HYPNOTICS AND SHIFT WORK

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Sleep disturbance associated with working irregular hours has been studied by several authors (Tune, 1969; Kripke, Cook, & Lewis, 1971; Foret & Lantin, 1972; Ehrenstein & Muller-Limroth, 1975; Knauth & Rutenfranz, 1975; Knauth & Ilmarinen, 1975; and Masterton, 1965), while the effects of working in unusual environments have been investigated in polar explorers (Lewis, 1961; Natani, Shurley, Pierce, & Brooks, 1970), in man in the arctic (Semagin, 1961; Weitzman, deGraff, Sassin, Hansen, Gotlibsen, Perlow, & Hellmann, 1975), antarctic (Patterson, 1975) and in solitude underground (Mills, 1964), and in submariners (Kleitmen, 1949) and astronauts (Adey, Kado, & Walter, 1967; Kelloway, 1966). Aircrew involved in world-wide operations also work at unusual times and have to cope with time zone changes (Klein, Bruner, & Ruff, 1966; Nicholson, 1970). In each case a satisfactory sleep pattern is important in maintaining well-being and operational efficiency, and careful planning of work schedules is usually the most important approach to the problem.

Studies on the work-rest patterns of aircrew operating world-wide (Figures 1 & 2) suggest that in carefully controlled schedules sleep disturbance rather than sleep loss is the problem. Modification of the sleep pattern within rest periods plays a particularly important role (Figure 3), but, nevertheless, the irregular nature of their work and rest causes difficulties even though the time available for sleep usually appears to be of sufficient duration. It may be difficult to cope with some reduction in sleep when this is superimposed on an irregular pattern of rest. For this reason hypnotics have been used. However, the drug must not only be effective at times of the day when the period for rest may not coincide with the circadian desire for sleep, but must also be free of residual effects on performance. It is these aspects of the use of hypnotics in the management of disturbed rest which have been of particular interest to our group, and studies have led to advice on the use of hypnotics by aircrew in the United Kingdom. Though this work has been directed toward aircrew, it is equally relevant to other shift workers involved in skilled activity.

Performance Studies

Residual impairments of performance with the overnight ingestion of hypnotics have been clearly established over the past few years, but it is now clear that residual sequelae are not an inevitable concomitant of a useful hypnotic. It is true that many of the commonly used hypnotics have residual effects on performance in doses within their normally accepted therapeutic range, but hypnotics free of residual sequelae are now available. Several centres have been involved with the problem of residual effects, and a variety of tasks have been used to detect impaired performance the next day. Our work has been concerned mainly with visuo-motor coordination (Borland & Nicholson, 1974) and the residual and immediate effects related to dose and time have been investigated. The results are broadly similar between the various groups involved.

