

USE OF HYPNOTIC DRUGS BY HOSPITAL PATIENTS

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Recent research into the nature of sleep and dreams has increased our understanding of the effects of hypnotic drugs. While hypnotics in common use are "effective" in inducing sleep and reducing night awakenings when taken occasionally, many do not permit the normal pattern of the stages of sleep. They may also induce tolerance and cease to be effective after use for only a few consecutive nights. Further, some produce dependence with symptoms which include disturbed sleep and dreams on cessation of the drug. Thus their effects tend to encourage their continued use. To obtain some idea of the proportion of the population taking these drugs, a survey was carried out to determine which hypnotics were being used, and how often, by medical and surgical patients in the wards of the Alfred Hospital and at home. Of all patients aged between 20 and 80 years, 33% of males and 41% of females were taking hypnotics "frequently" or "occasionally" at home. The frequency of use increased with age. In hospital wards, 75% of males of all ages and 80% of females were given hypnotics at some time. At home more barbiturates were being taken than non-barbiturates, but the reverse situation has developed in recent years in hospital. The condition of many patients, whose insomnia is being treated with barbiturates, would probably improve if these drugs were withdrawn while they continued to take a non-barbiturate hypnotic such as nitrazepam. Treatment of long-term insomnia with drugs is not satisfactory at present, and further research is needed.

INSOMNIA is one of the most common symptoms seen in patients in general hospitals. In a *questionnaire* survey of the sleep habits of male medical and surgical patients, it was found that 15% of all ages and 35% of those over 50 years of age complained of long-term disturbances to their sleep at home (Johns *et alii*, 1970). These complaints included relatively long delays before falling asleep, frequent night awakenings associated with subjectively poor quality sleep of short duration, and sometimes early morning waking. Approximately 12% of all Pharmaceutical Benefit prescriptions in Australia—6,500,000 prescriptions *per annum*—are for hypnotic and sedative drugs (Director-General of Health, 1969). Similarly, in the United Kingdom, there are about 22,000,000 prescriptions *per annum* for hypnotics (Dunlop, 1970). The problem of insomnia must be very widespread in the community as a

whole. Over the past 15 years, there has been a rapidly growing interest in the physiology and pathology of sleep (Luce and Segal, 1967, 1970), largely due to advances in methodology (Johns, 1971). These methods, and the greater understanding of the nature of sleep which has followed their application, have added new dimensions to the description of the effects of hypnotic drugs (Oswald, 1968).

SLEEP RESEARCH AND THE EFFECTS OF HYPNOTIC DRUGS

As a result of research in the many sleep laboratories which have been established throughout the world in recent years, it is now known that sleep is not just the absence of wakefulness. There are two quite distinct and actively induced physiological states—dreaming and non-dreaming sleep—which affect the whole body (Jouvet, 1967).

Non-dreaming sleep is divided into four stages (1 to 4), defined on the basis of the frequency and amplitude of the electroencephalogram (EEG). Dreaming almost always occurs when the stage 1 EEG coincides with rapid eye movements (REM), the presence of which is indicated by the electro-oculogram. There are usually four or five cycles of these sleep stages during a night's sleep, with dreaming periods each lasting between five and 40 minutes, reappearing about every 90 minutes. The pattern of occurrence and total duration of each sleep stage are fairly constant for each person, but vary with age as well as with various psychiatric and physical illnesses, and with the administration of certain drugs (Kales, 1969). We seem to have physical and psychological requirements for both dreaming and non-dreaming sleep, but the precise functions of each are not yet fully elucidated (Wilkinson, 1965).

Clinically useful hypnotic drugs must now be shown to have the following properties: (i) to initiate physiologically normal sleep rapidly and to maintain it with few interruptions for several hours; (ii) to permit the usual cyclic pattern of sleep stages and their normal duration during the night; (iii) to have low toxicity in overdose; (iv) to have a minimum of side effects and after effects; (v) not to induce tolerance, in which the usual dose ceases to be effective after short-term use; (vi) not to produce dependence in the patient so that withdrawal symptoms appear when the drug is no longer being administered.

