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SLEEP-WAKE VARIATIONS AND DRUG SELF-ADMINISTRATION

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INTRODUCTION

Many central nervous system (CNS)-active drugs have profound effects on sleep and alertness. Yet, only recently has the possibility that the sleep-wake altering effects of CNS-active drugs might contribute to their use and abuse received scientific attention. The effects of a drug or its discontinuation on the sleep-wake system may serve as the basis for the initiation or the maintenance of drug taking behavior. This paper will review recent evidence linking sleep-wake variations with drug self administration.

DEFINITIONS AND SCOPE

Sleep-Wake variations.

Within large samples of self-described healthy normals, wide variations in nocturnal sleep time and sleep efficiency and in daytime level of sleepiness-alertness have been reported. In his book, *Sleep and Wakefulness,* Kleitman described the self-reported variations of sleep durations over several thousands of nights (16). Some reported as little as 6 hrs nightly and some over 9 hrs nightly and night-to-night variations within subjects were as great as 3 hrs. Current sleep laboratory data show that sleep efficiency in self-described 30-39 yr old normal sleepers, who underwent an 8 hr polysomnogram (NPSG) scheduled according to habitual bedtimes, ranged from 83-98% of time in bed, which is 6.6-7.8 hrs (± 1 sd) sleep time. In 50-59 yr old normals, sleep efficiency ranged from 71-96% or 5.7-7.7 hrs (36). In a report of NPSG-defined sleep in a large sample of insomniacs with a similar age range to the normals above, sleep time varied from 1.7 hrs to 8.8 hrs (6). While allowed *ab libitum* sleep in this study, compared to age-matched normals also under *ad libitum* conditions, 50% of the insomniacs could not be differentiated from the normals by their total sleep times. That is, there was an extensive overlap among the normals and insomniacs in nocturnal sleep efficiency.

The same large variation in daytime alertness has been reported. The generally accepted method of documenting level of daytime sleepiness-alertness is the Multiple Sleep Latency Test (MSLT) (32). Average daily sleep latency on 4 to 5 tests conducted throughout the day at 2-hr intervals is the gold standard of sleepiness-alertness measures. In a large sample of self-described normal sleepers without

complaints of daytime sleepiness or daytime napping, average daily sleep latency on this measure varied from 2 to 20 min (18). About 20% of these non-complaining young adults had average daily sleep latencies shorter than 6 min. A MSLT sleep latency of less than or equal to 5 min is considered to be pathological (32). For example, patients with sleep disorders, such as obstructive sleep apnea syndrome or narcolepsy, and with complaints of excessive daytime sleepiness, typically have sleep latencies less than or equal to 5 min (41). Again, overlap between the normal and patient population is found.

Experimental approaches.

As the preceding information clearly indicates, substantial overlap exists between the self-report of disturbed sleep and wake and the objective indicators of variations in sleep and wake state. Given this overlap, another approach to relating drug self-administration to sleep-wake function is to focus on the symptom. This symptom-based approach defines subject patients by the presence or absence of complaints of insomnia or daytime sleepiness, regardless of NPSG or MSLT result. Comparison of a symptom-defined population to normals without objectively documented sleep and wake disturbances allows one to assess the extent to which the perception of poor sleep and wake determines drug self-administration.

Finally, the strongest scientific approach is to study non-complaining individuals who show normal indications of sleep and wake and then to experimentally disturb their sleep and wakefulness. Thus, for example, studies have introduced auditory tones to produce fragmented sleep with frequent arousals, administered caffeine to reduce sleep efficiency, or used the first-night effect as a model of transient insomnia (23, 25, 33). To produce daytime sleepiness, other studies have reduced nocturnal bedtime to 4 or 5 hrs (30, 35). Such approaches provide control for various other factors associated with disturbed sleep and unusual daytime sleepiness (i.e., non-conducive sleep environment, shifting sleep schedule, or restricted sleep schedule) in self-described normals. Similarly, these approaches control for the potential confounding factors found within clinical populations. In addition, comparison of a clinical population to healthy normals in whom the symptom has been produced allows one to separate the sleep-wake determinants from other clinical determinants of drug self-administration.

