# Hypnotics and hangovers: a pilot study of chlormezanone in general practice

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SUMMARY. Ten patients were included in this pilot study of chlormezanone, assessing its effects on duration and quantity of sleep and daytime performance using a pursuit rotor and a digit symbol test. Comparisons of the sleep assessments favoured chlormezanone, although the differences were not statistically significant. There was no evidence of any reduction in daytime performance after chlormezanone. The comparison of chlormezanone and placebo on the pursuit rotor test and the visual analogue assessment of hangover both slightly favoured the drug, but there were no significant differences. The study has demonstrated that it is feasible to evaluate hypnotic drugs more exactly in general practice.

## Introduction

HYPNOTIC drugs have periodically come under critical review, especially as they are taken by so many people in the Western world (Parish, 1971; Balter *et al.*, 1974; Balter and Bauer, 1975). Most studies in general practice have been of an epidemiological nature (Johnson and Clift, 1968; Grant, 1969), or have addressed themselves to specific aspects such as effectiveness as assessed by the patient (Costello and Smith, 1963; Middleton, 1978) or the likelihood of causing dependence (Clift, 1972). The trend is away from the barbiturates and bromides of earlier days and towards newer drugs, most of which are benzodiazepines, now well established as effective sedatives, fairly safe in overdose and not abused to the same extent as the barbiturates (*British Medical Journal*, 1974). A few other drugs are also available, one of these being chlormezanone, a muscle relaxant. The assessment of a new sleep inducer usually takes place with normal volunteers; this stage is followed by large-scale trials in general practice in order to establish efficacy and freedom from side-effects. Such assessment, quite reasonably, is usually carried out by the subjective reporting of patients, often helped by visual analogue scales (Tune, 1968). The evaluation of hangover effect can be assessed only partially by this method, as it is well known that people may consider themselves perfectly aware and with normal psychomotor function when, in fact, their behaviour belies their statement.

Hangover effects of hypnotic drugs have been carefully assessed using objective tests of psychomotor function (Oswald, 1979) and EMG recordings (Oswald, 1973), both in normal volunteers and in hospital outpatients. It has been suggested (Malpas *et al.*, 1974) that heightened anxiety makes hangover effect less likely. We have been unable to find any objective studies of this phenomenon from general practice, but as most hypnotic drugs are prescribed by general practitioners it is obviously desirable for the doctor to know the likelihood of hangover effect with any particular drug, whether or not it is dose-related, and whether it is more likely to occur in any particular type of psychological profile.

Previous work (Clift, 1975) has shown that, in general practice, most of those presenting with sleep disturbance have an organic basis (such as pain) or a psychiatric illness (such as depressive illness) as the reason for their insomnia, and in these cases there are more appropriate treatments than hypnotic drugs. The remainder of patients can often be helped by a social worker or a psychologist, but a number may also be treated with hypnotic drugs. It is from this group that the patients in this study are drawn.

The problem of hangover related to hypnotic dosage is reviewed in an editorial (*British Medical Journal*, 1980), where the advantages of hypnotics with a short

half-life of less than 8 to 10 hours are studied. In this article chlormezanone is not mentioned. This drug was originally introduced as a muscle relaxant and produces tranquillization through a depressant effect on subcortical areas of the central nervous system (Cohen, 1960). The cerebral cortex is not thought to be significantly affected and hangover effects should in theory be minimal or absent.

## Aim

1. To assess the efficacy of a single dose of chlormezanone in patients with insomnia not requiring other medication for an underlying cause.
2. To measure any residual effects the next day.

## Methods

### *Trial design*

Once we had decided that a hypnotic was to be prescribed, the patient was invited to participate in the trial and told that we were studying the efficacy of a hypnotic drug in current usage. Patients were informed that they would have to visit the surgery each day for a week at 08.30, and that any tablets to be taken would be provided by the doctor. No other sedative drugs were to be taken at the same time. The following patients were excluded:

1. Those under 16 years old.
2. Those weighing less than 50 kg or more than 110 kg.
3. Pregnant patients.
4. Those with known hepatic or renal insufficiency.
5. Patients on any chronic medication other than the contraceptive pill.
6. Patients requiring other medication for any underlying cause of the insomnia.

