for the drug which caused the hangover. No cases of skin rash or other hypersensitivity phenomena were reported.

The results show that in a dosage of 100 mg., phenobarbitone, butobarbitone, and quinalbarbitone have similar hypnotic power. This agrees with the work of Lasagna (1956). A similarity of hypnotic effect in this dosage has previously been noted between quinalbarbitone and pentobarbitone (Goldstein, 1953; Belleville and Fraser, 1957) and between butobarbitone and amylobarbitone sodium (Stewart, 1956). In the present series a hangover was reported in 6.4% of patients taking 100 mg. of phenobarbitone and in 12.5% (average over three trials) of patients after taking 100 mg. of quinalbarbitone. No hangover was reported after 100 mg. of butobarbitone had been given to 27 patients.

When the dose was doubled subjects found quinalbarbitone more effective than both butobarbitone and phenobarbitone. The superiority of quinalbarbitone over phenobarbitone was less convincing than that of quinalbarbitone over butobarbitone. Butobarbitone was found to be more effective than phenobarbitone. The incidence of hangover calculated for each drug over two trials had increased, though it was less with butobarbitone (11.3%) than with quinalbarbitone (21.3%) and phenobarbitone (22.4%).

The similarity of hypnotic power of these drugs in the normal dose and the low incidence of hangover with phenobarbitone are contrary to general teaching. Physicians' opinion on the comparative merits of barbiturates have recently been shown to mimic the views expressed in influential medical textbooks (Lasagna, 1962). Thus little account has been taken of the now considerable evidence supporting the similarity of hypnotic effect. Failure to recognize the position earlier has been attributed to the difficulties inherent in carrying out true comparative trials in human subjects, making allowance for the presence of placebo reactors: and also to neglect of detailed clinical

observation after the administration of barbiturates in hypnotic doses.

Summary

The hypnotic effects of phenobarbitone, butobarbitone, and quinalbarbitone have been compared by sequential analysis using a method which involved inert tablets and the double-blind technique. With doses of 100 mg. no differences were demonstrated. With doses of 200 mg. the order of effectiveness in descending order was quinalbarbitone, butobarbitone, and phenobarbitone.

With both doses butobarbitone gave rise to least hangover. With 100-mg. doses phenobarbitone caused less hangover than quinalbarbitone.

There seems little justification for classifying barbiturates into short-, intermediate-, and long-acting groups.

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CONTROLLED COMPARISON OF FOUR SEDATIVE DRUGS IN ELDERLY PATIENTS

BY

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The evaluation of hypnotics has always been made difficult by lack of agreement on the importance of the parameters measured. One review (*Brit. med. J.*, 1962) states: "The estimation of what constitutes 'sound sleep' is in itself a major problem"; while Hinton and Marley (1959) point out that the perfect solution to the problem of measuring the depth of sleep remains elusive.

The methods of evaluating hypnotics can be divided into the two main groups of objective and subjective. Objective methods include measurement of nocturnal motility by mechanical means or, more commonly, the observation of patients at intervals by attendant staff who note whether or not the patient is asleep. Satisfactory correlation between both of these methods has been shown by Hinton and Marley (1959), Cox and Marley (1959), and Hinton (1961).

Subjective methods entail questioning the patient on the night's sleep. An overall evaluation of the night's sleep has

often shown poor correlation with objective assessments (Straus *et al.*, 1955; Hinton and Marley, 1959; Cox and Marley, 1959), although other workers have found some degree of correlation (Foltz *et al.*, 1955; Hare, 1955; Lasagna, 1956; Stewart, 1956). This apparent unreliability of patients' opinions has tended to discredit such subjective assessment, and in many studies inquiries are limited to the presence or absence of actual side-effects. It is unfortunate that this should have occurred, for, as mentioned by Lasagna (1954), "subjective evaluation is important, if for no other reason than that the clinical use of hypnotic agents is most frequently concerned with the alleviation of patients' complaints."

We agree that the patient's own evaluation of the night's sleep is an important measure of an hypnotic. Indeed, we consider that it must be the most important single assessment because the patients alone can judge the measure of success of what is, after all, mainly symptomatic treatment.