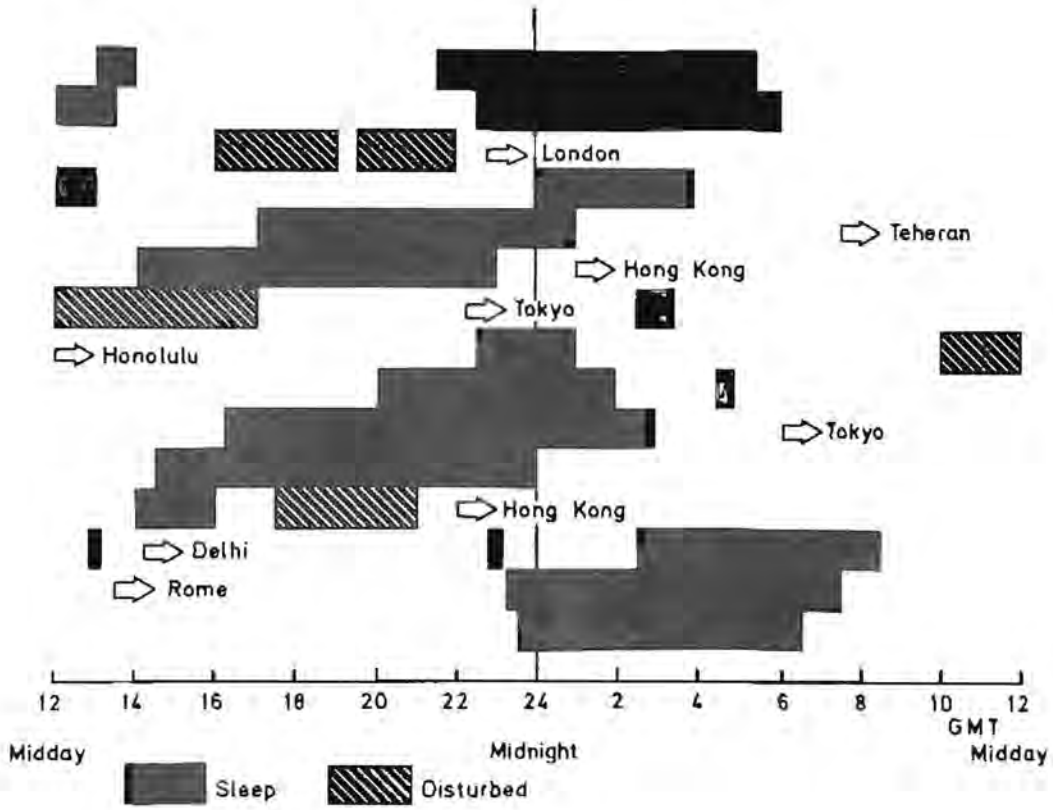

Figure 1. Sleep pattern during an eastward flight from London to Honolulu and return. The flight was via Rome, Delhi, Hong Kong, and Teheran. The illustration is read from the bottom line up. The pilot slept from 2300 to 0630 hours GMT London preceding the flight to Rome. Periods of sleep which were considered by the pilot to be satisfactory are in black rectangles, and disturbed sleep is hatched.

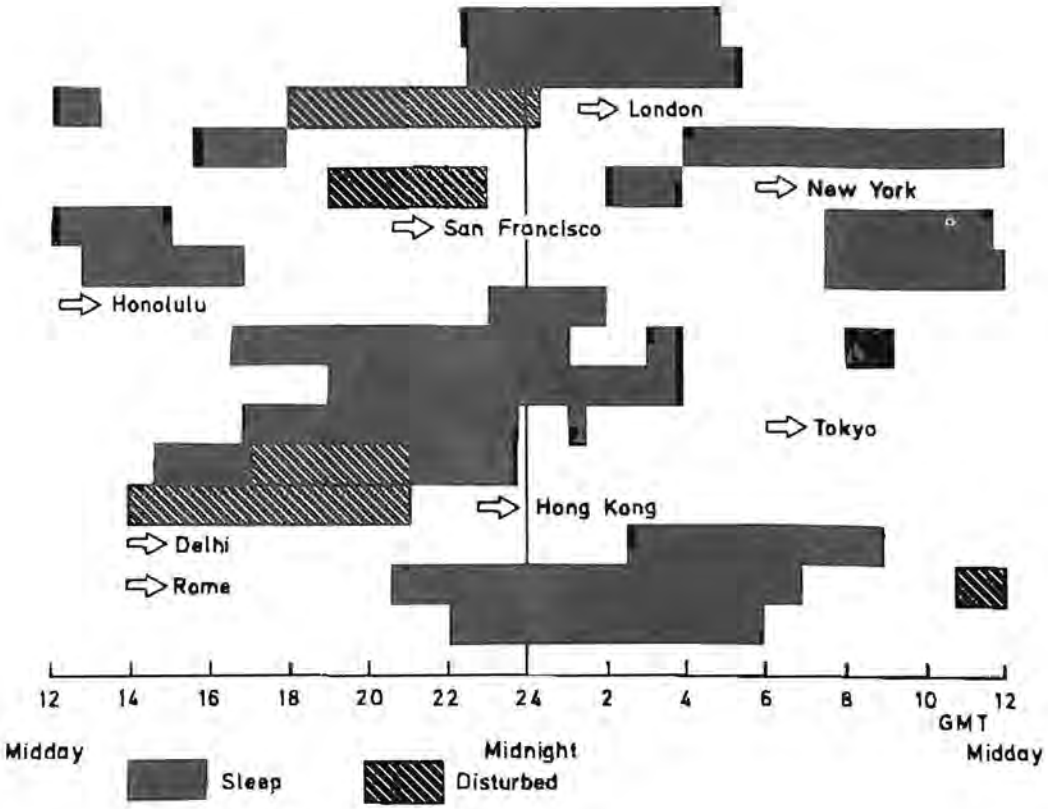

Figure 2. Sleep pattern during an eastward round-the-world flight via Tokyo. The illustration is read from the bottom line up. The pilot slept from 2200 to 0600 hours GMT London preceding the flight to Rome.