This was a double-blind cross-over trial of chlormezanone and placebo. Ten patients were included in the study and were randomly allocated to one of the groups shown in Table 1.

Although the trial originally included 12 patients, two withdrew (one from each group), apparently because they were unable to attend for the necessary follow-up appointments. The clinical psychologist did the assessments in the surgery, normally from 08.30 to 09.15. The detailed order of assessment was as follows:

*Day 1: Friday*
Subjects were given:
a) The Anxiety Scale Questionnaire (ASQ; self-analysis form) (Krug *et al.*, 1976). The test was first published in 1957 and it includes the best 40 anxiety items among several thousand personality items which were examined by Cattell and his co-workers. There are five important components in the scale:

| | |
|---|---|
| Factor Q4: | tense/relaxed |
| Factor O: | apprehensive/self-assured |
| Factor C: | emotionally stable/emotionally unstable |
| Factor L: | suspicious/trusting |
| Factor Q3: | uncontrolled/self-controlled |

A further division of items is made into those which appear more cryptic or less obvious (covert anxiety), and those which manifestly refer to anxiety and to anxiety symptoms (overt anxiety). Thus three kinds of score for the test may be obtained: a general anxiety score based on all 40 items, scores on covert and overt anxiety, and a breakdown of total anxiety into five personality components in anxiety.
b) The Digit Symbol Test. This is a sub-test of the Wechsler Adult Intelligence Scale (Wechsler, 1955) and involves the copying of symbols. It requires smooth visual/motor co-ordination. There is a learning factor involved, the amount of learning appearing to depend largely on the adequacy of concentration.
c) The Pursuit Rotor Test. This is a test of visual/motor co-ordination. The subject is required to keep a stylus on a moving spot of light. The time the subject can keep his stylus on the moving spot is measured at 10-second intervals.

**Table 1.** The treatment (tablets) given in the two groups.

| | Day | | | | |
|---|---|---|---|---|---|
| Group | 1 | 2 | 3 | 4 | 5 |
| C/P (chlormezanone/placebo) | None | 2 placebo | 2 chlormezanone | 2 placebo | 2 placebo |
| P/C (placebo/chlormezanone) | None | 2 placebo | 2 placebo | 2 chlormezanone | 2 placebo |

*Day 2. Sunday*
Subjects in Groups 1 and 2 were given two placebo tablets to take on Sunday night.

*Day 3. Monday*
The subjects returned with their record form, consisting of four analogue scales, details of duration of sleep and so on. They were assessed on the Digit Symbol Test and the Pursuit Rotor Test. Subjects in Group 1 were given two chlormezanone tablets to take half an hour before retiring; subjects in Group 2 were given two placebo tablets.

*Day 4. Tuesday*
Subjects returned with the questionnaire and were assessed on the Digit Symbol and Pursuit Rotor tests. Group 1 subjects were given placebo tablets, and Group 2 chlormezanone.

*Day 5. Wednesday*
Questionnaires were returned and subjects assessed on the Digit Symbol and Pursuit Rotor tests. Subjects in both groups were given placebo tablets.

*Day 6. Thursday*
Questionnaires were returned and Digit Symbol and Pursuit Rotor tests given. Subjects in both groups were given no treatment (that is, no tablets).

*Day 7. Friday*
Questionnaires were returned. Digit Symbol and Pursuit Rotor tests were given. No treatment.

### *Questionnaires*

The patients recorded the length of time needed to get to sleep and the duration of sleep, together with a visual analogue assessment of quality of sleep, quantity and content of dreams and any hangover effects. The scores from the ASQ (Krug *et al.*, 1976) were recorded for each patient on entry to the study.

