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Effects of Hypnotics on Anxious Patients

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Introduction

The sedative effects of single doses of hypnotic drugs in normals are still detectable on behavioural tests 13 hours after administration, and on the electroencephalogram (EEG) at 18 hours (Malpas *et al.*, 1970), and similar results have been noted by other workers (Lader and Walters, 1971). Using measures of driving skill, Betts *et al.* (1972) have also found that normal subjects may be impaired after five doses of amylobarbitone sodium taken over the preceding 36 hours. However, the relevance of all these results to the prediction of effects in patients for whom the drugs are prescribed is uncertain, as our preliminary report indicated (Legg *et al.*, 1973). Here we present the more detailed results of a study carried out on anxious out-patients, using behavioural and EEG measures to determine whether or not persistent effects were present following a course of 7 days treatment with hypnotic drugs.

Method

A group of ten anxious female out-patients with an average age of 55·5 years (range 19 to 57 years), attending for psychiatric treatment and complaining of sleep disorders, was studied. Each patient was seen on four occasions, separated by intervals of one week, and at each visit except the final one each was given a week's supply of tablets to be taken at night, either nitrazepam (5 or 10 mg.), amylobarbitone sodium (100 or 200 mg.), or a placebo. Each received three out of the five possible treatments. The design was a balanced incomplete block (Cochran and Cox, 1957) arranged so that with ten subjects each treatment was given six times. Order effects were balanced, and the patients were allotted randomly to treatment sequences. The study was carried out double blind, and the code was held by the hospital pharmacist.

The drugs and placebos were made up as matching capsules. The dose was one capsule each night, and each treatment was continued for seven consecutive nights. The change from one treatment to another was made on the night following the visit to hospital. Day time placebo tablets were given twice daily throughout the study: no other tranquillizers or night sedatives were prescribed, but one patient continued with phenytoin as an anti-convulsant throughout the study, at a dose of 100 mg. twice daily.

At each attendance at hospital, which was always in the afternoon, the patients were seen by a psychiatrist (D.F.S.), who rated anxiety and sleep disorders using visual analogue scales (Aitken, 1969). The patients were then seen by A.M. for behavioural testing, using digit symbol substitution and card sorting tasks as carried out in previous studies (Malpas *et al.*, 1970). These gave measures both of speed of reaction and of performance. In addition the patients were asked to rate their sleep from the previous night, their feelings at the moment, and also their psychiatric symptoms according to the same visual analogue scales as had been prepared by the psychiatrist and used in his assessment. On their initial and final visits all patients were given the Middlesex Hospital Questionnaire (Crown and Crisp, 1969) which assesses the severity of psychiatric symptoms.

On the second, third and fourth occasions a 30 minute EEG was recorded in a standard manner (Malpas *et al.*, 1970); subsequently the EEGs were masked and coded and then rated blind by two of us independently (D.F.S. and N.J.L.). The first 20 minutes of each record was divided into ten-second epochs, and each epoch was given a score on a four-point scale depending on the main type of electrical activity seen. The criteria, based on previous studies (Malpas *et al.*, 1970; Speirs *et al.*, 1972), are as follows:

0—Any epoch showing alpha activity for more than 50 per cent of the time.

1—Any epoch showing alpha activity for less than 50 per cent of the time, and containing no paroxysmal features of sleep.

2—Any epoch containing one definite paroxysmal feature of sleep, that is vertex sharp waves, spindles at 12 to 14 cycles per second, lambdoid waves (at least 50 microvolts in amplitude), or K complexes.

3—Any epoch showing continuous delta activity for more than 50 per cent of the time.

There was complete agreement between the raters on 15 of the 30 EEGs, but out of the total of 3,600 epochs rated there was a discrepancy in 533. This was invariably of one point and was resolved by discussion between the two raters together and re-examination of the EEGs, which were still masked

and coded. The main difficulty was the transition from stage 0 to 1, since tense individuals may have records in which alpha activity is sparse.

The ratings obtained were then summed to give a total score for each EEG—a measure of both depth and duration of drowsiness and sleep. In addition the time to reach the maximum rating for any two consecutive epochs—the deepest sleep—in the EEG was also determined.

Results

The sleep and symptom ratings obtained on the first visit, before trial medication was begun, were used as a baseline, and the differences between treatments were assessed using an analysis of variance based on the incomplete design.

On the sleep questionnaires the patients rated their sleep as worse after placebo but improved after drug. The ratings for nitrazepam and amylobarbitone were significantly different from placebo ($P < 0.05$) at the higher doses but not at the lower doses, and there was no difference between the two drugs. No consistent hangover effects such as difficulty in waking or a feeling of drowsiness during the day were reported after any treatment.

Analysis of the results from behavioural testing showed no difference between any of the drug regimes and placebo. However the total EEG scores averaged over all patients were higher after drug than after placebo, but only the difference between placebo and nitrazepam 10 mg. reached the 5 per cent level of significance (see Table I). No patient obtained a score of more than 2 on any epoch rated; the time taken to reach this point of 'deepest sleep' was longer after placebo than after any drug treatment ($P < 0.05$) but there was no difference between drugs.

Patients consistently rated their symptoms worse than did the psychiatrist on the visual analogue scales, and these differences were statistically significant ($P < 0.01$, see Table II).

