Benzodiazepines for the treatment of sleep disorders

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SLEEP DISTURBANCES affect about 35% of all adult Americans each year.[1] Their severity and prevalence tend to be greater in older people and in women.[1,2]

Benzodiazepines often are used to treat disorders of sleep. The application of these agents is largely for the management of insomnia, but they can also be useful in controlling certain nocturnal behaviors of which the sleeper is unaware.

BENZODIAZEPINES FOR INSOMNIA

Benzodiazepines have become the first-choice hypnotics for the treatment of insomnia. Barbiturates as well as non-benzodiazepine, non-barbiturate drugs such as chloral hydrate either have fallen into disuse or been relegated to niches for use with uncommon types of patients.

The efficacy of benzodiazepines for the treatment of insomnia is well established and has been measured by subjective and objective criteria. Subjective criteria include the estimates by sleepers themselves of the amount of time taken to fall asleep, the number of hours slept, the number of awakenings, the quality or depth of sleep, and the sense of refreshment and restored alertness. Objective laboratory criteria obtained with polygraphic sleep-recording methods[3] include the sleep latency (time from lights out to sleep onset), duration of sleep, number and duration of nocturnal awakenings, and sleep efficiency (sleep duration as a percentage of the time spent in bed).

The ability of benzodiazepine hypnotics to facilitate polygraphic sleep does not mean that such sleep is identical to spontaneous sleep. The latter represents the operation of homeostatic and circadian timing mechanisms. Sleep recorded after the administration of a benzodiazepine has fewer slow-wave epochs,[4–7] and the amplitude of delta waves, but not necessarily their number, is reduced.[6,8]

For reasons that are not fully understood, subjective and objective measures of sleep are often discrepant, and it is important not to devalue subjective estimates when patients overestimate sleep latency or underestimate sleep duration. After all, it is the subjective sense of the quality of their sleep that is burdensome to patients and motivates them to take sleeping pills or to seek other kinds of help. Hypnotic drugs may relieve symptoms more than they improve polygraphic sleep. A study we conducted illustrates this. A 30-mg dose of flurazepam, a long-acting hypnotic benzodiazepine, was administered to a group of elderly subjects who were insomniac (sleep efficiency < 87.5%) and had mild chronic lung diseases (1 L < FEV_1 < 79% and pCO_2 < 45 mm Hg). The subjects received placebo for the first four nights, flurazepam for the next 28 nights, and placebo for the final five nights. Sleep patterns were recorded in a hospital clinical research center for a total of 20 nights. Each morning after a sleep recording was made, the subjects completed a questionnaire about how they thought they had slept. On remaining nights spent at home, they also kept a log of how they slept. *Figure 1* shows changes in the sleep latency, i.e., the number of minutes required to fall asleep, as measured objectively and estimated by the subjects.

Sleep latency decreased sharply when administration

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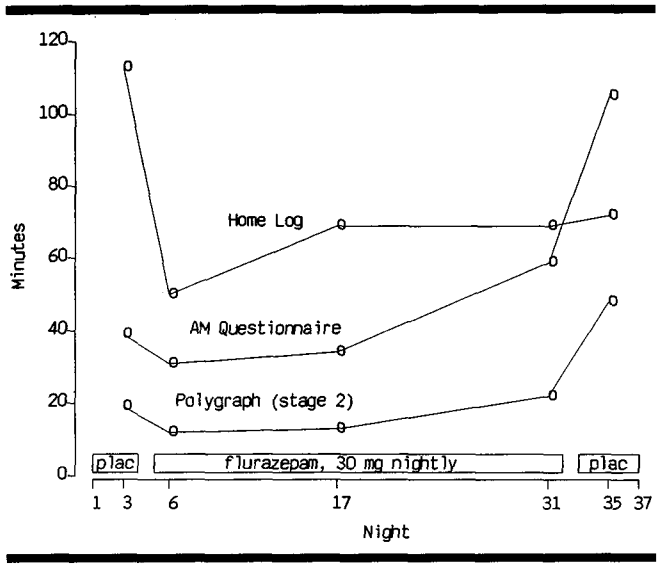

FIGURE 1. Mean latency to sleep onset in minutes, for six elderly insomniacs who received placebo (plac) for four nights; flurazepam, 30 mg, for 28 nights; and placebo for the last five nights. Sleep latency was measured in the laboratory by polygraphic sleep recordings (Polygraph), by sleep questionnaire completed by subjects in the lab in the morning (AM Questionnaire) and in the morning at home (Home Log).