### *Time involved*

The time needed by the psychologist was as follows:

| | |
|---|---|
| 1. ASQ | 5–10 minutes |
| 2. Digit Symbol Test | 1½ minutes |
| 3. Pursuit Rotor Test | 9 minutes |

**Table 2.** Anxiety scores of all patients.

| Patient number | Group | Sex | Age | Component Q3 | C | L | O | Q4 | Anxiety score |
|---|---|---|---|---|---|---|---|---|---|
| 1 | C/P | F | 20 | 11 | 2 | 3 | 15 | 14 | 45 |
| 4 | C/P | M | 31 | 0 | 5 | 0 | 4 | 5 | 14 |
| 6 | C/P | F | 64 | 7 | 7 | 5 | 12 | 17 | 48 |
| 7 | C/P | M | — | 8 | 6 | 5 | 12 | 15 | 46 |
| 11 | C/P | F | — | 5 | 4 | 3 | 13 | 16 | 41 |
| 2 | P/C | F | 30 | 3 | 0 | 2 | 4 | 8 | 17 |
| 5 | P/C | M | 24 | 9 | 8 | 2 | 12 | 12 | 43 |
| 9 | P/C | F | 28 | 12 | 7 | 5 | 13 | 17 | 54 |
| 10 | P/C | M | 56 | 7 | 2 | 6 | 12 | 15 | 43 |
| 12 | P/C | F | 32 | 14 | 9 | 5 | 17 | 17 | 62 |
| Mean (standard deviation) | | | | | | | | | 41.3 (11.4) |

*Patient characteristics*

Of the 10 patients, half were in Group C/P and half in Group P/C; there were three women and two men in each group.

*Statistics*

The small size of the study precluded parametric statistical analysis. The best of the non-parametric tests is the Wilcoxon Matched Pairs Test, which was used throughout the study (Siegel, 1956).

## Results

### Anxiety scores (ASQ)

On entry to the study, the anxiety score for each patient was determined as a total score and also as the five separate components listed above (see Table 2). Eight patients demonstrated high levels of anxiety, their scores being above the 90th percentile on the normal distribution curve. Amongst the general population the anxiety score mean is 41.3 (s.d. 11.4).

### Effects of chlormezanone or placebo

Mean or median values are shown separately for the two groups, but statistical tests were confined to comparisons of chlormezanone and placebo on the third and fourth nights, based on the combined data.

*1. Time to get to sleep*

An estimate of the time to get to sleep was obtained by taking the difference between the time recorded for going to bed and the last time recorded before going to sleep. Median, rather than mean values, were used. The combined medians for chlormezanone and placebo were 1 h 8 min and 1 h 5 min respectively, and there was no significant difference.

*2. Duration of sleep*

The duration of sleep was determined by taking the difference between the last time recorded before going to sleep and the time on waking. The combined chlormezanone mean was 6 hr 12 min (s.d. = 1 h 10 min) compared with 5 h 41 min (s.d. = 1 h 31 min) for the corresponding placebo assessment. Although eight out of 10 patients recorded longer durations of sleep on chlormezanone compared with placebo, the difference was not statistically significant.

*3. Quality of sleep*

The quality of the patient's sleep was assessed on a standard 10 cm visual analogue line as a deterioration from "the best undisturbed sleep ever". The combined chlormezanone mean was 39.6 mm (s.d. = 26.5 mm) compared with 53.6 mm (s.d. = 27.6 mm) for the corresponding placebo assessment. Although eight out of 10 patients rated the quality of their sleep as better after chlormezanone than placebo, the difference was not statistically significant.

*4. Quantity of dream*

The quantity of dreams was recorded by the patient on a 10 cm visual analogue scale. Since the left-most point on the line corresponds to "most of the night spent dreaming", an increase in distance represents a reduction in the time spent dreaming. The combined chlormezanone mean was 80.3 mm (s.d. = 32.6 mm) compared with 81.8 mm (s.d. = 31.0 mm) for the corresponding placebo assessment, an insignificant difference.

