarbital (Nembutal)									
Secobarbital (Seconal)									
Amobarbital (Amytal)									
Seco+amobarb (Tuinal)	4.4	24-70	doubt	15-20	15-40	++++	+++++	↓↓	±
Glutethimide (Doriden)	1.8	18	doubt	10-40	5	+++++	+?	↓?	?
Ethchlorvynol (Placidyl)	1.7	20	doubt	14->70	6+	++++?	?	↓	↓
Methaqualone (Quaalude)	0.7	4	?	10-20?	18-70	+++++	?	?	?
Methyprylon (Noludar)	1.0	8	doubt	15-67	4	?+	?	?	?
Chloral hydrate (Noctec) and triclofos and betachlor	2.0	0.7	slight or moderate	10	6-8 (trichloro-ethanol)	+++	++	0	0
Flurazepam+ (Dalmane)	13.6	0.9	moderate?	300 10+ETOH	80	+	±	↓	↓↓↓↓
Doxepin (Sinequan)	?	2-4?	?	20	?	0	?	?	?

*Crude relative estimate only of overdoses per 100,000 prescriptions. A physician who wrote 10,000 barbiturates prescriptions in a lifetime could expect 2-7 overdose deaths among his patients.

Chlordiazepoxide (Librium) and diazepam (Valium) are generally similar. Chlordiazepoxide's active metabolite is produced too slowly for sleep induction and is very long-lived. Diazepam (and metabolites) have half-lives of about 40 hours, while those of oxazepam (Serax), lorazepam (Activan), and triazolam are in the 5-20 hour range.

III. RECOMMENDATIONS

A. THINK BEFORE YOU USE A SLEEPING PILL! Take a history. See if there are indications of a specific sleep disorder.

B. One of the better hypnotics (Perhaps flurazepam, triclofos, or doxepin) may be prescribed for short-term transient or situational insomnia. Outpatients receiving hypnotics should be warned about hangover, alcohol, and driving. One drink is too much for benzodiazepine users who drive.

C. Chronic insomnia should be approached with a careful history, an attempt to make a diagnosis, and sometimes, sleep disorders clinic referral. Hypnotics are rarely indicated.

D. In some cases of chronic insomnia, psychological training may be useful. Patients with trouble relaxing may read before going to bed, while patients who become anxious while trying to fall asleep in bed should get up out of bed until they are sleepy. Relaxation methods (Jacobsonian relaxation, autogenic training, transcendental meditation, biofeedback, etc.) may be useful for selected patients. General hygenic methods include avoidance of alcohol, sedatives, and caffeinated beverages, use of regular exercise, and extreme regularity in sleep hours, especially in the time of arising. Insomniacs should not sleep late even if they have trouble falling asleep, and they should avoid naps.

BARBITURATES AND SEDATIVE HYPNOTICS

1) Barbiturates:
   a) Secobarbital
   b) Pentobarbital
   c) Phenobarbital

   Sedative hypnotics:
   a) Quaaludes
   b) Placidyl
   c) Doriden
   d) Chloral hydrate

2) Uses:
   a) Antianxiety agents
   b) Epilepsy (phenobarbital)
   c) Insomnia
   d) ECT (Brevitol), anesthesia
   e) Getting high

3) Pharmacologic principles:
   a) Tolerance (develops rapidly)
   b) Withdrawal (severe)
   c) REM suppression and rebound
   d) Addiction

4) Mention mostly to condemn:
   a) Easily addicting
   b) Withdrawal dangerous

c) Very dangerous in an overdose

d) Interacts with metabolism of other drugs

5) Treatment of addiction or withdrawal:

a) Early symptoms

b) Late symptoms

c) Treat with intoxicating doses of secobarbital or phenobarbital and decrease slowly (10-14 days)

6) Symptoms of intoxication:

a) Lateral nystagmus

b) Ataxia

c) Dysarthria

d) Labile affect

7) Symptoms of Withdrawal:

a) Insomnia

b) Agitation

c) Tremors

d) Seizures

e) Delirium (confusion, delusions, hallucinations)

f) Hyperpyrexia

g) Vasomotor lability (Hypertension, tachycardia, hypotension)

h) Sweating

MINOR TRANQUILIZERS

1) Indications:

   a) Anxiety (anticipatory)

   b) Depression (Neurotic ?)

   c) Psychosomatic illnesses (GI, Bronchial, etc.)

   d) Treatment of delirium tremors

   e) Insomnia

   f) Seizures (Diazepam)

2) Available drugs:

   a) Serax - Oxazepam

   b) Valium - Diazepam

   c) Librium - Chlordiazepoxide

   d) Atarax - Hydroxyzine

   e) Miltown - Equanil - Meprobamate

   f) Dalmane - Flurazepam

3) Dosages:

   a) Librium 5-25 mg., 1-3 x/day

   b) Valium 2-10 mg., 1-3 x/day, 15 mg. h.s.

   c) Dalmane 15-30 mg. h.s.

4) Pharmacologic properties:

   a) Mild tolerance develops

   b) Withdrawal symptoms can occur

   c) Safe in an overdose (except meprobamate which is dangerous)

   d) Valium addicting at 60 mg/day x 6 weeks

   e) Librium addicting at 250-300 mg/day x 6 weeks

5) Side effects:

   a) increased hostility

   b) ataxia

   c) sleepiness

   d) dysarthria

   e) rashes

   f) agranulocytosis

   g) disinhibition in elderly

6) Overdosage:

   a) Valium and librium very safe

   b) Miltown relatively dangerous

   c) Addiction potential:

      (1) sedative hypnotics

      (2) meprobamate

      (3) diazepam or chlordiazepoxide