Drug use-abuse.

Many of the CNS-active drugs that affect sleep and wake are also drugs that have abuse liability. Some of these CNS-active drugs have well documented therapeutic effects on sleep and wake. Differentiating drug abuse and therapeutic drug use becomes a critical issue and is an area of extensive debate (37, 40). Drug abuse or addiction is generally defined by the presence of physiological dependence or behavioral dependence. Physiological dependence is a state induced by repeated drug use that results in a withdrawal syndrome when the drug is discontinued or an antagonist is administered. Many of the CNS-active drugs produce physical dependence, although the syndrome intensity, relation to therapeutic dose, and duration of use vary among drugs. Physiological dependence may be a

component of, but it is not a necessary nor a sufficient condition, to produce behavioral dependence. This paper focuses on behavioral dependence, not physiological dependence.

Behavioral dependence is a pattern of behavior characterized by repetitive and compulsive drug-seeking and consumption. This pattern of behavioral dependence becomes evident in assessing the conditions under which a drug is self-administered and by the characteristics of that self-administration behavior. Some potentially differentiating and defining characteristics of drug-seeking versus therapy-seeking behavior are presented in Table 1. In drug-seeking the focus is on the drug and its effects, while in therapy-seeking the focus is on the illness or condition for which the drug provides relief. The construct of therapy-seeking is used in a broad sense to include patients seeking medication for their symptoms and normal individuals seeking to overcome daytime sleepiness resulting from sleep loss or drug or alcohol use. Of great clinical concern are the circumstances under which therapy-seeking shifts to drug-seeking behavior or therapy-seeking serves to maintain a pattern of drug abuse.

Table 1. - *Characteristics of drug-seeking and therapy-seeking behavior.*

Characteristics of drug-seeking behavior
• Drug chosen over placebo
• Drug chosen over other commodities or activities (within limits)
• Drug has discriminable subjective effects
• Drug taken in excessive, non-therapeutic amounts
• Drug taken on chronic basis-leading to tolerance and physical dependence
• Drug taken in non-therapeutic context
Characteristics of therapy-seeking behavior
• Drug has demonstrated efficacy
• Duration and dose of self-administration is limited to therapeutic effects
• Drug is believed to be or has been experienced as being efficacious

SEDATIVE DRUGS

Benzodiazepine receptor agonists.

The benzodiazepine receptor agonists (BzRA) comprise one class of drugs for which the issue of drug-seeking versus therapy-seeking has been extensively debated (37, 40). The therapeutic indications for this class are insomnia and anxiety. In the 1980s, self-administration studies were done in normals, persons with a substance abuse history, and patients with anxiety disorders. Study results showed a generally low behavioral dependence liability. The BzRAs were self-administered by substance abusers at low and declining rates over time (12), and they were not self-administered differentially relative to placebo by normals or patients with anxiety disorders (8,9). A recent study, however, has found that some

patients with anxiety disorder self-administered alprazolam relative to placebo, raising questions as to what factor(s) may account for these individual differences (21).

The other indication for the BzRAs is insomnia. Our laboratory has conducted a series of studies assessing the conditions and characteristics of BzRA self-administration when the compounds are available as "hypnotics". In contrast to the studies cited above in which the drug was self-administered in the daytime, in these studies self-administration was assessed before bedtime (i.e., "hypnotic"). The BzRA used in these studies was triazolam, 0.25 mg. Triazolam was chosen as it is the most widely studied hypnotic for efficacy and safety and it possesses the same pharmacological properties as the other BzRAs. In a single-choice paradigm, in which participants choose to self-administer the available capsule or to choose no capsule, insomniacs self-administered active drug on 67-88% of opportunities (25, 28, 29). The self-administration rate for active drug was similar to that for placebo, 81-85%. These self-administration rates were consistent across three independent studies. Finally, these self-administration rates remained stable across two consecutive weeks of nightly choice (22).

