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Hypnotics and Sleep Physiology: A Consensus Report

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Summary. The effects of hypnotics on descriptive and functional aspects of electrophysiological sleep parameters are assessed in this report. Because of the arbitrary definition of some of the criteria underlying the conventional sleep stage scoring procedure, computer-aided methods of EEG analysis have become increasingly important for recording and interpreting pharmacological effects on sleep. Of particular interest are the changes of EEG slow-wave activity, since this parameter varies as a function of prior sleep and waking. Several types of interaction between hypnotics and sleep regulation are discussed, some recent pharmacological developments are highlighted, and some common problems in clinical trials are specified.

Key words: Sleep – Physiology – Hypnotics – Benzodiazepines – Electroencephalography

Introduction

Problems related to drugs and insomnia were the topic of a Consensus Conference convened in 1983 by the National Institute of Mental Health and the Office of Medical Applications of Research of the National Institutes of Health (Consensus Conference 1984). The conference focused on practical aspects of sleep-promoting medication such as treatment strategies, therapeutic indications and risks, but did not discuss how the sleep process is affected. In view of the recent methodological and conceptual advances in the field, and novel pharmacological developments, the Board of the European Sleep Research Society established a Committee with the task of critically evaluating the effects of hypnotics in relation to sleep physiology, and in particular on sleep architecture and the sleep EEG. The aim was to specify promising techniques and approaches which could provide a deeper insight into the interactions between hypnotics and sleep regulation. An effort was made to transcend the purely descriptive level and to include possible functional aspects as much as possible.

The members of the Committee are the authors of this report. In its working sessions the Committee prepared a draft report which formed the basis of a Consensus Conference (Zürich, 28 March 1990). Pharmaceutical firms that had shown interest in this project were invited to send their own experts or invited scientists to the Consensus Conference. In addition to the members of the Committee the participants of the Conference were M. Gerber (Switzerland) and C. Idzikowski (United Kingdom) (both from Janssen); P. Attali (France) and P. Borderies (France) (both from Synthélabo); D. Gorra (France) and F. Kelly (United Kingdom) (both from Rhône-Poulenc); I. Hindmarch (University of Surrey; invited by Upjohn) and K. Starz (United States; from Upjohn).

Effect of Hypnotics on Electrophysiological Sleep Parameters: Descriptive Aspects

The advent of sleep polygraphy has made it possible to document the action of hypnotics on sleep in more detail. In particular, the method provided an objective way of assessing sleep parameters such as total sleep time, the number of awakenings after sleep onset, sleep latency and sleep efficiency. In addition, effects of different settings on sleep stages and sleep architecture could be determined (e.g. a reduction of REM sleep or slow wave sleep, a prolongation of the latency to REM sleep). The widespread acceptance and use of the sleep scoring criteria of Rechtschaffen and Kales (1968) have facili-

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tated the comparison of sleep recordings obtained in different laboratories, and thereby promoted the exchange of information. In recent years, computer-aided sleep staging procedures have been developed to score sleep automatically according to standard criteria.

While the general use of the conventional scoring system has greatly promoted human sleep research and sleep medicine, its limitations have become increasingly apparent. One of the main problems derives from the arbitrary specification of some of the criteria. This is exemplified by the substates of the non-REM sleep stages 2, 3 and 4, for which the major discriminating criterion is the abundance of EEG delta waves within a scoring epoch. The frequency range (0–2 Hz), the minimum amplitude of delta waves (75 μV), and the prevalence in a scoring epoch (20–50% for stage 3; > 50% for stage 4) are all arbitrary. Consequently, variations that are unlikely to be of major physiological relevance (e.g. interindividual or age-related variations in EEG amplitude) may markedly affect the sleep stage distribution. Even more important for the present considerations are the drug-induced changes. Drugs affecting those EEG parameters that are critical for scoring (e.g. the amplitude of delta waves) appear to give rise to prominent changes in sleep architecture, whereas equally potent drug effects on other EEG parameters (e.g. an augmentation of beta activity) do not affect the sleep stage distribution. For example, after administration of a benzodiazepine (BDZ) hypnotic, the sleep EEG was still massively altered in the drug-free post-drug night, whereas sleep architecture as defined by the standard sleep scores, was no longer significantly changed (Borbély et al. 1985a). In conclusion, the scoring procedure may give rise to misleading results by either exaggerating the drug-induced changes of sleep architecture or by inadequately reflecting alterations of the sleep EEG.