The unhappy picture which is beginning to emerge from laboratories where hypnotic drugs are being fully evaluated in patients suffering from insomnia indicates

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that most commonly used hypnotics fail to meet all of these requirements (Oswald, 1968; Hartmann, 1969; Kales *et alii*, 1970 a, b, c). Many first decrease the duration and the proportion of dreaming sleep, at least for the first few nights, and then cause a rebound of excessive and sometimes disturbing dreams on drug-free nights, to avoid which some patients will continue taking hypnotics (Evans *et alii*, 1968; Evans and Ogunremi, 1970). This change appears to be dose-dependent, and is especially marked with the barbiturates. The pattern of non-dreaming sleep stages may be affected also, with less stage 3 and 4 sleep on nights when hypnotics are taken (Hartmann, 1969). Prolonged experiments with patients suffering from severe insomnia have shown that tolerance to some of these drugs develops rapidly. The dose of chloral hydrate (1,000 mg) or glutethimide (500 mg) which was "effective" for a few nights had no significant effect on insomnia after about one week of continuous use (Kales *et alii*, 1970c). The effects of such drugs when taken intermittently for long periods have not been established.

Dependence on barbiturate hypnotics and sedatives is known to be a common problem in the community, producing a syndrome involving agitation, tremor, confusion and insomnia (Abrahams *et alii*, 1970; Whitlock, 1970). However, dependence can also develop on some non-barbiturate hypnotics (Essig, 1964; Isbell and Chrusciel, 1970). The extraordinary situation may arise in practice where patients with chronic insomnia have become tolerant to and dependent on hypnotics, mainly barbiturates, taken initially because of anxiety and insomnia, and where these drugs are actually producing a syndrome in which insomnia is a prominent symptom (Jacobson, 1970). Such patients require many weeks to be weaned from these drugs, but then they sleep better than they did while taking them (Oswald and Priest, 1965). While most of the hypnotics are free from fatal side effects, the non-fatal complications of some of them, such as methaqualone with diphenhydramine, are among the most commonly reported in the United Kingdom (Dunlop, 1970). Objective tests of physical and psychological performance after single doses of commonly used hypnotics indicate a "hang-over" effect which continues for many hours the next day (Malpas *et alii*, 1970; Walters and Lader, 1971). Probably the strongest indictment against hypnotics is the fact that several hundred people die from overdoses of these drugs each year in Australia.

From the information available at present about the efficacy of different hypnotic drugs it may be concluded as follows: when used occasionally, most commonly used hypnotics will induce sleep and reduce the number of night awakenings. However, none of the barbiturate hypnotics induces physiological sleep, even with short-term use, but the importance of these changes is uncertain. Barbiturates produce tolerance and physical dependence on repeated use and are relatively toxic in overdose. Their use in the treatment of insomnia should be restricted, especially when more than a few nights are involved.

Of the non-barbiturates, some, such as glutethimide, have all the disadvantages of the barbiturates. Other non-barbiturates such as methaqualone (with or without

diphenhydramine), nitrazepam, chloral hydrate and methyprylon may permit a night's sleep which is more nearly normal than with the barbiturates, and in some cases may produce less dependence and be less toxic in overdose. Whether many of these drugs induce tolerance as rapidly as chloral hydrate or glutethimide remains to be established. Flurazepam, a new benzodiazepine drug in the U.S.A., related to nitrazepam and not yet available in Australia, seems to have few disadvantages, inducing and maintaining sleep after several weeks' continuous use (Kales *et alii*, 1970 b, c). However, the treatment of long-term insomnia with drugs is not very satisfactory at present. As more detailed experiments are performed, so most of the available drugs prove to be less effective than was previously thought.

PRESENT INVESTIGATION

In the light of such information, we have investigated the use of hypnotic drugs by patients at Alfred Hospital, Melbourne, both when they are at home and in the hospital wards. The emphasis of this study has differed from others which, for example, from the point of view of the psychiatrist, have shown a high rate of barbiturate dependence and a relatively high incidence of hypnotic drug overdose among hospital patients and in the general community (Buckle *et alii*, 1965; Abrahams *et alii*, 1970; Whitlock, 1970). The emphasis here has been on finding out which hypnotic drugs are being taken and how often by hospital patients for the treatment of insomnia.

Methods

In a detailed study of sleep habits at home, medical and surgical in-patients were given a self-administered *questionnaire* about sleep (Johns *et alii*, 1970). One question asked if, in recent months at home, sleeping tablets had been taken "frequently", "occasionally" or "never". The name of the type of drugs taken was also requested. Male patients were selected over a period of a few weeks in 1969 and females in 1970, and were all those in the general medical and surgical wards who were willing and able to fill out the sleep *questionnaire* and the Comell Health Index *questionnaire* in their own time. There were between 10 and 24 males and 20 females in each decade of ages from 20 to 80 years. The diagnoses of the 214 patients studied were not taken into account in their selection, but included the usual wide range to be found in a teaching hospital. There were approximately equal numbers of medical and surgical patients.