Table I
EEG changes

	EEG sleep ratings (total score over 20 mins.)	Time of onset of 'deepest sleep' reached (minutes)
Placebo	23·9	19·8†
5 mg. nitrazepam ..	69·7	10·7
10 mg. nitrazepam ..	91·3*	10·2
100 mg. amylobarbitone	47·9	11·3
200 mg. amylobarbitone	30·2	14·3

* Differs from placebo value, $p < 0.05$.
† Differs from each drug, $p < 0.05$.

The changes in the patients' rating of their symptoms between the first visit and the fourth showed a small but statistically significant improvement ($P < 0.05$). A similar trend in the doctor's ratings was not significant. Somewhat surprisingly, there were no consistent changes in symptoms with any particular drug treatment, but in general more improvement was noted after drug than placebo. The scores on the Middlesex Hospital Questionnaire were similar to but somewhat higher than those for a female psychiatric population (Crown and Crisp, 1969). There was no change in the scores over the trial period.

Discussion

It is of interest in this study that there was a discrepancy between the psychiatrist's rating and the patients' rating of symptoms using the visual analogue scale (Aitken, 1969). The patients themselves consistently indicated their symptoms as worse than did the psychiatrist, a finding similar to that of Beaumont *et al.* (1970). The main point, however, of the investigation relates to the persistent effects of hypnotics. Whereas in a study of healthy young adults we found both EEG and behavioural changes for as long as 18 hours after the administration of single

Table II
Mean symptom rating on Visual Analogue Scales
Differences between psychiatrist's and patient's assessments

	Placebo	Nitrazepam 5 mg.	Nitrazepam 10 mg.	Amylobarbitone 100 mg.	Amylobarbitone 200 mg.
Psychiatrist	3·6	3·1	2·7	2·5	2·5
Patient ..	4·95	4·90	4·75	4·09	4·05

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doses of hypnotics (Malpas *et al.*, 1970), with anxious patients the results have been different. Behavioural changes were not observed, and though the EEGs rated for drowsiness and sleep did show differences between drug and placebo the levels reached were but a fifth of those obtained by normals (Malpas *et al.*, 1970).

The lack of persistent sedative effects on behavioural measures, and the minor changes in the EEG, may be due in part to the development of drug tolerance, since the hypnotics were taken for seven consecutive nights rather than in a single dose as in our earlier investigations. It is difficult to accept this as the whole explanation of the results, and it does appear that psychiatric patients may react differently to both the therapeutic qualities and unwanted effects of psychotropic drugs. Such a finding is in keeping with the study of Bloomfield *et al.* (1967) and is of considerable importance for the treatment particularly of ambulant psychiatric out-patients, who are undertaking skilled tests such as driving (see Betts *et al.*, 1972). Clearly the present findings indicate that behavioural and EEG testing of drug effects on patients merit further investigation.

Summary

Hypnotics were given in courses lasting seven days to anxious patients in a double-blind placebo controlled study. The effects were assessed weekly on subjective, behavioural and EEG ratings. After a course of drug, but not of placebo, the EEG showed impairment in terms of drowsiness and sleep. Anxious patients appear to have fewer persistent effects of hypnotics than the normals examined in an earlier investigation, a finding of considerable importance to psychiatric practice, and a starting point for future study on ambulant patients.

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References

Aitken, R. C. B. (1969). 'Measurement of feelings using visual analogue scales.' *Proceedings of the Royal Society of Medicine*, **62**, 898–92.

Beaumont, G., Rooney, J. F. F., Murphy, J. E., and Donald, J. F. (1970). 'The use of patients self rating scales in assessment of anxiolytic drugs.' 7th CINP Meeting Prague, Czechoslovakia.

Betts, T. A., Clayton, A. B., and Mackay, G. M. (1972). 'Effects of four commonly-used tranquillizers on low speed driving performance tests.' *British Medical Journal*, **4**, 580–84.

Bloomfield, S. S., Tetreault, L., Lafreniere, B., and Bordeleau, J. M. (1967). 'A method of evaluation of hypnotic agents in man.' *Journal of Pharmacology and Experimental Therapeutics*, **156**, 375–82.

Cochran, W. G., and Cox, G. M. (1957). *Experimental Designs*. London: Chapman and Hall.

Crown, S., and Crisp, A. H. (1969). *Manual of the Middlesex Hospital Questionnaire*. Devon, England: Psychological Test Publications.

Lader, M. H., and Walters, A. J. (1971). 'Hangover effects of hypnotics in man.' *British Journal of Pharmacology*, **41**, 413.

Legg, N. J., Malpas, A., and Scott, D. F. (1973). 'Effects of tranquillisers and hypnotics on driving.' *British Medical Journal*, **1**, 417.

Malpas, A., Rowan, A. J., Joyce, C. R. B., and Scott, D. F. (1970). 'Persistent behavioural and electroencephalographic changes after single doses of nitrazepam and amylobarbitone sodium.' *British Medical Journal*, **2**, 762–5.

Speirs, C. F., Virden, S., and Scott, D. F. (1972). 'A simultaneous plasma level and EEG assessment of an oral hypnotic (Ethinamate).' *European Journal of Pharmacology*, **20**, 127–9.

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