Regular Review

The why and how of hypnotic drugs

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Complaints about sleep become commoner with advancing age, especially among women and among the nervous or introverted.¹⁻⁴ It is normal for people over 50 to waken more in the night, but that does not mean they will come to harm or that they need drugs.

Faced with someone complaining of difficulty in sleeping, the doctor's first task should be to wonder why she has come to see him. What has happened in her family recently? Her age and personality are not much different from a year ago, so why now? While she lies awake are there, perhaps, unusually depressed thoughts, out of proportion to reality? If so, endogenous depression may be a possibility, but an understandable reaction to life's problems is much the more likely. Thorough history taking holds the key.

The decision whether to start prescribing a hypnotic drug depends on the doctor's own temperament; there are large differences among practitioners in their rates of prescribing. Many feel a distaste for listening yet again to complaints about sleep, and in a 1976 survey 70% of the prescriptions for hypnotics in general practice had been written by the receptionist, compared with only 22% for other drugs.⁵ In hospital practice consultants commonly leave decisions about hypnotics to their house officers and the night nurse.

What the patient says about the effects of a hypnotic can again depend more upon her personality than upon the pharmacology of the drug.^{6,7} When a group of middle-aged introverts made ratings of the quality of their sleep both while on placebo and while on a hypnotic no difference emerged, whereas extraverts reported significantly better sleep on the hypnotic.⁶

At first hypnotic drugs make sleep less broken, start earlier, and last longer. Nevertheless, during a long period of taking barbiturates and glutethimide the sleep of patients does not seem to differ either objectively or subjectively from the sleep of others who complain about their sleep but do not actually take drugs.⁸ When nitrazepam has been taken for eight weeks, on the other hand, there is no loss of effectiveness, though when the drug is withdrawn there is a period of bad sleep.⁹

Advertising claims about induction of normal sleep patterns are things of the past, for all-night electrophysiological studies have shown how drugs alter the detailed structure of sleep. The use of benzodiazepines gradually leads to the loss of those periods of sleep accompanied by very slow EEG waves, and most hypnotics reduce the duration of paradoxical (REM) sleep. Does this matter? The first answer may be No, but a better reply is that we do not know enough about the function of sleep.

Sleep is widely assumed to have a restorative function. Breakdown and renewal of our tissues continues all the time, but waking activity, and its accompanying hormones, shifts the balance towards breakdown. The inactivity of sleep and its concomitant hormones¹⁰ shift the balance towards anabolism, so that there are now some 50 reports that protein synthesis or tissue mitoses are enhanced during sleep.¹¹ To what extent these relationships may be impaired by broken sleep or improved by drugged sleep has scarcely been investigated. The large secretion of human growth hormone at night normally depends on sleep with EEG slow waves^{12,13}; nevertheless, though it reduces slow-wave sleep, nitrazepam does not diminish the output of growth hormone.⁹ Corticosteroid secretion through the night is higher in poor sleepers.¹⁴ Adrenaline and corticosteroids are catabolic hormones: hypnotic and anxiety-reducing drugs reduce the secretion of corticosteroids even during sleep,^{15,16} and presumptively that of adrenaline too. There are therefore limited grounds for expecting clinical doses of drugs to facilitate restorative functions, but there is a dearth of research.

The benzodiazepine drugs have captured the market. I used to say that they were all the same. Diazepam, sold for daytime use, was reported to be as effective at night as nitrazepam, sold as a hypnotic.¹⁷ But I was wrong: they are not all the same under clinical conditions. Some have pronounced cumulative effects, for they have active metabolites that are only slowly eliminated. Flurazepam, which figures in 47% of prescriptions for hypnotics in the United States,¹⁸ is an example that is cumulative over 10 days.¹⁹ There is thus almost as much in the brain by day as by night, and so flurazepam causes impaired skills and judgment by day.

In a recent study, 12 poor sleepers with an average age of 53 received placebos nightly for two weeks, then flurazepam 30 mg nightly for three weeks and then placebos again. One day each week they were given tests at 08 00, 12 30, and 16 30, for two hours each time. At another time of the year, and with balance of order, they simply took placebos for seven weeks. On all the tests of mental concentration and manual dexterity, flurazepam impaired performance compared with continuous placebo intake, and this was true morning, noon, and evening. One test was of ability to sustain alertness for an hour and to listen for 40 randomly distributed bleeps of 400 msec among 1800 slightly longer bleeps. The figure illustrates the fall in the daily mean percentage of target hits. During the first week of flurazepam (after two nights' intake) the fall did not reach significance. In the second week the impairment was significant ($P < 0.02$), and in the third week even more so ($P < 0.005$). The drug takers also made their own ratings: they recognised

their impairment in the first week but completely failed to in the third.²⁰

The investigation was part of a larger study amounting to 450 person-weeks of pill intake, but only 63 weeks taking flurazepam. There were seven crises during it. One woman became depressed and threatened murder, another began uncharacteristic weeping and quarrelling with her employer, another crashed her car. When the code was finally broken, all seven of the incidents had been associated with flurazepam, a degree of coincidence that cannot be attributed to chance.

Benzodiazepines are very safe in overdose, but the impairment of social judgment and the release of aggression they bring out,^{21 22} whether they have been prescribed for day-time or night-time intake, place them alongside alcohol as culprits in that blunting of discretion that precedes taking an overdose—one of our modern epidemics.

Benzodiazepines are, however, here to stay. Which among them should be prescribed? As a psychiatrist I see only the rarest justification for their daytime use, except to enable the doctor to feel he is not being inactive. The drugs prevent

patients clearly seeing their problems and then facing them—though admittedly the drugs are less dangerous and cheaper than alcohol. The choice of hypnotic should favour one whose action is confined as far as possible to night-time. After a single dose an old-fashioned drug like diazepam or flurazepam may cause little impairment by day,²³ but in clinical usage it is cumulative. Newer benzodiazepines are effective in small dosage, so that even if the primary compound is converted to much the same metabolites as the older members of the family it does not matter, because the absolute amounts are so small. A compound that is itself active and is fairly quickly metabolised into non-active compounds is another sensible alternative. We must always bear in mind that unwanted effects of all such drugs are more common for older patients, whose brains are more sensitive to a given tissue concentration.²⁴

Hypnotic drugs that are cumulative over a long period do not give rise to abrupt worsening of sleep after withdrawal, for they disappear only gradually.²⁰ The short-life hypnotics, however, may produce a rebound worsening of sleep when intake stops. The poor sleep and bad dreams will last several nights, indeed weeks, but patients can be helped through this period if warned in advance and given sufficient encouragement.

As the weeks pass after the withdrawal of any regular hypnotic, the dominant role of the normal biological clock will reassert itself despite having for so long been swamped into insignificance by powerful drugs that may have been acting throughout the 24 hours. At this time and later patients should be advised to avoid stimulant beverages in the evenings. Regular physical exercise, of which most middle-aged people take too little, should be encouraged. Exercise by day enhances subsequent sleepiness,²⁵ and increases the nocturnal release of growth hormone.²⁶ Finally, Clift's research in general practice has shown that education of the patient to regard any hypnotic drug as a temporary expedient will diminish the long-term usage that is so common.²⁷

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