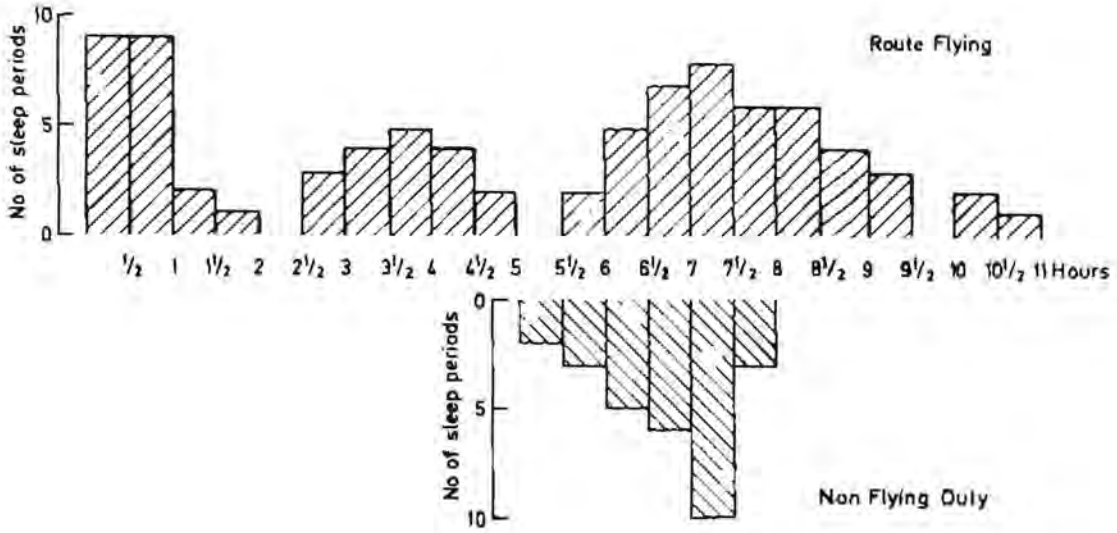

Figure 3. Histogram of duration of individual sleep periods during non-flying duty and during route flying. The data cover one month. It can be seen that the sleep periods include naps of approximately 1/2-1 hour duration, short periods of sleep of around 3 1/2-4 hours and periods of sleep of normal length.

The task requires the subject to position a spot inside a randomly moving circle displayed on an oscilloscope. The movement of the spot is controlled by a hand-held stick, and an error signal, proportional to the distance between the spot and the centre of the circle, controls the difficulty of the task by modulating the mean amplitude of the movement of the circle. The technique provides the adaptive component which maintains optimum performance by the operator. At the start of each experiment the circle is stationary. The subject positions the spot inside the circle, and with a negative error signal the circle moves away from the spot. When the spot can no longer be maintained inside the target circle due to the increasing difficulty of the task, the task becomes less demanding. At zero error the task requires about 25 s to reach maximum difficulty, whereas a constant displacement between the spot and the centre of the circle of 4 cm reduces the task to zero difficulty within 6 seconds. Subjects are aware of the penalty of error signals, and so they try to avoid all errors, though the task does not permit the maximum performance level to be reached.

Experiments were carried out in sound-attenuated and air-conditioned rooms. The subjects were required to attain a steady performance level before drug studies were carried out. In those familiar with the technique, steady performance was reached within about 5 days' practice, but novices usually required at least 2-3 weeks practice to achieve this level. Each assessment lasted 10 mins and trained subjects attained their plateau of performance within the first 100 s of the run. The mean amplitude of the task over the final 500 s was computed, and this was the performance measure. The subjects were informed at this time when the period of time commenced. Healthy male volunteers (age range 21-45 years), who were not involved in any form of therapy acted as subjects. Instructions were given to avoid alcohol but there were no restrictions on the consumption of non-alcoholic beverages.