The use of hypnotic drugs by patients while in hospital was investigated solely from the medical records after discharge from the wards, by selecting names at random over a period of three weeks from those patients' records which were awaiting return to the Medical Records Department. Only patients discharged from the psychiatric ward were excluded. A record was kept of all hypnotic drugs administered each night to patients who had been in hospital for more than four days. Data collection was stopped when there were 20 male and 20 female patients in each decade of ages from 20 to 80 years—240 patients in all. The number of nights on which hypnotics were given was recorded as a proportion of the total number

of nights in hospital. The type and dose of each hypnotic drug were also noted.

Information about the overall pattern of use of hypnotic drugs for all in-patients and out-patients at Alfred Hospital in recent years was derived from the purchasing records of the hospital pharmacy for the period 1965-1970.

The differences between frequency distributions were tested by means of χ^2 tests, with statistical significance being accepted at the 5% level.

RESULTS

Hypnotic Drugs Used at Home

Figure 1 shows the percentages of male and female patients in each decade of ages from 20 to 80 years who reported taking sleeping tablets at home "occasionally" or "frequently". The proportion of patients using hypnotics, and the frequency with which they used them, increased with age in both males ($P < 0.005$) and females ($P < 0.02$). In general, females used hypnotics more frequently at home than males ($P < 0.02$). Approximately 12% of all male patients and 25% of all female patients

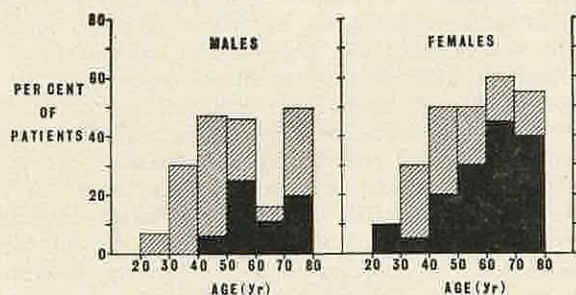


FIGURE 1: Percentage of male and female patients of various ages using hypnotic drugs "frequently" (black) or "occasionally" (cross-hatched), at home.

were taking hypnotic drugs "frequently", and another 21% of males and 16% of females were taking them "occasionally". The types of hypnotic drugs reported to be taken were similar for male and female patients. Fifty-six per cent of all patients taking hypnotics were able to identify them by name. Barbiturates were named more commonly than non-barbiturates (in the ratio of three to two). Amylobarbitone, pentobarbitone compound, and pentobarbitone sodium were the most commonly identified hypnotics used at home. Methaqualone with diphenhydramine was the most commonly used non-barbiturate, while several other drugs were used occasionally. A few patients took bromides or aspirin as hypnotics. They could easily obtain these without prescription, whereas all the other hypnotics required a doctor's prescription.

Hypnotic Drugs Used in Hospital

Figure 2 shows the percentages of male and female patients of various ages who were given hypnotics while in hospital. A breakdown of these figures distinguishes those taking hypnotics on more than 50% of their nights in hospital, and those taking hypnotics less frequently. These criteria for describing the frequency of hypnotic drugs used in hospital are different from those relating to home use; consequently, the figures are not strictly comparable in the two situations.

Seventy per cent of male patients and 80% of female patients were given hypnotics at some time while in hospital. The greater percentage among females was statistically significant ($P < 0.02$). While there was a tendency for older patients to take hypnotics more frequently than the young, this was not statistically significant in either sex, in marked contrast to the situation at home. Fifteen per cent of males and 30% of females took hypnotics on virtually every night in hospital, while others took them intermittently. For instance, some patients were given hypnotics for a few consecutive nights after admission to hospital, or before