Novel computer-aided methods of EEG analysis are being increasingly applied to describe effects of hypnotics on sleep. By using the EEG as a biological signal, they provide a way for a continuous, quantitative description of the changes during sleep without the need for sleep stage criteria. The application of such methods in the study of BDZ hypnotics and non-BDZ hypnotics had made in possible (1) to quantify the changes of the EEG in specific frequency bands such as slow waves, spindles and high-frequency activity (Johnson et al. 1976; 1979; 1983; Feinberg et al. 1977; 1979; Johnson and Spinweber 1981; Borbély et al. 1983, 1985a; Gaillard and Blois 1983, 1989; Trachsel et al. 1990); (2) to discriminate effects of BDZ on the amplitude and frequency of EEG slow waves (Feinberg et al. 1977, 1979; Johnson et al. 1979; Wright et al. 1986); (3) to detect residual effects which are not always evident from the sleep scores, and which may indicate a persistent drug level in the brain (Johnson et al. 1976; Johnson and Spinweber 1981; Borbély et al. 1983, 1985a); and (4) to identify those EEG changes that are specific to certain sleep stages (e.g. alpha activity being augmented by BDZ in non-REM sleep, and reduced in REM sleep; Gaillard and Blois 1989), and others that are to a large extent sleep-stage independent (Borbély et al. 1985a).

Effect of Hypnotics on Electrophysiological Sleep Parameters: Functional Aspects

Physiology

Even though the functions of sleep are still largely unknown, processes that are highly correlated with sleep regulation can be specified. The experimental manipulation of the waking period preceding sleep is a potent tool for exploring their characteristics. Thus sleep following prolonged sleep deprivation typically exhibitis a shortened onset latency, a prolonged duration, and an increased amount of slow-wave sleep (SWS) and REM sleep (for references, see Borbély 1982). A moderate extension of the waking period mainly gives rise to an increase in SWS. Computer-aided EEG analysis has provided a quantitative description of slow-wave activity (SWA; activity in the delta frequency range) and its time course during sleep. SWA is typically highest in the first non-REM sleep episode and progressively declines over consecutive episodes (Sinha et al. 1972; Church et al. 1975). Experiments in which sleep was preceded by waking periods of various durations showed that SWA increases as a monotonic function of prior waking (Borbély et al. 1981; Dijk et al. 1987a); experimental variations of sleep duration revealed that SWA responded sensitively to the amount of SWA in the preceding sleep period (Akerstedt and Gillberg 1986). There is good evidence that SWA is a correlate of an intensity parameter of non-REM sleep which is homeostatically regulated. Non-REM sleep homeostasis is operative even within a single sleep period. Thus the selective deprivation of SWA in the first part of sleep resulted in a selective rebound in the second part (Dijk et al. 1987b; Dijk and Beersma 1989). There is also evidence for a homeostatic regulation of REM sleep. Under appropriate experimental conditions even a moderate REM sleep deficit is followed by a compensatory increase (Brunner et al. 1990).

In addition to the homeostatic aspect of sleep regulation, a circadian, sleep/wake-independent process plays an important role (Patrick and Gilbert 1896; Czeisler et al. 1980; Zulley 1980; Akerstedt and Gillberg 1981; Benoit and Foret 1988). It is apparently controlled by a circadian pacemaker or an "internal clock", and exerts a major influence on parameters such as sleep duration, sleep latency and REM sleep (see Borbély 1982). Intensive light has been shown to modify circadian rhythms including the sleep/wake rhythm (Wever et al. 1983; Czeisler et al. 1986, 1989; Dijk et al. 1987c; Clodoré et al. 1990).

A third important feature of sleep regulation is the cyclic alternation of non-REM sleep and REM sleep episodes, which is probably generated by a "REM sleep oscillator" (see McCarley and Massaquoi 1986).

