# Absence of REM Rebound after Barbiturate Withdrawal

Abstract. *Administration of three different barbiturates reduced rapid eye movement (REM) sleep. Drug withdrawal led to a return to baseline REM values without significant overshoot. Similar results are observed with administration of benzodiazepines in pharmacologically equivalent dosages; therefore, a distinction between these two drug classes on the basis of withdrawal effects on the sleep electroencephalogram appears unwarranted. Further investigation is required to determine why high REM levels are sometimes associated with the withdrawal of sedative-hypnotic agents.*

Different psychoactive drugs produce markedly different effects on the sleep electroencephalogram (EEG). We believe that the available data, while often contradictory (*1*), permit the hypothesis that the patterns of these effects are common within a particular drug class but differ across classes. Verification of this hypothesis could lead to a method for classifying psychoactive drugs and might also provide clues to their mechanisms of action.

Although the sedative-hypnotic agents have been intensively studied, disagreement remains regarding their effects on sleep. While it is clear that barbiturates produce an initial suppression of rapid eye movement (REM) sleep with some return toward baseline levels as the drug is continued (*2–5*), the effects of barbiturate withdrawal seem to us less certain (*6*). It has been generally accepted (*1*) that withdrawal of these drugs leads to an elevation of REM sleep above baseline levels (REM rebound). Most observers agree that similar rebounds do not follow withdrawal of benzodiazepines, a new class of sedative-hypnotic agents, and they have therefore suggested that these drugs produce effects on sleep fundamentally different from those of the barbiturates (*7*). Since the pharmacologic actions of these two drug classes are qualitatively similar, such a difference would argue strongly against the hypothesis stated above.

Here we present data from three experiments which show that REM rebound does not regularly ensue after a period of barbiturate-induced REM suppression. In experiment 1, three schizophrenic patients and three patients with personality disorder received placebos for five nights, 200 mg of phenobarbital for four or five nights, and placebos (withdrawal) for four or five nights. In experiment 2, four medical students were first studied for four baseline nights; then one received 200 mg of secobarbital for eight nights and the other three received 200 mg of secobarbital for one night and then 100 mg for seven nights (*8*). All subjects were then studied for three consecutive withdrawal nights. In experiment 3, after four baseline nights four medical students were given 32 mg of amobarbital twice daily (8 a.m. and 1 p.m.) for 2 days and then three times daily (8 a.m., 1 p.m., and 5 p.m.) for 4 days and then studied for three withdrawal nights. This experiment was aimed at determining whether suppression of a hypothesized REM cycle during waking (*9*) would be followed by increased REM sleep at night. Our methods for recording and scoring sleep variables have been described (*10*). All sleep records were coded and scored without knowledge of drug treatment. In experiment 1, subjects as well as the experimenters were ignorant of drug treatment.

Results for all three studies are shown in Fig. 1. Each of the barbiturates significantly reduced both REM density (the proportion of epochs of REM sleep positive for REM activity) and the percentage of time occupied by the associated "emergent" stage 1 EEG (*11*). These are the two accepted measures of REM sleep. During withdrawal, neither measure showed a significant elevation above baseline (rebound) for any of the drugs tested. While Fig. 1 might appear to show a trend toward rebound for eye movement density during secobarbital withdrawal, the paired *t* value for this comparison (1.10) did not approach significance. The results of experiment 3 also show that daytime administration of amobarbital reduces rather than increases REM sleep at night and argues against the notion that REM processes occur in occult form during wakefulness.

Our results show that barbiturates as well as benzodiazepines can suppress REM sleep without being followed by withdrawal rebound. These chemically different but pharmacologically similar drug classes share several other effects on sleep physiology. Both produce a proportionately greater suppression of eye movement activity than of emergent stage 1 EEG, and both suppress stage 4 sleep, the latter effect being more marked for benzodiazepines than for barbiturates. For both drug classes the suppression of eye movement occurs rapidly; the reduction of stage 4 sleep occurs more slowly and requires repeated administration. After withdrawal, return to baseline levels is rapid for eye movement but delayed for stage 4 sleep (*2–5, 7*).