Furthermore, questioning on side-effects alone may give misleading information: Stewart (1956) noted that many patients found it difficult to differentiate between tiredness due to lack of sleep and hangovers from oversedation. Hare (1955) and Stewart (1956) also found that patients could not always sort out many factors in a multi-question approach, and this is particularly likely to be true in elderly patients.

It was therefore felt that an adequate assessment of hypnotics should include an overall evaluation of the night's rest by the patients and an objective measurement, such as hourly checks by nurses. These principles have been incorporated into a blind controlled trial of four types of sedative agents in elderly subjects.

Choice of Hypnotics

Of the many agents that can be used as hypnotics in the elderly there are two main groups, generally referred to as (a) sedatives and (b) tranquillizers. The former can be divided into barbiturates and non-barbiturates and the latter into phenothiazines and non-phenothiazines.

The barbiturate chosen was amylobarbitone sodium 200 mg., which was thought to be typical of the group, and, although classified as an intermediate-acting barbiturate, has been shown by Hinton (1961) to induce sleep as quickly as quinalbarbitone sodium in the dosage used. Dichloralphenazone ("welldorm") 1.3 g. was chosen as the non-barbiturate hypnotic, as it is considered to be safe, effective, and particularly suitable for geriatric patients (Howell, 1960).

In the tranquillizer group, chlorpromazine was the obvious choice as being representative of the phenothiazines, but promazine was preferred because of its lower incidence of side-effects. This was given at a 50-mg. dose in a resinated form ("sparine latab") which has been reported as being safer and more suitable for elderly patients (Brigstocke, 1961; Llewellyn, 1961). Of the non-phenothiazine tranquillizers, meprobamate ("equanil") 800 mg. was chosen as being widely used for a long time.

Method of Trial

All the drugs were given as tablets, but as the dosage of the drugs being compared were so dissimilar it was impracticable to provide them in identical form. The trial was so designed that the observers assessing the effects were completely unaware of the drug that had been given.

The four drugs and a placebo (lactose) were each given for one night from Monday to Friday in a random order, using a Latin square design. The subjects included in the trial were patients in a geriatric unit who were not having sedative therapy during the day and who were intelligent and co-operative enough to answer questions about their night's rest when asked next morning. Patients accepted for the trial were allowed at least a few days to settle in the ward before starting the study. A total of 65 patients took part in the trial. All were female, and, apart from one patient of 47 with tabes dorsalis, their ages ranged from 59 to 93 years.

The day sister administered the test drug at 9.15 p.m. The night staff made hourly assessments from 10.30 p.m. to 5.30 a.m., noting whether the patient was awake or asleep at each hour. At 8 o'clock the next morning the day staff nurse asked the patients for an overall evaluation of the night's rest in the categories of very good, good, bad, or very bad, and also for any specific side-effects. Neither the night nurse making the hourly checks nor the

staff nurse questioning the patients was told by the day sister which drug had been administered.

Sequential Analysis

The sequential method (Armitage, 1960) based on simple preferences between each drug and the placebo was used to obtain preliminary results and to determine the duration of the trial. The charts used (Fig. 1 and 2) are such that the chance of an apparently significant result is 5% if there is no difference between the treatments, while the chance of an apparently non-significant result is less than 5% if 80% or more of the preferences in the population samples are for one treatment. The trial was stopped when all eight lines—that is, four for the patients' and four for the nurses' score—had crossed the boundary. By this method it appeared that the patients showed a significant preference for dichloralphenazone and for meprobamate compared

FIG. 1.—Patients' opinion.

FIG. 2.—Nurses' two-hourly check.

with the placebo, but were evidently unable to make such a distinction between the other two drugs and the placebo (Fig. 1). The striking feature of the nurses' scores (Fig. 2) was the similarity between all four lines, although at the arbitrary 5% level only the differences for promazine and meprobamate were significant.

Qualitative Analysis

To obtain the maximum information from the trial account must be taken of the strength of the preferences (as measured by the score) and of the relation between the two methods of assessment. Neither of these factors plays a part in the sequential analysis described. For this purpose the nurses' assessment was scored with one point for each hourly check at which the patient was asleep, allowing a maximum of 8 points. The patients' evaluation was scored as follows: very good, 3; good, 2; bad, 1; and very bad, 0. Although 65 patients completed the trial, data were missing in six cases, and another four patients had to be excluded as they did not form a complete Latin square; as will be seen, their inclusion would have upset the balance of the trial.