*5. Content of dreams*

Where relevant, the patients made a visual analogue assessment of the content of their dreams on a 10 cm line from 0 ("dreams exceptionally vivid or unpleasant") to 100 mm ("cannot remember anything about the dreams except they were present"). It was not possible to calculate mean or median values, as several patients did not complete the scale. No statistical comparison of chlormezanone and placebo was possible.

*6. Hangover*

The patients made an assessment of the severity of any hangover effect on a 10 cm visual analogue scale. The distance measured was from the left-most point, corresponding to "woke up refreshed and completely clear-headed", and so a reduction represents an improvement. The combined chlormezanone mean was 39.5 mm (s.d. = 22.9 mm) compared with 58.4 mm (s.d. = 20 mm) for the corresponding placebo assessment. The difference was not statistically significant.

*7. Pursuit rotor*

On each assessment day, six one-minute trials were carried out and separate figures were recorded for the six 10-second periods within each. It was thus possible to examine changes within and between the six trials and so test for any difference in performance, for example at the beginning or end of a trial. With this in mind, the best statistic to summarize the patient's performance may be selected; for example, the results from the first 10-second period from each trial could be excluded. It

**Table 3.** Pursuit rotor scores and anxiety scores.*
a) Group C/P (chlormezanone/placebo).

| Patient number | Sex | Age | Anxiety score (ASQ) | Pursuit rotor—mean value (seconds) | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Baseline | Placebo | Chlormezanone | Placebo | Placebo | No treatment |
| 1 | F | 20 | 45 | 6.328 | 6.165 | 7.451 | 5.923 | 5.978 | 6.616 |
| 4 | M | 31 | 14 | 9.323 | 9.634 | 9.665 | 9.717 | 9.614 | 9.778 |
| 6 | F | 64 | 48 | 5.639 | 6.759 | 6.978 | 7.391 | 8.085 | 7.998 |
| 7 | M | — | 46 | 7.422 | 8.149 | 8.859 | 9.184 | 9.175 | 9.351 |
| 11 | F | — | 41 | 3.635 | 4.996 | 5.706 | 3.596 | 6.293 | 6.349 |
| Mean | | | | 6.469 | 7.141 | 7.732 | 7.162 | 7.829 | 8.018 |
| Standard deviation | | | | 2.109 | 1.798 | 1.562 | 2.496 | 1.647 | 1.551 |

b) Group P/C (placebo/chlormezanone).

| Patient number | Sex | Age | Anxiety score (ASQ) | Pursuit rotor—mean value (seconds) | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Baseline | Placebo | Placebo | Chlormezanone | Placebo | No treatment |
| 2 | F | 20 | 17 | 6.543 | 7.222 | 8.154 | 7.537 | 8.287 | 8.304 |
| 5 | M | 24 | 43 | 8.500 | 9.174 | 9.535 | 9.583 | 9.639 | 9.745 |
| 9 | F | 28 | 54 | 7.093 | 8.484 | 8.911 | 9.083 | 9.476 | 9.491 |
| 10 | M | 56 | 43 | 6.972 | 7.754 | 8.233 | 8.354 | 8.278 | 8.289 |
| 12 | F | 32 | 62 | 4.294 | 3.399 | 5.354 | 6.029 | 3.721 | 6.321 |
| Mean | | | | 6.680 | 7.207 | 8.037 | 8.117 | 7.880 | 8.430 |
| Standard deviation | | | | 1.523 | 2.253 | 1.601 | 1.400 | 2.412 | 1.354 |

*Further details of the scores given below are available from the authors.

was found that there were no consistent trends in the mean values and so it was decided to use the simple mean of all 36 values on each assessment day to examine changes over the course of the study. The combined mean taking all values together for the chlormezanone assessment was 7.925 sec (s.d. = 1.413 sec) compared with 7.600 sec (s.d. = 2.030 sec) for the corresponding placebo assessment. The difference was not statistically significant.