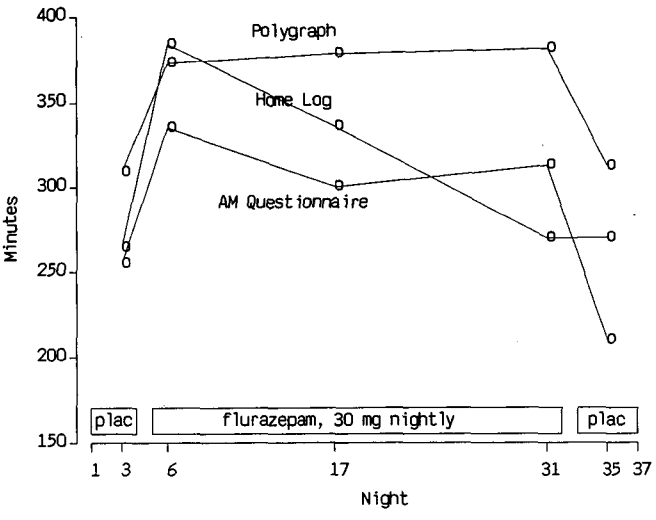

FIGURE 2. Mean nightly duration of sleep in minutes among subjects described in *Figure 1*.

of flurazepam was started. Note that during the initial placebo period, subjects felt they had taken much longer to fall asleep than the period determined by the polygraph recording. As soon as flurazepam was given, the recorded sleep latency decreased, but the subjective estimate made at home decreased the most. Evidence of drug tolerance during the 28 nights of flurazepam use is shown. When flurazepam was withdrawn, both the measured sleep latency and estimates made by the subjects in the laboratory increased sharply. These findings show that the greatest therapeutic effects of hypnotic drugs, as well as the sharpest adverse effects of their withdrawal, may be subjective in character. *Figure 2* shows similar data for the duration of sleep. Again, the initial change effected by flurazepam is largest for a subjective measure (the home-log estimates), while the largest decrease in sleep duration after drug withdrawal was for the same subjective measure. The changes in the polygraphic measures were significant (*Table 1*), as was an improvement in sleep efficiency. It is worth adding that several of these measures were actually worse after drug withdrawal than before flurazepam administration. It is clear why subjects and their physicians are often tempted to restart treatment with a hypnotic agent after a planned brief course has been completed.

In addition to their nocturnal symptoms, patients with insomnia also may complain of daytime problems that they attribute to sleeplessness. The disturbed sleep of the insomniac does not necessarily have the same daytime effects as does sleep deprivation in normal people. When insomnia is associated with depression, for example, daytime dysphoria may be better considered representing an affective component of the depression rather than a consequence of the disturbance of sleep that usually accompanies depression. As a result, treating the nocturnal symptoms of depression may not be sufficient in these patients.

The most important consideration in the choice of a benzodiazepine hypnotic agent is its duration of action. A hypnotic drug is expected to produce effects for as long as the patient wants to sleep and to lose its effect during the waking period. The termination of drug action is not perfectly predictable. Short-acting hypnotics are likely to lose their effects during sleep, resulting in "early morning" or "rebound" insomnia.[9,10] However, the short-acting benzodiazepine triazolam has been shown to extend sleep in a sleep-reversal paradigm.[11] Conversely, the effects of long-acting hypnotics such as flurazepam can persist into the waking period and cause unwanted residual or "hangover"