It seems important to determine whether this pattern of effects is uniquely associated with sedative-hypnotic agents and whether quantitative variations within this pattern are related to

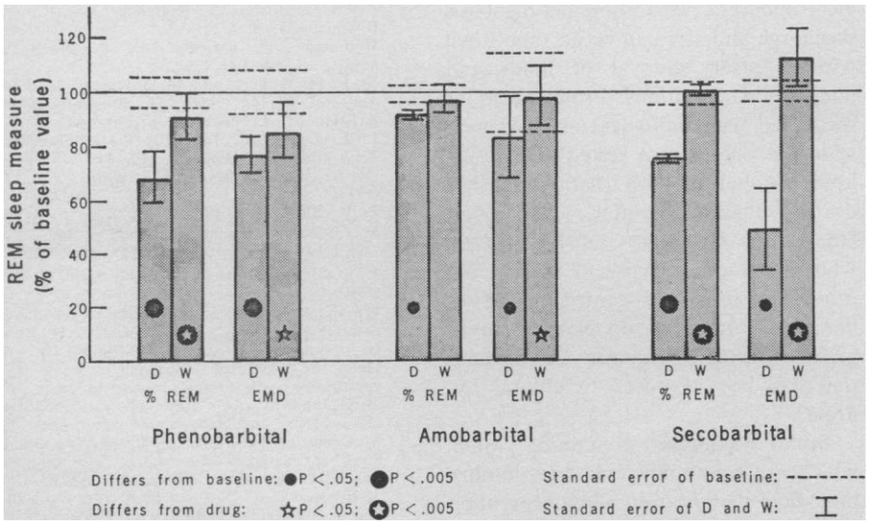


Fig. 1. Effects of administration and withdrawal of three barbiturates on two measures of REM sleep. Abbreviations: D, drug; W, withdrawal; % REM, time occupied by low-voltage, nonspindling EEG associated with rapid eye movements; EMD (eye movement density), proportion of 4-second epochs (amobarbital and secobarbital) or 20-second epochs (phenobarbital) of stage REM in which eye movement occurred. Significance levels are for one-tailed paired *t*-tests for the predictions: drug < baseline < withdrawal.

quantitative differences in pharmacologic actions (*12*). Further studies are also required to determine whether the suppression of rapid eye movements by sedative-hypnotic agents represents a primary inhibition of oculomotor function (*13*) that becomes apparent during REM sleep or whether it reflects instead a specific effect upon phasic REM processes.

The absence of REM rebound after barbiturate withdrawal under the conditions of our studies is paralleled by results of a recent study of the effects of ethyl alcohol on sleep. Gross *et al.* (*14*) found that high dosages (3.2 g per kilogram of body weight per day) of alcohol administered for 4 to 6 days severely depressed REM sleep. Nevertheless, withdrawal led only to a return to baseline levels without significant overshoot. These results call into question the assumption that the high level of REM sleep found in some patients with delirium tremens (*15*) represents a rebound phenomenon. This extraordinarily intense REM activity is perhaps the most striking abnormality of brain physiology apparent in human delirium. It is therefore of interest to determine the factors responsible for its sporadic occurrence.