After the initial proposition of a qualitative model of sleep homeostasis (Feinberg 1974), the interactions between the homeostatic and circadian facets of sleep regulation have been formalized in the two-process model (Borbély 1982; Daan et al. 1984). The properties of the homeostatic process S (i.e. a sleep/wake-dependent variable representing non-REM sleep intensity) were derived

from EEG SWA. The model is able to account for changes in sleep under such diverse conditions as sleep deprivation, prolonged bedrest, an environment free of time cues, and shift-work. Recently, the model was extended to account for changes in daytime vigilance (Folkard and Akerstedt 1987, 1988), sleep latency (Borbély et al. 1989) and intra-episodic variations in SWA (Achermann and Borbély 1990). In the framework of the model, different types of pharmacological effects (permissive, homeostatic or circadian) on sleep have been specified (Borbély 1990).

Interpreting the Effect of Hypnotics on Sleep and the Sleep EEG

The decline of SWA over consecutive non-REM sleep episodes, the progressive lengthening of REM sleep episodes, and the non-REM/REM sleep cyclicity are three salient features of sleep architecture which reflect the influence of major regulatory processes on sleep. Hypnotics may have prominent actions on the sleep stages. Typical changes induced by BDZ hypnotics include the reduction of SWS and REM sleep, and the prolongation of REM sleep latency. In view of the prominent role of these stages in sleep physiology, the suppression of SWS and REM sleep by BDZ hypnotics has been interpreted as an impairment of the recuperative aspects of sleep (Schneider-Helmert 1988). However, caution is indicated in drawing such conclusions, because the single administration of BDZ hypnotics (Borbély et al. 1985a; Achermann and Borbély 1987) and non-BDZ hypnotics (Trachsel et al. 1990; Brunner er al. 1991) does not disrupt the salient features of sleep architecture. Thus the declining trend of SWA and the non-REM/REM sleep cyclicity persist in drug nights. The prolongation of REM sleep latency after BDZ hypnotics (Gaillard and Blois 1983, 1989; Belyavin and Nicholson 1987) may be due, in part, to a drug-induced inhibition of EEG desynchronization rather than to the disruption of the REM sleep generating processes (Borbély and Achermann 1981). According to this interpretation the processes underlying sleep regulation are little affected by BDZ hypnotics administered at a single hypnotic dose. In the framework of the two-process model it has been proposed that they exert a permissive action on sleep by lowering the threshold of sleep onset or by increasing the threshold of sleep termination (Borbély 1990). Experiments are needed to investigate the changes occurring during repeated administration.

Hypnotics are known to exert marked effects on the sleep EEG. The reduction in the amplitude of slow waves by BDZ hypnotics results in a reduction of the sleep stage scored as SWS, although the incidence of slow waves may not be affected (Feinberg et al. 1977, 1979). When interpreting these effects one should be aware that some of the changes may reflect a pharmacological influence on EEG generating mechanisms rather than on sleep processes. This interpretation is supported by the observation that the typical BDZ-induced effects on EEG spectra (i.e. reduction of SWA, enhancement of activity in the spindle frequency band) are present in all sleep stages (Borbély et al. 1985a), although some stage-specific effects on alpha activity have been described (Gaillard and Blois 1989). As has been mentioned before, the use of the conventional sleep stage criteria may yield fortuitous drug effects on the sleep stage distribution which are of little physiological relevance.

The BDZ-induced changes of the sleep EEG do not always parallel the time course of the hypnotic action. Thus after administration of short half-life hypnotics (i.e. triazolam or midazolam) the depression of SWA persisted unmitigated throughout the sleep period, while the hypnotic action declined (Borbély et al. 1985a; Trachsel et al. 1990). Moreover, the reduction of SWA was present even in the post-drug night, at a time when the hypnotic effect had vanished or was strongly attenuated (Borbély et al. 1985a; Gaillaird and Blois 1989). Other EEG effects, such as the increase of EEG activity in the spindle frequency range, were more closely related to the sleep-promoting action (Borbély et al. 1983; Johnson et al. 1983; Trachsel et al. 1990).

When sleep is disturbed, hypnotics may counteract the intrinsic or extrinsic sleep-disrupting influences by virtue of their permissive action on sleep, and thereby normalize the sleep pattern. Consequently, the percentages of SWS and REM sleep may be increased. For example, when experimental subjects slept under non-sleep-conducive conditions, the administration of a BDZ hypnotic increased SWS in comparison to placebo, although ordinarily the compound depresses SWS (Balkin et al. 1989). Therefore, the basic action of a drug on sleep and the sleep EEG may be misinterpreted when its permissive action on sleep is not taken into consideration.