TABLE 1
EFFECTS OF 21 CONSECUTIVE NIGHTS OF FLURAZEPAM ADMINISTRATION (30 MG) ON SIX ELDERLY INSOMNIACS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Effect	During Drug Administration					
	Baseline	Early	Mid	Late	Withdrawal	F-ratio
Sleep						
Latency to stage 2 (minutes)	19	12	13	22	48	4.23 ($p<.05$)
Duration (minutes)	309	373	378	381	312	5.28 ($p<.01$)
Efficiency (%)	75	84	84	81	67	6.32 ($p<.01$)
Breathing while asleep						
Abnormal events/hour	11	11	6	8	8	1.73
Mean event duration (seconds)	21	21	19	18	19	1.11
Obstructive events (% events)	20	23	20	28	27	1.11
Minimum O_2 saturation (%)	88	90	90	92	92	0.86
O_2 saturation <85% (% time)	0.1	0	0.1	0.1	0	0.43

effects on alertness and performance.[12] Such effects decrease with nightly use despite persistence of pharmacological activity.[13]

Half-lives of drugs may be markedly prolonged in the elderly, kinetics resulting in accumulation of the drug to toxic levels. Furthermore, some elderly are more sensitive to the sedating and amnestic effects of benzodiazepines, responses that may result in falls, nocturnal episodes of confusion, and agitation. Certain benzodiazepines (triazolam, lorazepam, alprazolam) appear more likely than others to cause anterograde amnesia.[14] This effect, which is probably dose-related, can be a serious drawback, not only for the elderly, who are probably at greater risk of developing memory loss, but also for people in critical occupations and those who may have to perform on call at night.[15] After initial reports of dangerous increases of sleep-related respiratory impairment with the use of benzodiazepines,[16] numerous studies have shown that benzodiazepines are fairly safe in this regard, even in high-risk, elderly subjects with pulmonary disease.[17,18] Among the elderly insomniac subjects described earlier, no significant changes were found in five measures of sleep-disordered breathing (*Table 1*). There are even reports that benzodiazepines reduce sleep-related breathing impairments.[19,20]

Insomnia is not a disorder as such. Rather, it takes many forms and has many causes.[21] Several relevant forms of insomnia will now be reviewed.

REACTIVE INSOMNIAS (ADJUSTMENT SLEEP DISORDER)

It is widely assumed that most cases of insomnia are of short duration and occur in response to major life events. Nonprescription hypnotics (antihistaminics) often are used for self-medication, or benzodiazepines are prescribed to control the problem. Major considerations in prescribing for such patients are avoidance of residual daytime effects and patterns of drug use that will lead to dependency. Use should be limited to a few nights and doses should not be escalated.[22]

CIRCADIAN RHYTHM SLEEP DISORDERS

Short-term insomnia may be caused by changes in the timing of sleep relative to biological time. Biological time is measured by the circadian timing system. A common cause of such changes in timing is travel across time zones ("jet lag"). The mismatch between the timing of sleep and the biological clock stems from a delay in the resetting of the biological clock to that of the new time zone. If the traveler attempts to sleep when it is night in the environment but "day" by the reckoning of the biological clock, he or she will experience difficulty in falling asleep or, depending on the direction of travel, difficulty in sleeping through the night.

Mismatches between the time of sleeping and the time told by the biological clock have been modeled in the laboratory. In early efforts, the sleep period was shifted by 12 hours.[23] This shift resulted in an inability of the subject to sustain sleep for a normal period. Administration of a benzodiazepine (flurazepam) before sleep at the new time increased the duration of sleep but failed to reverse the poor feelings of the subjects as they kept a vigil during the night.[24] A more recent experiment of this type demonstrated that waking performance could be improved by facilitating sleep with a short-acting benzodiazepine (triazolam).[11] The temporal dislocations of jet lag can be modeled more closely in special laboratories where subjects can be shielded from external time clues.[25] In such settings, the sleep period can be advanced or delayed by arbitrary amounts almost without the subject being aware of the maneuver, and experimental "countermeasures" to the adverse effects of the shift can be systematically tested.