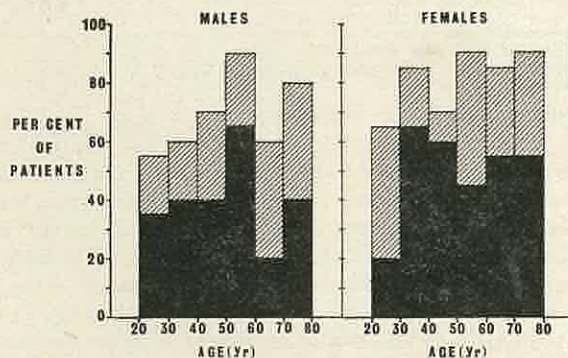


FIGURE 2: Percentage of male and female patients of various ages given hypnotic drugs on more than 50% of nights (black), or less frequently (cross-hatched), while in hospital.

a major operation, then slept without them for several nights. Hypnotics were less frequently given on the first night or two after a surgical operation when opiates were often administered parenterally. An unknown but probably small proportion of patients may have been given hypnotic tablets without actually taking all or any of them on a specific night.

The hypnotics most commonly used in Alfred Hospital wards were nitrazepam, methaqualone with diphenhydramine, and dichloralphenazone. Amylobarbitone sodium and pentobarbitone sodium were next most commonly used, but considerably less often than the non-barbiturates. Other drugs used less frequently again were chloral hydrate (usually mixed with brandy), glutethimide, diazepam, chlorpromazine and quinalbarbitone sodium. Marked differences in the types of hypnotic prescribed for different age-groups or sexes were not found. Thirty-five per cent of patients took more than one type of hypnotic at different times, possibly because of side effects, or tolerance developing to a particular drug in the usual dose administered. The doses of hypnotic drugs administered varied from night to night in some cases, but the majority of patients took the maximum recommended dose—two tablets in the case of the three non-barbiturates, that is 10 mg of nitrazepam, 500 mg of methaqualone plus 50 mg of diphenhydramine, or 1,300 mg of dichloralphenazone.

Changes in Hypnotic Drugs Used at Alfred Hospital in Recent Years

The total number of tablets and capsules of hypnotic drugs dispensed each year at Alfred Hospital has increased only slightly during the last six years, and is approximately

TABLE 1
Relative Amounts of the Main Hypnotic Drugs Used at Alfred Hospital over the Period 1965-1970

Rank ¹	1965, 1966 ²	1967, 1968 ²	1969, 1970
1	Amylobarbitone sodium 200 mg	Methaqualone Hcl 250 mg with diphenhydramine Hcl 25 mg	Methaqualone Hcl 250 mg with diphenhydramine Hcl 25 mg
2	Pentobarbitone sodium 100 mg	Amylobarbitone sodium 200 mg	Pentobarbitone sodium 100 mg
3	Quinalbarbitone sodium 100 mg	Pentobarbitone sodium 100 mg	Nitrazepam 5 mg
4	Pentobarbitone sodium compound capsules	Pentobarbitone sodium compound capsules	Pentobarbitone sodium compound capsules
5	Dichloralphenazone 650 mg	Dichloralphenazone 650 mg	Dichloralphenazone 650 mg
6	Butobarbitone 100 mg	Quinalbarbitone sodium 100 mg	Butobarbitone 100 mg
7	Amylobarbitone sodium 100 mg	Butobarbitone 100 mg	Amylobarbitone sodium 200 mg
8	Amylobarbitone plus quinalbarbitone sodium 100 mg	Amylobarbitone plus quinalbarbitone sodium 100 mg	Quinalbarbitone sodium 100 mg

¹ Rank = most used drug.

² Small amounts of glutethimide used, but figures not available.

650,000 *per annum*. However, the types of drugs most frequently prescribed have changed considerably. Table 1 shows the relative amounts of the principal hypnotics dispensed over the last six years. The most obvious change has been the rapid increase in the use of non-barbiturate hypnotics; methaqualone with diphenhydramine began to be prescribed on a large scale in 1967 and soon became the most prescribed hypnotic drug. The popularity of this mixture seems to be based on claims that, relative to barbiturates, it is not only less likely to produce dependency, but is also safer in large doses. Over the past two years, nitrazepam has had a similar rise in popularity. Amylobarbitone sodium (200 mg) and quinalbarbitone sodium (100 mg) appear to be the drugs whose overall popularity has decreased most. Pentobarbitone sodium and pentobarbitone compound are now the most prescribed barbiturates, while dichloralphenazone has retained the same relatively high popularity throughout this period.

DISCUSSION

The percentages of patients of different ages and sex in the present study who took hypnotics at home are similar to those reported by McGhie and Russell (1962), who used a *questionnaire* among healthy adults in the general community in Scotland. They found, as we have, that females of all ages took hypnotics more often than males, and that the elderly took them more often than the young of both sexes.