These results with a single-choice methodology showing placebo is self-administered at the same rate as active drug, suggest that the BzRAs have a very low abuse liability. Yet, they also raise the question whether placebo and active drug can be discriminated by the insomniacs. In a forced-choice paradigm in which the participants sampled both capsules and then chose between active drug and placebo, the active drug was chosen on 80% of opportunities (29). Thus, based on their preferences in a forced-choice, insomniacs do discriminate placebo and active drug. This clear preference then raises the question whether active drug is preferred because it is effective in improving sleep or because it produces non-therapeutic effects desirable to the insomniacs.

Among other criteria listed in Table 1 as distinguishing therapy-seeking versus drug-seeking is whether the dose is escalated over time. In a laboratory study, insomniacs were given the opportunity to self-administer multiple capsules (3 total) before sleep (28). In this single-choice paradigm, they self-administered a stable number of triazolam capsules nightly during the one-week study, achieving an average dose of 0.27 mg; that is essentially 1 capsule nightly, which is close to the indicated dose for triazolam, 0.25 mg. In contrast, the number of placebo capsules self-administered nightly was higher on average (i.e. 2 capsules per night), variable night to night, and tended to increase from the first to last night. A similar absence of active hypnotic dose escalation was reported in an epidemiologic study of insomnia and its treatment (2). Of the 2.6% of respondents who reported having used a prescription hypnotic in the past year, only 8% reported an unsupervised increase in dose.

Another of the criteria listed in Table 1 is whether the drug is self-administered outside of the therapeutic context. For a hypnotic, daytime self-administration would be considered outside of the therapeutic context. Another study assessed insomniacs for their self-administration of triazolam 0.25 mg and placebo before bedtime versus their self-administration during the day, at 9 am (31). As in

previous studies, the insomniacs self-administered both capsules on 80% of opportunities at bedtime; however, they self-administered on only 20% of opportunities in the daytime and the majority (70%) of insomniacs took active drug only once or never during the daytime opportunities. Insomniacs who self-administered drug during the daytime were "hyperaroused"; that is, their sleep latencies on the MSLT were unusually long, being two standard deviations beyond the mean of a large sample of healthy adults, as well as, beyond the mean of those insomniacs who did not consistently choose capsules during the day (18). The drug lowered the daytime MSLT sleep latencies of the "hyperaroused" insomniacs to normal levels, again suggesting the daytime self-administration of this subsample was therapy-seeking and not drug-seeking.

The differentiation of therapy-seeking versus drug-seeking can be further evaluated by comparing persons with insomnia complaints, but normal sleep, to insomniacs with disturbed sleep and normals with normal sleep. As noted earlier, the symptom-based approach provides a means to differentiate perceived sleep problems from physiologically disturbed sleep. Thus, in the studies cited above, all insomniacs showed disturbed sleep on a screening NPSG, defined as a sleep efficiency $\leq 85\%$. In two of those studies, persons with persistent insomnia complaints, but sleep efficiencies $\geq 85\%$ (i.e. patients with sleep state misperception disorder), were also studied (25, 28). Self-administration of a capsule before sleep, either placebo or active drug, in these insomniacs was intermediate (49% of opportunities) to the insomniacs with disturbed sleep (81%) and the normals (26%). This result suggests that the perception of a sleep disturbance contributes to the self-administration of hypnotics, but less so than disturbed sleep *per se*.

If the hypnotic self administration described above is therapy-seeking rather than drug-seeking behavior, it should also relate to the extent of sleep disturbance (see Table 1). Night-to-night variability in self-ratings of the speed of falling asleep, the total amount of sleep, morning ability to concentrate, and morning sleepiness were found to be predictors of hypnotic self-administration (22). Greater reported disturbance of sleep or morning alertness predicted greater likelihood of self-administering a capsule before sleep the next night. Basal NPSG differences in sleep between subjects were also shown to be predictive of hypnotic self-administration (31). Reduced stage 3-4 sleep and increased stage 1 sleep were the best predictors of subsequent hypnotic capsule self-administration. In an epidemiological study of the use of prescription medications as aids to sleep over the past year (reported by 5% of the population), the factor most strongly associated with sleep aid use was difficulty falling asleep (15). Thus, in both laboratory and epidemiological studies within-subject and between-subject variations in nocturnal sleep relate to hypnotic self-administration.