Barbiturates

Initial studies were carried out with heptabarbitone and pentobarbitone sodium. With heptabarbitone decrements in performance were observed 10 h after 200 mg, 10 & 13 h after 300 mg and 10, 13, 16 & 19 h after 400 mg (Borland & Nicholson, 1974), and with pentobarbitone sodium the residual sequelae during the day after overnight ingestion of 200 mg were very similar to those observed with heptabarbitone 400 mg (Borland & Nicholson, 1975a). The residual effects on visuo-motor coordination were related to dose both in their persistence and in the decrement at a given time interval (Figure 4), and in this way the studies supported previous investigations (Von Felsinger, Lasagna & Beechler, 1953; Malpas, Rowan, Joyce & Scott, 1970; Bond & Lader, 1972) and showed, as did Kornetsky, Vates and Kessler (1959), that impaired performance may be more severe and may persist longer with higher doses which are still, nevertheless, within the usually accepted therapeutic range.

1,4-Benzodiazepines

Preliminary studies with barbiturates had established the sensitivity of a tracking task to the residual sequelae of drugs both in relation to time and to dose, and so the technique was used in the investigation of the benzodiazepines (Borland & Nicholson, 1975b). It was found that, although performance was impaired 16 h after flurazepam hydrochloride (30 mg) and to, at least, 19

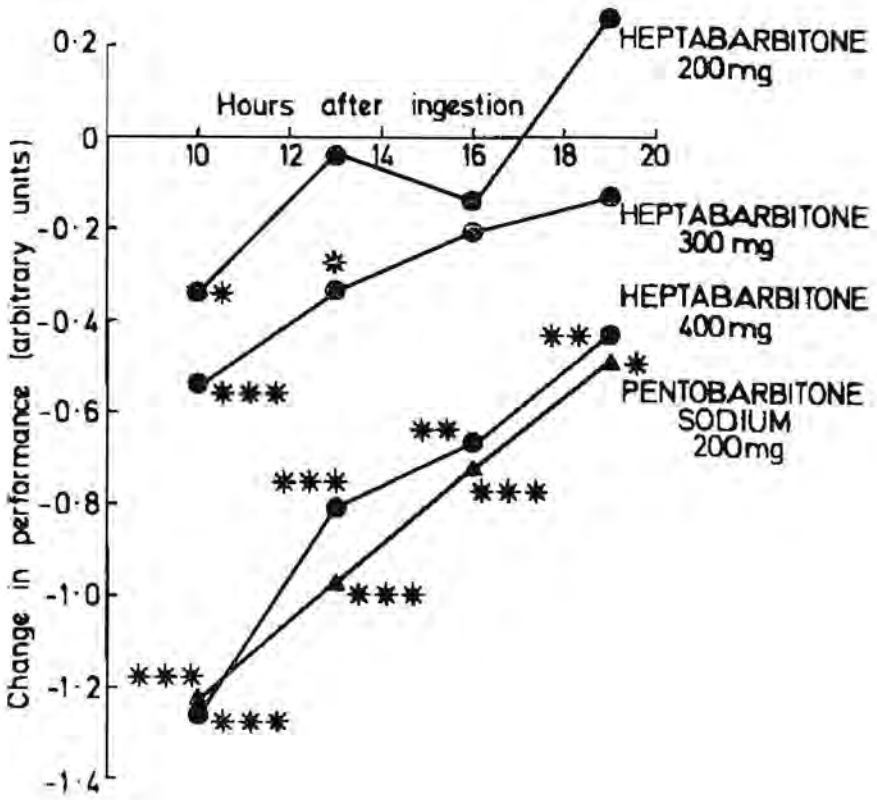

Figure 4. Effect of 200, 300, & 400 mg heptabarbitone and 200 mg pentobarbitone sodium on visuo-motor coordination (arbitrary units). Significance levels: * $p < .05$; ** $p < .01$; *** $p < .001$.

h after nitrazepam (10 mg), the effects with diazepam (10 mg) were more limited (Figure 5). Studies on the immediate effects of diazepam (10 mg) showed that performance decrements were limited to a few hours after ingestion and that there was little likelihood of residual impairment with overnight ingestion as long as the dose did not exceed 10 mg (Borland & Nicholson, 1977).