The role of the GABA-BDZ-Receptor Complex

It has been reported in early studies that the reduction of SWS persists after discontinuation of BDZ hypnotics (Gaillard et al. 1973). It has been hypothesized that this effect may be due to a prolonged alteration of physiological sleep regulation (Borbély et al. 1983). The BDZ antagonist flumazenil was capable of reversing several effects of flunitrazepam on sleep (e.g. prolonged total sleep time, reduced waking after sleep onset, increased sleep efficiency, shortened sleep latency, prolonged REM sleep latency) and on the sleep EEG (enhanced alpha and spindle activity). However, flumazenil did not antagonize the BDZ-induced depression of SWA in the delta and theta range (Gaillard and Blois 1983; 1989). In fact, this antagonist reduced SWA when administered alone. These results indicate that the reduction of SWA by BDZ hypnotics may not be mediated by the GABA-BDZ-receptor complex. On the other hand, zopiclone and zolpidem, non-BDZ hypnotics that are ligands of the GABA-BDZ receptor complex, induced spectral changes that were similar to those induced by BDZ hypnotics (Trachsel et al. 1990; Brunner et al. 1991). These findings suggest that a "spectral EEG signature" may reflect the agonist effect of hypnotics on the GABA-BDZ-receptor complex.

Measuring Effects of Hypnotics on the Recuperative Property of Sleep

Sleep loss or repeated sleep disruption results in increased daytime sleepiness and reduced performance (Bonnet 1985; for a review, see Carskadon and Dement 1987). Sleep may be considered to have recuperative properties, since it reverses or prevents the deleterious effects of prolonged waking. The multiple sleep latency test (MSLT) or similar tests are being widely used as a measure of daytime sleepiness. Sleep latency has been shown to be affected by acute or cumulative sleep loss, excess sleep, circadian influences, and hypnotics (Carskadon and Dement 1987; Roehrs et al. 1989).

It has sometimes been assumed that the reduced daytime vigilance due to disturbed sleep can be normalized by hypnotics. However, the question arises whether because of the alteration of the sleep EEG by hypnotics, the "restorative potency" of a drug-promoted sleep is impaired. The limited evidence available does not support this assumption. Thus when sleep restriction was combined either with a rapidly eliminated BDZ hypnotic or with placebo, daytime sleep latency was correlated with the duration of prior sleep, but was not significantly affected by the hypnotic (Borbély et al. 1985b).

The use of the MSLT as an index of daytime sleep propensity in pharmacological studies is not without problems. Although a reduction of sleep latency may reflect a residual daytime activity of the drug (e.g. Roehrs et al. 1986), a normal or prolonged sleep latency is more difficult to interpret. Withdrawal effects giving rise to rebound insomnia are well documented for short-half-life BDZ hypnotics (Gillin et al. 1989; Roehrs et al. 1990) and may occur even after a single dose (Mattmann et al. 1982; Mamelak et al. 1990). Moreover, increased daytime anxiety or tension has been reported after repeated administration (Morgan and Oswald 1982; Kales et al. 1983a, b; Adam and Oswald 1989a). Therefore it is possible that increased values in the MSLT are not a sign of enhanced daytime vigilance, but of increased anxiety and tension, due to drug withdrawal. To assess daytime residual effects of hypnotics, additional vigilance tests and performance measures are required, since the changes of the MSLT and other measures may dissociate (Johnson et al. 1990). The analysis of the waking EEG as an indicator of daytime sleep propensity (Torsvall and Akerstedt 1987, 1988; Akerstedt 1988) is a promising procedure that should be developed further.