Of the hypnotic drugs used at home and identified by patients in the present survey, 60% were barbiturates of various kinds and 40% non-barbiturates, most of which were available only on prescription from a doctor. Abrahams *et alii* (1970) carried out a survey to establish the frequency of dependence on barbiturates and other drugs in Brisbane. In composite samples of medical, surgical and psychiatric patients, matched for age and sex with the general population, between 12% and 23% of the various groups, and 10% of the "healthy" people attending a chest clinic were considered to be dependent on barbiturates. Marked dependence, defined as consumption of more than 400 mg of barbiturate sedatives and hypnotics per day for at least three months, was seen most commonly in psychiatric patients, and produced a syndrome well described by Whitlock (1970). More females were dependent on barbiturates than males, and

the incidence increased with age. The major source of these patients' drugs was the general practitioner. The results on frequency of use are in general agreement with those of Alfred Hospital patients, which suggests that the figures are typical of patients throughout Australia.

When patients are admitted to hospital they commonly complain of disturbed sleep, the degree of which depends on the psychological and physiological characteristics of each patient, and the type of illness from which he is suffering, as well as on environmental factors in the hospital ward. Disturbance as a result of noise from other patients or medical staff is fairly common in the ward at night. Also, it may be considered necessary for the patients to be disturbed in order to receive treatment (injections, observations of pulse, temperature and blood pressure, etc.) at frequent intervals. Anxiety, associated with acute illness and hospital admission, accentuates the problem of insomnia, especially in the elderly who tend to suffer from poor quality sleep under normal circumstances (Johns *et alii*, 1970). In an attempt to overcome these difficulties, hypnotic drugs are very commonly prescribed. The choice of whether or not a hypnotic is prescribed for a particular patient depends initially on the junior medical staff, some of whom will prescribe drugs for almost all patients. Whether or not the hypnotic is taken often depends both on the nurse dispensing it in the ward and on the patient's wishes. He may sleep poorly for a few nights and then request a hypnotic himself, or he may decline to take a tablet at the usual time when they are dispensed (between 9 and 9.30 p.m.), feeling that he will be able to sleep without the drugs.

The predominance of barbiturate hypnotics used at home is in contrast to the current predominance of non-barbiturates used in hospital. The hospital pattern has arisen only in the last four years, and it may be that a rapid change away from barbiturates will now occur in general practice. The experience in Britain appears similar, in that a recent report of all drugs dispensed during a three-month period from out-patient clinics at Guy's Hospital, London (Knight, 1970), revealed similar prescribing habits to those at Alfred Hospital. However, in the whole of the United Kingdom, as in Australia, 75% of all prescriptions for hypnotics written on the National Health Service were for barbiturates, and only 25% for non-barbiturates (Dunlop, 1970). By contrast,

in Boston, U.S.A., the hypnotic most commonly prescribed in a series of eight hospitals, and indeed the most common of all drugs given to 38% of several thousand patients, was chloral hydrate (Shapiro *et alii*, 1970).

The results of sleep research are beginning to be felt in the prescribing habits of doctors, especially in the move away from barbiturates. The recent increase in popularity of nitrazepam and methaqualone with diphenhydramine in Australia, and flurazepam in U.S.A., are probably improvements in the treatment of insomnia and, at least in the case of nitrazepam, there is a reduction in toxicity compared with barbiturates. For the treatment of short-term insomnia associated with a recognizable anxiety reaction, any of the latter drugs or chloral hydrate could be recommended. This is probably so for all hospital patients who are "occasional" users of hypnotics at home. The treatment of long-term insomnia should be aimed primarily at its cause, whether this be anxiety neurosis, depression, or physical disorders which are associated with sleep disturbances such as thyroid disease or cardiac failure. It may be that placebos, which are as effective as 100 mg of phenobarbitone in the treatment of mild insomnia (Nicolis and Silvestri, 1967), could be used to advantage if drug treatment for insomnia is being considered. There is little doubt that barbiturates should be avoided in such situations, although it must be remembered that another hypnotic (for example, nitrazepam) should be prescribed for use during the period of barbiturate withdrawal. Clearly, there is a need for continuing basic research into the nature of sleep and the treatment of insomnia, a condition which affects more than 30% of hospital patients at home, and 75% while in hospital.

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