Alcohol.

The epidemiological study cited above also revealed that 13% of the sample had used alcohol as a sleep aid (15). Given these epidemiological study results and earlier Gallup survey results showing use of alcohol as a sleep aid by 25% of insomniacs (1), studies of the behavioral dependence liability of alcohol relative

to sleep and wake variations have also been initiated. One of the earliest descriptions of the potentially disruptive effects of alcohol on sleep is that of Kleitman and colleagues (20). Alcohol in doses of 60-75 ml decreased body motility and temperature compared to normal in the first half of the sleep period, but these measures were increased during the second half. Presently, the strong association of disturbed sleep and alcoholism is well established (39), and studies have reported that those alcoholics showing the most persistent and disturbed sleep are those showing an increased risk of relapse (5). The focus of our current studies is on nonalcoholics who are social drinkers and have insomnia. The issue is: could therapy-seeking behavior become drug-seeking behavior? A recent epidemiological study showed a trend for new-onset alcoholism to follow a history of insomnia (4). Our recent laboratory study showed that insomniacs chose an ethanol beverage 67% of nights, while normals with a similar social drinking history chose the ethanol on only 22% of nights (26). The ethanol dose self-administered was 0.45 g/kg, which raised breath ethanol concentration to 0.04%. During sampling nights, a 0.50 g/kg dose significantly improved the disturbed sleep of the insomniacs, specifically increasing the amount of stage 3-4 sleep to that of the normals. Thus, the acute sleep effects of ethanol appear to be associated with the reinforcing effects of ethanol as a hypnotic for insomniacs. But, how the beneficial sleep effects may change with time and how this apparent therapy-seeking behavior may change with time are the critical questions being pursued.

STIMULANT DRUGS

Caffeine.

Caffeine is well known for its stimulating effects. The stimulating and disruptive effects on sleep were described early on by Kleitman and colleagues (16,20). Caffeine (260 and 390 mg) increased body motility and temperature across the whole night (20) and shortened total sleep time (16). More recently, a number of studies have used performance measures to document caffeine's stimulating effects. Several studies of the stimulating effects of caffeine have been done using the MSLT (35,42). Caffeine 250 mg increased MSLT average daily sleep latency compared to placebo and improved auditory vigilance performance, although tolerance to these effects developed in several days (42). Clearly, caffeine can reverse sleepiness. As we noted earlier, sleepiness can be induced in healthy normals by reducing sleep time. In a study of caffeine (75 and 150 mg) effects after 8 hrs versus 5 hrs of bed time, average daily sleep latency on the MSLT was reduced by the sleep restriction (35). Both caffeine doses restored MSLT scores to the 8 hrs sleep time placebo level and also prevented the slowed vigilance performance seen after 5 hrs bed time. In other words, caffeine restored alertness and averted performance failures in sleepy people.

Whether caffeine is a drug of abuse has been a matter of recent debate. Surveys indicate that the vast majority (90%) of the US population consumes caffeine in one form or another (13). Most consume the equivalent of 3 cups (300 mg) or less

a day. But a small percentage daily consume 500 mg or more. Laboratory studies of caffeine's self-administration have shown a number of conditions under which caffeine is self-administered, but only about half of subjects self-administer caffeine across all the studies (13, 19, 38). Again the issue is whether the caffeine self-administration is therapy-seeking or drug-seeking behavior. In the case of stimulants, the therapy being sought is alertness and improved performance by a sleepy person. Two pieces of evidence suggestive of therapy-seeking for the caffeine self-administration observed in the studies above are that (1) the self-administration was enhanced when a behavioral requirement was imposed on subjects (38) and (2) those who self-administered caffeine reliably experienced fatigue and sleepiness during a placebo substitution (19). Our studies with methylphenidate, described below, have begun to assess this relation of stimulant self-administration to sleepiness levels.