What is needed is a means of rapidly resetting the biological clock to the "destination" time of day. Recently, triazolam has been found to reset the biological clock of rodents in directions related to the time of administration. Triazolam also appears to alter how long it takes human rhythms to adjust to an 8-hour delay shift of the sleep-wake cycle.[26,27] If benzodiazepines are found to reset the human biological clock, they also may find application in the management of other circadian rhythm sleep disorders. Closely related to jet lag are the problems of shift workers, who also try to fulfill their need for sleep at times during the circadian cycle when the propensity for sleep is low.[28]

Shifts in the timing of sleep also may serve as models for certain transient insomnias experienced in everyday life. Many people, for example, delay their bedtimes and times of arising on weekends. These changes may induce resetting of the circadian timing system to a later hour, and may result in sleep-onset insomnia when attempts are made to return to the usual schedule on Sunday nights. Similarly, there exist chronic sleep-onset insomniacs whose difficulty falling asleep appears to stem from mismatch between the sleep schedule and the circadian timing system rather than any intrinsic inability to sleep (delayed sleep phase syndrome).[29,30] It remains to be seen whether benzodiazepines may be useful in the treatment of such types of insomnia.

RESTLESS LEGS SYNDROME AND PERIODIC MOVEMENTS IN SLEEP

One of the most frustrating causes of insomnia is the restless legs syndrome. This condition was first described by Willis in 1685: "Wherefore to some, when being a Bed they betake themselves to sleep, presently in the Arms and Leggs, Leapings and contractions of the Tendons, and so great a Restlessness and Tossings of their Members ensue, that the diseased are no more able to sleep, than if they were in a Place of the greatest Torture."

This description remains as good as any contemporary one. The underlying mechanism is unknown, but it is common in patients with renal failure. The syndrome has also been associated with anemias and peripheral neuropathies. Clonazepam has been found effective in controlling this syndrome.[31–33]

When people with restless legs syndrome do manage to sleep, they nearly always have periodic movements of the legs and, less often, of the arms or trunk.[34] The intervals between movements are typically 20 to 40 seconds. These movements, once termed "nocturnal myoclonus,"[35] are in fact slower than myoclonic movements. They are often but not always associated with brief arousals from sleep, usually without awareness. Periodic movements are associated with many other sleep disorders, including those associated with insomnia and excessive daytime sleepiness[36] and are also found in nocturnal electromyogram recordings of asymptomatic people, especially the elderly.[37] For this reason, most people with periodic movements would probably not benefit from treatment. Those who may benefit have frequent movements associated with brief arousals or restless legs syndrome. The benzodiazepine clonazepam at doses of 0.5 mg to 2 mg per night, reduces periodic movements and associated symptoms of insomnia and excessive daytime sleepiness.[38–40] Clonazepam also may suppress associated nonobstructive apneas during sleep.[19] Opioids and l-dopa/carbidopa can also be effective in the management of periodic movements and restless legs.

PSYCHOPHYSIOLOGICAL INSOMNIA

Acute, reactive insomnias sometimes become persistent when patients become anxious about sleep and overreact. The anxiety may stem from narcissistic concerns ("How will I look if I don't sleep?") or from concerns regarding next-day effects on cognition ("How will I work productively if I don't sleep?"). In severe cases, patients start worrying about sleep early in the day (anticipatory anxiety). The anxiety builds as bedtime approaches and usually results in difficulty falling asleep. Nocturnal awakenings are likely to be protracted because anxieties are activated as soon as the patient awakens. During the night, the anxiety often concerns getting some sleep before it is time to get up for work. The problem is also often compounded by extending the sleep period, because spending more time in bed than is biologically necessary for sleep promotes the fragmentation of sleep to "fill" available time. Such a problem is especially likely to develop in elderly insomniacs, who may need less sleep than younger people, and whose sleep fragments more easily.[41] While benzodiazepines may be helpful in controlling anxiety in such people, it is at least equally important to institute a regular, rational sleep schedule. The length of the scheduled sleep period should not exceed the sleep requirement by more than about a half hour. Sleep need may be estimated from the premorbid sleep pattern (if not too distant in time) or from age norms.[42]

A small proportion of anxious insomniacs never sleep as well off benzodiazepines as with them.[43] In our view, such patients can continue taking small doses, such as 2–5 mg of diazepam nightly, which usually suffice, as long as they are followed up at regular intervals.