The analysis of the two scores, the patients' opinion and the nurses' hourly check, was carried out on the assumption that they were normal variates. In fact, the nurses' score had a very skew distribution; the average was 5.5, the maximum possible score 8, and the minimum actually recorded being 1.

Table I shows that, as might be expected, there was a significant difference between patients by both methods of assessment. It also shows that, judged by the patients' evaluation, there were significant differences due to treatments and due to order of administration.

TABLE I.—Analysis of Variance of the Two Assessments

	d.f.	Mean Squares	
		Patients' Opinion	Nurses' Score
Patients	54	2.25*	51.09*
Treatments	4	1.14*	1.46
Order	4	1.26*	2.40
Residual	212	0.26	1.20

* Significant at 1%.

The effect of the order of administration was unexpected and is dealt with first. It can be seen from Table II and Fig. 3 that both methods show a similar pattern, with a striking tendency for an improvement in sleep to be

TABLE II.—Effect of Order of Administration

Night	Average Scores in Terms of Deviations from the Grand Mean	
	Patients' Opinion	Nurses' Assessment
1 (Monday)	+0.01	-0.19
2 (Tuesday)	-0.12	-0.16
3 (Wednesday)	-0.16	-0.01
4 (Thursday)	+0.05	+0.03
5 (Friday)	+0.22	+0.33

recorded at the end of the week. Although Table I shows that the order-effect in the analysis of the nurses' score was not significant, no account was taken there of its linear trend, which, as can be shown, was unlikely to have been due to chance.

These findings, of course, do not affect any conclusions on the difference between hypnotics—that is the object of the Latin square design.

The effect of the different hypnotics is shown by the mean scores given in Table III. On the average the patients

clearly preferred meprobamate and dichloralphenazone to the other three agents. By the same assessment meprobamate and dichloralphenazone were significantly better than the placebo.

FIG. 3.—Effect of order of administration.

TABLE III.—Effect of Hypnotics

	Average Scores in Terms of Deviation from the Grand Mean	
	Patients' Opinion	Nurses' Assessment
Amylobarbitone sodium, 200 mg. ..	-0.14	+0.03
Promazine resinate, 50 mg. ..	-0.05	+0.10
Meprobamate, 800 mg. ..	+0.13	+0.05
Dichloralphenazone, 1.3 g. ..	+0.17	+0.12
Placebo	-0.12	-0.28

The nurses' scores did not show any significant difference between the five regimes taken separately; if, however, we consider the four drugs together, they may be shown to have a significant effect on nurses' score, as compared with the placebo. The difference between the mean nurses' score for the four drugs was remarkably small. The conclusions reached regarding the effects of the different treatments are therefore essentially similar to those suggested by the sequential analysis of preferences.

An analysis of co-variance showed that patients who slept longer, as judged by the nurses' checks, tended to report good nights. Not only did patients who throughout the trial consistently slept badly have lower scores on both methods, but also, taking individual patients, the analysis shows that the same "good" nights were, on the average, shown by both methods. The analysis also shows that the correlation between the two assessments was not simply a result of both being correlated with order of administration.

Discussion

The patients' final opinion of the night's sleep is presumably partly based on its duration and partly on its quality, including the condition on waking. The analysis of co-variance in this trial confirms this view. Our results suggest that, at the dosages used, all four drugs are of similar effectiveness in producing sleep but that meprobamate and dichloralphenazone have properties, such as lack of morning drowsiness, which account for the particular preference for them.