Effect of BDZ Hypnotics on Circadian Rhythms

When sleep occurs during a circadian phase of habitual waking, sleep is likely to be disturbed and, consequently, sleepiness during the subsequent waking period is enhanced. Drugs that could shift the phase of circadian rhythms may promote the adaptation to altered sleep-waking rhythms which typically occur during shift-work or transmeridian travel. Recent studies in hamsters have suggested that the rapidly eliminated BDZ hypnotics triazolam and midazolam exert a chronopharmacological action by altering the phase of the circadian rest activity rhythm (Turek and Losee-Olsen 1986; Wee and Turek 1989). A phase response curve has been established for triazolam (Turek and Losee-Olson 1986). However, since restraining the animals prevented the effect of triazolam (Van Reeth and Turek 1989), the phase-shifts seem to be due to a drug-induced motor activation of the hamsters (Mrosovsky and Salmon 1987) rather than to an effect of the BDZ on the circadian pacemaker. There is presently no evidence that BDZ hypnotics affect circadian rhythms in humans. However, as recent studies with exposure to intensive light have shown (Czeisler et al. 1986, 1989), there are potent non-pharmacological means to rapidly phase-shift the human circadian rhythm.

Withdrawal Effects of Hypnotics: Repercussions on Sleep

It was reported in early studies (Oswald and Priest 1965) that tolerance and withdrawal effects may impair sleep. Administration of a barbiturate hypnotic caused an initial depression of REM sleep; this effect subsided after repeated administration of the drug, and reappeared after an increase in the dose (Oswald and Priest 1965). Discontinuation of either a barbiturate or BDZ hypnotic was followed by a prolonged REM sleep rebound, an increased incidence of nightmares, and more intense body movements during sleep (Oswald 1965; Oswald and Priest 1965). However, in another early study, a REM sleep rebound was not observed within the first 3 days after discontinuation of barbiturate hypnotics (Feinberg et al. 1974). During prolonged administration of hypnotics, increaed restlessness in the last part of sleep (Ogunremi et al. 1973) and early morning awakening have been reported (Kales et al. 1983b). The latter observation was not confirmed by other authors (see Gillin et al. 1989 for references). After discontinuation of hypnotics rebound insomnia and rebound anxiety have been reported (Adam et al. 1976; Kales et al. 1978, 1983a, Morgan and Oswald 1982; Adam and Oswald 1989a). These problems can be alleviated by tapering the doses at the end of pharmacotherapy (Greenblatt et al. 1987). The literature of rebound insomnia has been extensively reviewed (Gillin et al. 1989).

The issue of withdrawal effects is raised in the present context because it is relevant for interpreting the effect of hypnotics upon repeated administration. Sleep architecture may undergo complex changes due to direct drug effects, withdrawal effects, and physiological regulatory responses to the hypnotics.

Recent Pharmacological Developments

In this section some developments are highlighted which are of therapeutic relevance or which promise to offer new insights into the mechanisms underlying sleep regulation and the sleep EEG.

Two new non-BDZ compounds (zolpidem, an imidazopyridine, and zopiclone, a cyclopyrrolone) have been recently introduced as hypnotics in some countries. They both bind to the GABA-BDZ-receptor complex, although the precise binding site of these compounds and of the BDZ hypnotics may differ. It is still too early to decide whether substantial differences exist with respect to the effects on sleep physiology, and other aspects that are relevant to pharmacotherapy.

It has been proposed that SWS is important for brain restitution (Horne 1979; Adam 1980; Oswald 1980; Horne 1988). Accordingly, drugs enhancing SWS have been of particular interest. Whereas it was recognized several years ago that drugs with serotonin antagonist properties enhance SWS (Spiegel 1981; Oswald et al. 1982), more recently a massive increase of SWS was reported for the relatively selective $5HT_2$ antagonists ritanserin and seganserin (Idzikowski et al. 1985, 1987; Dijk et al. 1989; Sharpley et al. 1990). Although ritanserin caused some improvement of sleep in insomniacs (Adam and Oswald 1989b), its therapeutic profile differs from that of hypnotic drugs and remains to be more fully specified. One of the main questions is whether these compounds induce a physiological type of sleep intensification analogous to the effect of prolonged waking (Janssen 1987), or whether the changes occur at the level of the EEG generators and do not involve the basic sleep processes. There are data showing that the drug-induced changes of the EEG spectra differ from those of sleep deprivation (Borbély et al. 1988; Dijk et al. 1989).