Methylphenidate.

The psychomotor stimulant methylphenidate is used in the treatment of attention deficit-hyperactivity disorder and the sleep disorder narcolepsy. Methylphenidate is similar to amphetamine in its pharmacokinetics and pharmacological mechanisms. Whereas the abuse liability of amphetamine is well documented, that of methylphenidate is not well established, although case reports suggest an abuse potential. Studies of the performance effects of methylphenidate in healthy normals using standard laboratory assessments are somewhat inconclusive, which has led some to conclude that performance improvement is seen only in sleepy or fatigued individuals (17). Given the unclear evidence regarding methlyphenidate's abuse liability, but the suggestive evidence that the drug restores alertness and performance in sleepy individuals, we initiated a series of studies to assess its performance, subjective, and reinforcing effects as a function of state of sleepiness.

The first study from this laboratory assessed the alerting and performance enhancing effects of methylphenidate 10 mg bid in healthy normals after basal sleep and sleep deprivation (3). Average daily sleep latency on the MSLT was increased in both conditions relative to placebo, but performance assessments showed beneficial effects only after the prior sleep deprivation. That is, only sleepy individuals experienced the improved performance with methylphenidate. A second study sought to determine whether sleepiness would enhance the self-administration of methylphenidate (27). The only previous study found that methylphenidate 20-40 mg was self-administered on 28% of opportunities (7). After basal sleep (8 hrs time in bed) these healthy normals self-administered methylphenidate on 29% of opportunities, while after 4 hrs of bedtime the previous night they self-administered methylphenidate on 88% of opportunities. In the performance assessments the drug improved performance only after prior sleep loss. Thus, methylphenidate self-administration was associated with performance improvement and therefore, the self-administration behavior was suggestive of therapy-seeking in the broad sense outlined earlier. Again, the question is raised as to the conditions and personality factors that may predict a shift from therapy- to drug-seeking.

Cocaine.

The CNS stimulant with undisputed abuse liability is cocaine. While very few NPSG studies have examined the effects of cocaine and its discontinuation on sleep and daytime alertness in cocaine abusers, a number of clinical assessments have reported that cocaine discontinuation is associated with difficulty falling asleep and excessive daytime sleepiness (11). However, these clinical studies had not documented the cumulative history of cocaine exposure, level of cocaine exposure prior to the discontinuation, and other drug use, which are critical factors in understanding cocaine's effects on sleep and daytime alertness. Thus, studies of the effects of cocaine and its discontinuation on mood and sleep in cocaine-dependent subjects were conducted under highly controlled laboratory conditions (14). Intranasal cocaine (600 mg/day) severely disrupted sleep, delaying its onset for up to 3-4 hrs and suppressing REM sleep. During the first two discontinuation days, average daily sleep latency on the MSLT was less than 5 min, probably due to the severe sleep disruption, and multiple sleep onset REM periods were seen on the MSLT, probably due to the REM suppression. Even after 14 days of abstinence, a sleep and REM disturbance remained. That the initial state of severe daytime sleepiness may lead to relapse to cocaine was suggested by an early study that showed intranasal cocaine reversed the disruptive effects of sleep deprivation on performance and mood (10). In this particular situation, the "therapeutic" effects of the drug may contribute to the maintenance of the drug abuse.

CONCLUSIONS

Variations in the quantity and quality of nocturnal sleep and level of daytime sleepiness-alertness are related to drug self-administration. The relation has been demonstrated both with CNS depressant and stimulant drugs. Most of the evidence for the compounds that have been studied in both classes suggests that the drug self-administration is therapy-seeking behavior. That is, the drug is self-administered to improve disturbed nocturnal sleep or to reverse increased daytime sleepiness. Of great concern are the circumstances under which therapy-seeking shifts to drug-seeking behavior or therapy-seeking serves to maintain (i.e. cocaine abuse) an established pattern of drug abuse.

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