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4. I. Feinberg, P. H. Wender, R. L. Koresko, F. Gottlieb, J. A. Piehuta, *J. Psychiat. Res.* **7**, 101 (1969).
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6. The following appear to be the crucial reports on which the notion of REM rebound following barbiturate withdrawal is based: I. Oswald and R. G. Priest [*Br. Med. J.* **2**, 1093 (1965)] administered 400 g of amobarbital to two subjects for nine nights, then increased the dosage to 600 mg for nine additional nights. The data were presented in a figure that shows an apparent elevation of percentage of REM sleep, maximal in the first three withdrawal nights. No statistical analysis was presented. In a retrospective analysis of these data, I. Oswald [in J. H. Price, Ed., *Modern Trends in Psychological Medicine* (Butterworths, London, 1970), pp. 53–77] did find significantly less ($P < .001$) eye movement activity in recordings made late in the withdrawal period (considered as baseline) compared to the first and third withdrawal nights for the two subjects. However, no mention is made of "blind" scoring, nor is the reason given for selecting these nights for analysis. Evans *et al.* (*2*) studied two subjects receiving 200 mg of amobarbital for 26 nights and one subject who was already addicted to Tuinal (300 mg each of amobarbital and quinalbarbital). Upon withdrawal, the first two subjects showed higher than baseline percentages of REM sleep, but no statistical comparisons were reported. The third subject showed low values for REM (15 percent) during drug administration; withdrawal led to an increase to values (25 to 30 percent) well within the normal range. A. Kales, T. A. Preston, T. L. Tan, C. Allen [*Arch. Gen. Psychiat.* **23**, 211 (1970)] found neither a significant suppression of REM sleep during drug administration nor rebound after withdrawal with 100 mg of pentobarbital administered for three nights. Nevertheless, they suggested that an "intranight" rebound had occurred, with more REM activity early and less later during the withdrawal nights. Such changes, which would be described more accurately as "redistributions" (*3*) rather than "rebounds," were not statistically documented. Nevertheless, the notion of an intranight REM "rebound" has gained widespread acceptance.
7. A. Kales, J. D. Kales, M. B. Scharf, T. L. Tan, *Arch. Gen. Psychiat.* **23**, 219 (1970); J. D. Kales, A. Kales, E. O. Bixler, E. S. Slye, *Clin. Pharmacol. Ther.* **12**, 691 (1971); A. Kales and M. B. Scharf, in *The Benzodiazepines*, S. Garattini, E. Mussini, L. O. Randall, Eds. (Raven, New York, 1973), pp. 577–598; W. C. Dement, V. P. Zarcone, E. Hoddes, H. Smythe, M. Carskadon, in *ibid.* pp. 599–611. However, one group of investigators believes that benzodiazepine suppression of REM sleep *is* followed by REM rebound (I. Oswald, S. A. Lewis, J. Tagney, H. Firth, I. Haider, in *ibid.*, pp. 613–625).
8. Most of the data in experiment 1 were reported by Feinberg *et al.* (*4*). One subject in experiment 2 omitted his 100-mg dose on the fourth night.
9. G. Globus, *Arch. Gen. Psychiat.* **15**, 654 (1966); I. Oswald, J. Merrington, H. Lewis, *Nature (Lond.)* **225**, 959 (1970).
10. I. Feinberg, R. L. Koresko, N. Heller, *J. Psychiat. Res.* **5**, 107 (1967).
11. W. C. Dement and N. Kleitman, *Electroencephalogr. Clin. Neurophysiol.* **9**, 673 (1957).
12. The already extensive literature on sedative-hypnotic agents is not easily interpreted with respect to this question, for few studies report measures of both eye movement activity and stage 4 EEG under the requisite conditions of administration and withdrawal. However, combined data from two studies suggest that this same pattern of effects is found for glutethimide, a hypnotic structurally related to phenobarbital [C. Allen, A. Kales, R. J. Berger, *Psychonomic Sci.* **12**, 329 (1968); L. Goldstein, J. Graedon, D. Willard, F. Goldstein, R. R. Smith, *J. Clin. Pharmacol. New Drugs* **10**, 258 (1970)].
13. For example, a specific effect of barbiturates on oculomotor (midbrain) structures is indicated by the capacity of these drugs to produce nystagmus in normal subjects, to temporarily abolish congenital nystagmus, and to alter the relation between accommodation and convergence.
14. M. M. Gross, D. R. Goodenough, M. Nagarajan, J. M. Hastey, in *Alcohol Intoxication and Withdrawal: Experimental Studies*, M. M. Gross, Ed. (Plenum, New York, 1973), pp. 291–304.
15. M. Gross *et al.*, *J. Nerv. Ment. Dis.* **142**, 493 (1966); R. Greenberg and C. Pearlman, *Am. J. Psychiat.* **124**, 133 (1967); L. C. Johnson, J. A. Burdick, J. Smith, *Arch. Gen. Psychiat.* **22**, 406 (1970).
16. We have recently found that rate of administration of dextramphetamine is a crucial factor in determining whether REM rebound occurs after its withdrawal (I. Feinberg, S. Hibi, M. Braun, C. Cavness, G. Westerman, A. Small, *Arch. Gen. Psychiat.*, in press). Gross and co-workers (personal communication) recently found blood alcohol levels and amount of baseline stage 4 sleep appear related to the occurrence of elevated REM with alcohol withdrawal.
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## Firing Patterns of Hypothalamic Supraoptic Neurons during Water Deprivation in Monkeys

Abstract. *Water deprivation in monkeys caused an acceleration of action potential firing of supraoptic neurons, but not of neurons located 2 to 3 millimeters above the hypothalamic supraoptic nucleus. Whereas in the normally hydrated animal only 12 percent of the neuroendocrine cells discharged periodically, the proportion of these periodic bursters increased markedly with increasing plasma osmolarity. This finding suggests that such periodically firing supraoptic neurons are those engaged in active neurohypophyseal hormone secretion.*

Several studies have been concerned with relating the electrophysiological activity of hypothalamic neuroendocrine cells with the amount of hormone released from their axon terminals located in the posterior pituitary lobe. Evidence for a causal relationship between neuronal firing and oxytocin release is available; thus, in lactating rats, an explosive increase in impulse activity of neuroendocrine cells consistently precedes the reflex secretion of oxytocin in response to suckling (*1*). In contrast, results on the correlation between neuronal firing and release of antidiuretic hormone in response to acute osmotic stimulation are less clear (*2*). We therefore studied the firing of supraoptic neuroendocrine cells during a prolonged and powerful osmotic stimulus; a water deprivation experiment was performed in monkeys, during which we noted an