L-Tryptophan, the precursor of serotonin, has been advocated as a physiological sleep remedy. However, large doses are required for a moderate and short-lasting hypnotic effect, and a "physiological" mechanism of action has not been unequivocally demonstrated (Schneider-Helmert and Spinweber 1986; Borbély and Youmbi-Balderer 1987). Owing to the recognition of the tryptophan-induced eosinophilia-myalgia syndrome in 1989 (Mesdger 1990), the use of this compound as a hypnotic was suspended.

The administration of various hormones (e.g. corticotropin-releasing hormone; Holsboer et al. 1988) may modify sleep, and the secretion of hormones may in turn undergo sleep-related changes (various pituitary hormones: Steiger et al. 1987a; Follenius et al. 1988; renin: Brandenberger et al. 1988). Some of the sleep-related neuroendocrine changes are modified by BDZ hypnotics (Copinschi et al. 1990). Recent experiments have demonstrated that growth hormone secretion is associated with the first non-REM sleep episode rather than with SWS (Steiger et al. 1987a; Born et al. 1988). The study of hormonal changes may shed light on mechanisms involved in physiological sleep regulation, and possibly pave the way for the development of new drugs.

Melatonin is currently under investigation as an agent that could counteract or prevent sleep disturbances and other undesired consequences of phase-shifting sleep with respect to circadian rhythms. There is evidence that repeated oral intake of melatonin (5 mg/day) reduces symptoms of jet-lag (including sleep disturbances) and promotes a resynchronization of circadian rhythms (Arendt et al. 1986, 1987; Petrie et al. 1989; Sarrafzadeh et al. 1990) without having a direct effect on sleep (James et al. 1987).

There is renewed interest in endogenous sleep promoting substances (Borbély and Tobler 1989; Inoué 1989). Several promising candidates have been specified in animal experiments (e.g. prostaglandins; Hayaishi 1988). In the search for these substances, molecular genetic techniques are being applied (Rhyner et al. 1989, 1990). This research field may provide new insights into fundamental neurochemical mechanisms underlying sleep regulation, and may eventually lead to the development of novel hypnotics.

After administration of the MAO-A inhibitor brofaremine, REM sleep was suppressed, whereas the cycle of nocturnal penile tumescence persisted (Steiger et al. 1987b). These results indicate that drugs may suppress selectively certain components of REM sleep, whereas others are left unaffected. Pharmacological effects on the REM sleep oscillator should be investigated in more detail.

New vigilance enhancing substances (e.g. the central alpha-1 adrenoceptor agonist modafinil; Billard et al. 1989; Saletu et al. 1989) are currently being tested. They may provide new ways for enhancing daytime vigilance. It will be important to investigate how such drugs affect sleep regulation.

Conclusions

The study of the interactions between hypnotics and physiological sleep regulation is important for assessing the effects of this class of compounds on sleep. The reliance on conventional sleep scoring is inadequate. Computer-aided methods for analysing effects of hypnotics on electrophysiological sleep parameters and for relating them to functional aspects of sleep will become increasingly important.

Of particular interest are effects on EEG SWA, a parameter reflecting non-REM sleep intensity and varying as a function of prior waking. BDZ hypnotics typically depress SWA, whereas some 5HT2-antagonists enhance SWA. These changes may reflect the modification of processes involved in EEG generation and/or of sleep regulation. Finally, there is a need for a better understanding of the neurophysiological and neurochemical events underlying the EEG generating mechanisms.

Appendix

Evaluating Hypnotic Drugs: Common Problems and Pitfalls in Clinical Trials

Properly conducted drug trials are a prerequisite for an objective evaluation of hypnotic drugs. While reviewing the literature the Committee has encountered a number of problems in the design and interpretation of clinical trials which render the evaluation of the results difficult. In the following, some of the more common issues are raised. However, the text is not meant to be a complete list of the problems encountered in drug trials.

The Need for Positive Controls. A new hypnotic drug must be compared with a placebo, but it is also important that investigators and patients should be "blind". If the new hypnotic has been established in preliminary work as effective, and induces heavy sleep, then the principal trials should include a positive control substance. If trials are conducted by merely comparing the new hypnotic with a placebo, neither investigator nor patients will be blind when making subjective judgements about subtle drug effects. Therefore, in the majority of instances it will be quite obvious when the new drug has been taken and when a placebo has been taken.