SLEEPING PROBLEMS RELATED TO PANIC DISORDER

Anxiety also can interfere with onset and continuity of sleep when that anxiety is not focused on sleep. A severe form, panic disorder, is discussed elsewhere in this issue. About 70% of patients with panic disorder experience at least occasional panic attacks during the night.[44] They may awaken with palpitations, sweating, hot/cold flushes, a sense of smothering or choking, feelings of unreality, and chest discomfort.[45] Attacks can therefore resemble REM behavior disorder (elsewhere in this issue), sleep terrors, or nightmares. In patients who are convinced that the episode is triggered by inability to breathe, a sleep recording should be performed to detect any sleep-related respiratory impairment. The chances that a typical attack will occur in the diagnostic sleep laboratory are low, and attempts to induce attacks with intravenous infusions of sodium lactate during sleep have not yet succeeded.[46] Insomnia is also frequent in patients with panic disorder. It is more related to anxiety ratings than it is to the frequency of panic attacks.[45] The treatment of panic disorder with benzodiazepines is discussed elsewhere in this publication, and these agents appear to be useful in the treatment of both nocturnal panic attacks and the associated insomnia.

SLEEP PROBLEMS RELATED TO MAJOR DEPRESSION

Probably the most severe and painful forms of insomnia are those associated with the major depressions. Some depressed patients insist that their affective disturbance is the direct result of their inability to sleep. In particular, they attribute daytime tiredness and lack of energy and initiative to sleeplessness. Yet, they are not sleepy in the daytime and indeed may complain of being as little able to nap during the day as they are to sleep at night. Such patients often demand to be treated with a sleeping pill. While the partial symptomatic relief afforded by hypnotics may be valued by such patients, it does not reverse major depression. Furthermore, benzodiazepines can exacerbate depression. Therefore, the wisest approach is to treat the depression with the most effective antidepressant agent available, avoiding those known to interfere with sleep such as fluoxetine and favoring those with sedative effects (amitriptyline).

INSTITUTIONAL USE

Benzodiazepine hypnotics are among the most frequently prescribed medications in hospitals and long-term care facilities. While sleep problems are common in certain institutionalized populations, such as the elderly living in nursing homes, the nature and causes of such problems remain obscure. Remarkably, the administration of hypnotics does not appear to be related to the occurrence of sleep problems.[47]

SOMNAMBULISM AND SLEEP TERROR

The most common forms of somnambulism and sleep terrors begin in childhood (after age 4 years) and generally disappear before the teen years. Most affected children experience only a small number of events, although they may occur nightly for short periods. Neither condition poses a direct medical risk, but somnambulism can result in serious accidents, and sleep terror can be very upsetting to parents and interfere with their sleep. Benzodiazepines can effectively suppress the occurrence of these events, perhaps by suppressing slow-wave sleep, since the parasomnias most often occur during periods of slow-wave sleep near the beginning of the night.[48] In deciding whether to treat these disorders, the clinician must judge whether the advantages of suppressing the episodes are outweighed by the risk of impairing daytime cognitive and psychomotor capacities. In cases of somnambulism, measures to safeproof the house (locks on windows, guard rails at the head of stairs, etc.) should always be taken. If drug treatment is used, the dose should be the lowest needed to adequately control the severity and frequency of episodes, and the medication should be discontinued as soon as possible.

Similar considerations apply to adult cases of these disorders. In cases of recrudescence after a long symptom-free period or with onset during adult life, the possibility that the problem may be caused by the administration or withdrawal of drugs should be assessed by clinical history and sometimes by drug testing. The possibility of nocturnal seizures should be consid-

ered and, if appropriate, one or preferably several consecutive all-night EEG recordings with video monitoring should be conducted in a sleep laboratory. Cases of such nocturnal behavior also may follow emotional trauma. The REM behavior disorder should also be ruled out (see Shenck in this volume). The dose needed to suppress the events is generally 5 to 20 mg of diazepam.[49] Alternative benzodiazepines include lorazepam and possibly clonazepam. Cases in adults that do not respond well to a benzodiazepine may respond to imipramine.[50]

ACKNOWLEDGEMENT

The research on flurazepam was supported by a grant from Hoffmann-La Roche Inc.

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