The anxiety scores were plotted out against each patient's mean pursuit rotor performance (average over the six days) (see Table 3). The pursuit rotor performance did tend to be reduced amongst patients with high anxiety scores but the correlation was not statistically significant (Spearman rank correlation coefficient, $r_s = 0.336$). However, it was evident that the performance was rather better amongst male patients. Since the male patients also had slightly lower anxiety scores, a larger study would be needed to establish any relationship between anxiety scores and pursuit rotor performance, taking the sex and also the age of the patient into account.

*8. Digit symbol test*

A maximum score of 90 was possible. The combined mean for the chlormezanone assessment was the same, 65.3 (s.d. = 23.7) compared with 65.2 (s.d. = 24.1) for the corresponding placebo assessment.

*9. Side-effects*

Only one patient (no. 4) reported a side-effect—at the end of the study he reported a tendency to get a headache mostly over the left ear. He also reported that his eyes watered.

## Discussion

This was a pilot study and the results do not allow a firm conclusion about after-effects when chlormezanone is used as a hypnotic.

It is interesting to observe the difficulty we found in getting together a number of patients suitable for this trial. It is now practice policy to treat sleep disturbance rationally (Clift, 1975), and as a result very few patients are in need of hypnotics. Of those who were deemed suitable, mainly people with insomnia of unknown origin or with insomnia associated with temporary anxiety, many found difficulty in making the necessary visits to the surgery, first thing in the morning, for psychomotor testing. The method itself demanded a considerable degree of perseverance on behalf of the psychologist, who had to attend regularly before his day's work started.

These difficulties obviously were overcome and it would be quite feasible to mount a similar trial collecting a larger number of patients over a much longer

period of time. Our results certainly do not suggest any hangover effect with chlormezanone and it seems likely that it does not differ significantly from placebo in this respect. Its value must therefore rest on its efficacy as a sleep-inducer. Previous reports on chlormezanone usage in healthy normal subjects (Friesewinkel, 1961; Linnoila, 1972) have shown no reduction in psychomotor performance, but as far as is known there has been no previous report on this effect when it is used as a hypnotic. Our own trial suggests that chlormezanone does have a mild hypnotic effect but the results do not permit us to draw firm conclusions.

Perhaps the most valuable feature of this trial is that it demonstrates that objective testing of psychomotor performance can be achieved with ordinary patients in a general practice setting. Because vast amounts of hypnotics are prescribed by general practitioners, it seems reasonable to study the side-effects of these drugs in the same environment, where the predisposing factors such as anxiety are present, and where any placebo effect associated with the doctor (Balint, 1957) is also weighed in the balance.

Several new hypnotics (*British Medical Journal*, 1980) with short half-lives and good margins of safety are now available and it would be of value to have a comparison in general practice conditions. Such a trial should include not only the study of hangover effects but also efficacy as sleep inducers, effect on dreams, effects of withdrawal, tolerance, toxic effects and, of course, an assessment of the development of dependence. The long-acting benzodiazepines such as nitrazepam and flurazepam may well be safe in overdose, but the patient is not immune from habituation (Clift, 1972) or hangover effect (Oswald, 1979). New drugs now being introduced need to prove themselves better in these respects.

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# Diabetes

The overnight urinary albumin excretion rate (AER) of 87 patients with insulin-dependent diabetes mellitus was measured in 1966–67. Fourteen years later information was obtained on 63 of the original cohort; those alive were restudied, and for those who had died relevant clinical information and cause of death were recorded. The development of clinical diabetic nephropathy ('Albustix'-positive proteinuria) was related to the 1966–67 AER values. Clinical proteinuria developed in only two of 55 patients with AER below 30 μg/min but in seven of eight with AER between 30 and 140 μg/min. Elevated levels of micro-albuminuria strongly predict the development of clinical diabetic nephropathy. These levels of AER are potentially reversible, and their detection and treatment may prevent diabetic renal disease.

Source: Viberti, G. C., Jarratt, R. J., Mahmud, U. *et al* (1982). Micro-albuminuria as a predictor of clinical nephropathy in insulin-dependent diabetes mellitus. *Lancet,* **1,** 1430-1432.