A detailed analysis of the effects of diazepam and its metabolites, 3-hydroxydiazepam (temazepam) and 3-hydroxy, N-desmethyldiazepam (oxazepam) (Clarke & Nicholson, 1978) was then carried out. Performance was observed from 10-16 h after overnight ingestion of diazepam (5 & 10 mg), temazepam (10, 20 & 30 mg) and oxazepam (15, 30 & 45 mg) and from 0.5-6.5 h after morning ingestion of diazepam (10 mg), temazepam (20 mg) and oxazepam (30 mg). Coordination was not altered with the overnight ingestion of diazepam (5 & 10 mg) (Figure 6), temazepam (10,20 & 30 mg)(Figure 7) or oxazepam (15 & 30 mg) (Figure 8). However, with 30 mg temazepam there was a trend toward impaired performance and with 45 mg oxazepam there was a decrement in performance 10 h after ingestion. With morning ingestion visuo-motor coordination was impaired at 0.5 & 2.5 h after 10 mg diazepam, at 0.5 h after 20 mg temazepam, and at 2.5 & 4.5 h after 30 mg oxazepam (Figure 9).

These observations were in broad agreement with other studies. Similar results with diazepam were reported by Seppala, Kortilla, Hakkinens, and Linnoila (1976) with coordination skills and visual functions related to driving. Recovery within a few hours after ingestion of diazepam has been observed by Hart, Hill, Bye, Wilkinson, and Peck (1976) with performance at a variety of tasks including auditory vigilance, reaction time, short term memory and digit symbol substitution. With temazepam our results were comparable with those of Hindmarch (1975), and suggested a residual effect with the 30 mg dose. Other workers have observed the slow onset of impaired performance with oxazepam, and Molander and Duvhok (1976) have recorded maximum depression of critical flicker fusion frequency 3.0 h after ingestion of 20 & 40 mg oxazepam and impaired coordination with 40 mg oxazepam.

It is clear that diazepam and its hydroxylated metabolites may be free of residual sequelae within certain dose ranges. However, there are certain points to be taken in to consideration when using these drugs. With diazepam 10 mg daily, accumulation of its long-acting metabolite, nordiazepam, is likely, and so diazepam is for occasional use as an hypnotic. Temazepam and oxazepam have the advantage over diazepam that their metabolism is not complicated by a long-acting metabolite, and daily ingestion of these drugs would therefore not be contraindicated, though the relatively slow absorption of oxazepam indicated by the delayed appearance of performance decrements could reduce its usefulness as an hypnotic.

More recently, flunitrazepam has been introduced. A dose of 1-2 mg taken at night leads to impaired performance the next day (Bond & Lader, 1975) and has adverse effects on sleep with unpleasant and emotional dreams (Monti & Altier, 1973; Jovanovic, 1977; Gaillard & Phellipeau, 1977). However, smaller doses may be more useful, and in this context recent studies using visuo-motor coordination (Nicholson & Stone, 1980) have shown that with 0.25 mg performance is impaired for only 2.0 h after ingestion, and that with doses up to 0.50 mg overnight there are no residual effects (Figure 10).