False Negatives. There is an unfortunate practice apparent in a great deal of psychopharmacological research literature, whereby conclusions are drawn from negative results. Statistically significant positive findings based on adequate tests in biomedical research can usually be accepted as reliable. Negative findings quite often mean inadequate research design and can only be accorded weight if the "power" of the research design can be calculated to have been of the order of 80% or more (Bausell 1986). It is important that investigators should use research procedures of established sensitivity and, if at all possible, sensitivity in their hands.

Inadequate Sample Size. In very recent years a major research group published a paper, the purpose of which was to convey the message that a particular adverse effect was not found with a well-known hypnotic. Yet they studied only seven patients taking that hypnotic and in their publication noted that the power of their research design was only 26%. They did not explain to the reader that the latter figure had meant they were three times more likely to miss the truth than to find it.

Insensitive Tests for Residual Effects. It is desirable that hypnotic drugs should be studied for effects on psychomotor performance the next day. A report that adverse effects were absent after some chosen dose is worthless unless the power of the procedure is specified. All too often it is obvious that there have been negative findings because the tests were of low sensitivity and because too small a number of subjects (often of inappropriate age) had been used.

Inadequate Tests for Detecting Tolerance and Withdrawal Effects. Pharmaceutical companies have sometimes launched new hypnotics accompanied by statements that tolerance and withdrawal effects have not been found to occur with their product. Such statements can be misleading if no adequately designed research has been carried out to test whether tolerance and withdrawal effects may occur. The research should employ test procedures that are sensitive and appropriate. Thus, if a short-life hypnotic is under consideration, withdrawal effects can be expected to be maximal in the first 24–48 h and it is not adequate to confine attention to a point 1 week after a final dose within a design that has perhaps covered several weeks from pre-treatment through treatment to placebo substitution. Once-weekly assessments may be convenient but are not adequately sensitive. In the study of withdrawal effects, daily assessments are needed and results should be presented on a daily basis, not averaged across several days. Averaging across 3 days may, for example, obscure a first night withdrawal effect.

Deficiencies in Reporting Side-effects. Patients are commonly reluctant to make complaints about their treatment and in the investigation of a hypnotic, an opportunity should be given to report side-effects in the ordinary language of the patient, not only in the morning about breakfast-time, when a report is made about sleep, but also at other times of the day. There should be a description of how the patient has been feeling during the day and of any unusual events during the day.

Inappropriate Study Populations. The complaint of insomnia is much more common in the middle aged and in elderly populations. It is they who take most hypnotic drugs, and they often do so for long periods. Research should therefore concentrate on such populations. This applies not only to clinical research on patients but to volunteer studies also. Studies on middle-aged volunteers selected because of chronic dissatisfaction with sleep are more relevant than on, for example, healthy young military personnel.

Insufficient Duration of Studies. The WHO Regional Office for Europe, in its "Guidelines for the Clinical Investigation of Hypnotic Drugs" in 1983 recommended that in research trials hypnotic drugs should be studied for periods of administration up to 6 months. Since a long-term use is to be expected for any new hypnotic, data on the effects and side-effects after intake for several weeks should be available.

Appropriate Use of Expert Opinion. New hypnotic drugs are developed only occasionally within any one pharmaceutical company. Company personnel are unlikely to have had experience in the research and development of a previous hypnotic. Sleep Research Societies have members who will have had experience in research with more than one hypnotic in the past, and who may be willing to provide scientific advice and to undertake research.

Concluding Remarks. The decision whether or not to prescribe an hypnotic is one that the individual clinician makes. In the last few years there has been much criticism of the prescribing of BDZs generally, including BDZ hypnotics, much of the criticism being in lay magazines or on the television. We are of the opinion that much of this criticism has been poorly informed and while we adhere to the view that drugs should never be unnecessarily prescribed or prescribed for unnecessarily long periods, it should always be remembered that doctors have an obligation to help and comfort their patients and not to discipline them. There are now a number of research papers demonstrating that self-judged poor sleep

or anxiety correlate in the long term with reduced life expectancy (e.g. Sims and Prior 1978; Wingard and Berkman 1983). There is not necessarily a causal relation, but we are not entitled to dismiss the possibility: patients who appreciate hypnotic drugs for long periods may "know" something that science cannot yet elucidate.

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