These findings are in agreement with those of other workers. Goodnow *et al.* (1951) and Felsing *et al.* (1953) have shown that very prolonged effects can occur after barbiturate medication, so that "hangovers" are to be expected. Even if not sufficiently severe to result in a definite complaint of hangover, slight morning drowsiness may be enough for the patient to rate the overall quality of the night's sleep poorly. Lasagna (1954), Straus *et al.*

(1955), and Isaacs (1957) all found a high degree of side-effects or patients' disapproval of a barbiturate compared with other drugs even though the barbiturate might be more effective in producing sleep. In contrast many workers have commented on the lack of hangovers with meprobamate (Selling, 1956; Kessler and Barnard, 1956; Gardner, 1957) and with chloral (Lasagna, 1956; Imboden and Lasagna, 1956)—the active component of dichloralphenazone—as compared with barbiturates. Perhaps this is even more likely to occur in elderly patients, who are reputed to tolerate barbiturates poorly.

Apart from the drug preferences by the patients, the main point of interest in the trial was the significant effect of the order of administration of the drugs. This trend may be an artifact due to an alteration in the nurses' or patients' attitude as the week progresses or may represent a genuine change in the pattern of sleep of patients in the ward. The order-effect was in fact greater than the drug-effect but did not influence the validity of the drug comparisons. This illustrates the necessity of a balanced design in this type of trial.

In conclusion, barbiturates in the dosages given do not appear to be satisfactory as routine hypnotics for the elderly, because they are not liked by the patients. It is obviously desirable to give drugs that have an effective hypnotic action and are liked by patients; meprobamate 800 mg. and dichloralphenazone 1.3 g. fulfil these requirements.

Summary

Amylobarbitone sodium 200 mg., dichloralphenazone 1.3 g., promazine resinate 50 mg., meprobamate 800 mg., and a placebo have been compared as hypnotics in a blind controlled trial in 65 elderly patients in a geriatric ward. Objective assessments were made by hourly checks and subjective assessments by asking patients for an overall evaluation of the night's rest. The importance of including

a subjective assessment of this sort in symptomatic therapy is stressed.

Analysis of the results demonstrated that all active drugs had hypnotic activity as compared with the placebo when judged by the nurses' hourly check. Meprobamate and dichloralphenazone were, however, preferred by the patients to the two other drugs and to the placebo. At the dosages used, meprobamate and dichloralphenazone are considered satisfactory hypnotics for use in elderly patients.

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RAPID METHOD OF SCREENING FOR BARBITURATES

BY

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Barbiturates are the most common poisons at the present time in the United Kingdom. Although ultra-violet spectrophotometry is necessary for absolute assay and hydrolysis procedures and paper chromatography for identification, there is an urgent need for a simple rapid screening test which demonstrates the presence or absence of any barbiturate on a small volume of blood. It is the purpose of this paper to describe such a method which gives an unequivocal answer on 2 ml. of blood in five minutes and requires no apparatus more elaborate than a magnetic stirrer and a water-pump. In addition there is no dirty glassware to be cleaned at the end of a determination, the apparatus being instantly ready for further tests.

Zaar and Gronwall (1961) showed that barbiturates form mercury salts that are soluble in chloroform and insoluble in water. Using an ingenious but relatively lengthy extraction device, they took advantage of this property to assay barbiturates in blood. Although the same principle is followed here, the extraction of the barbiturate from the blood into chloroform, the reaction with mercuric ions, and the colour tests with dithizone for any mercury barbiturate

in the chloroform are all performed in a 100-ml. beaker (see Diagram). The other important feature of the method is that extraction of the barbiturate from the buffered blood is performed by magnetic stirring, using only 10 ml. of chloroform. By this technique emulsions, which are routine if shaking in a separating funnel is used, do not occur even with haemolysed post-mortem blood. The small volume of chloroform also avoids the necessity for evaporation stages. If a water-operated magnetic stirrer is used the apparatus can be made portable, dependent only on a water supply. The only other equipment needed is a suction device; a simple water-pump is most convenient. The glass suction-tube ($\frac{3}{16}$ in. (0.5 cm.) diameter) is taped on to a supporting stand so that it dips into the beaker, thus enabling an aqueous phase in the beaker to be drawn off, leaving 10 ml. of the lower chloroform layer *in situ*.

The concentrations and volumes of reagents are chosen to give a positive reaction to barbiturate levels in blood of 1 mg./100 ml. or higher. Positive results will be obtained on blood from epileptics who may have normal phenobarbitone levels of 5 mg./100 ml. or from patients on long-