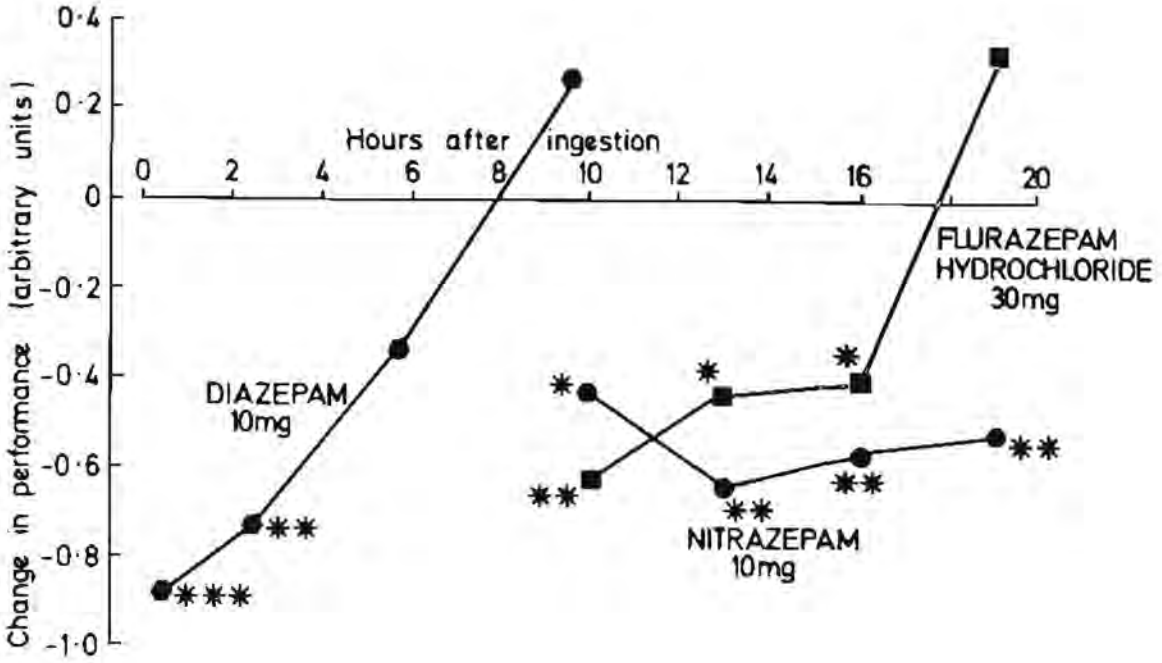

Figure 5. Effect of 10 mg diazepam ingested in the morning, and 10 mg nitrazepam and 30 mg flurazepam hydrochloride ingested overnight on visuo-motor coordination (arbitrary units). Significance levels: * P <.05; ** p < .01; *** p <.001.

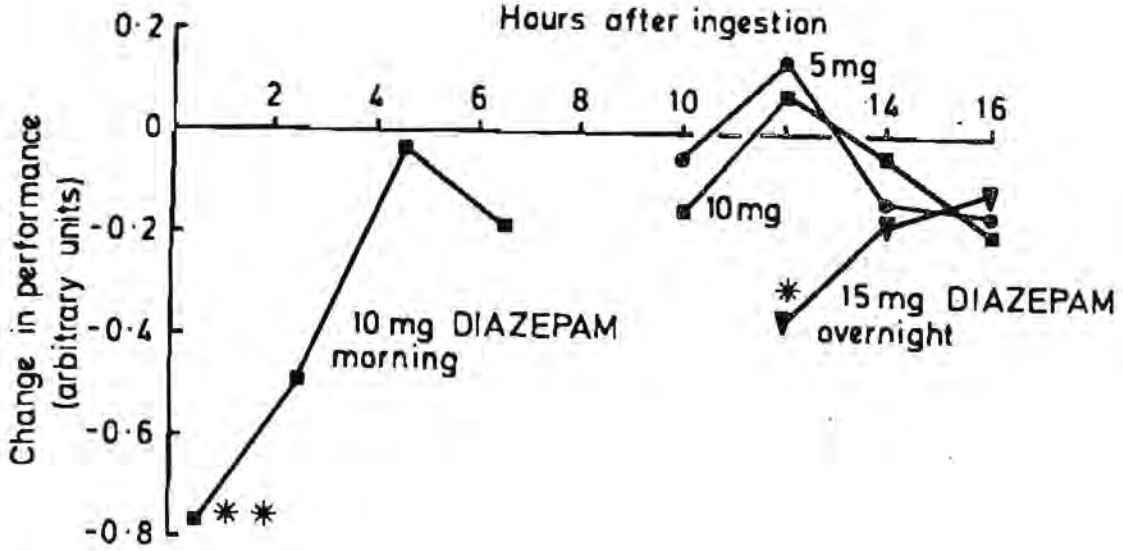

Figure 6. Effect of 10 mg diazepam ingested in the morning, and 5, 10, & 15 mg diazepam ingested overnight on visuo-motor coordination (arbitrary units). Significance levels: * $p < .05$; ** $p < .01$; *** $p < .001$.

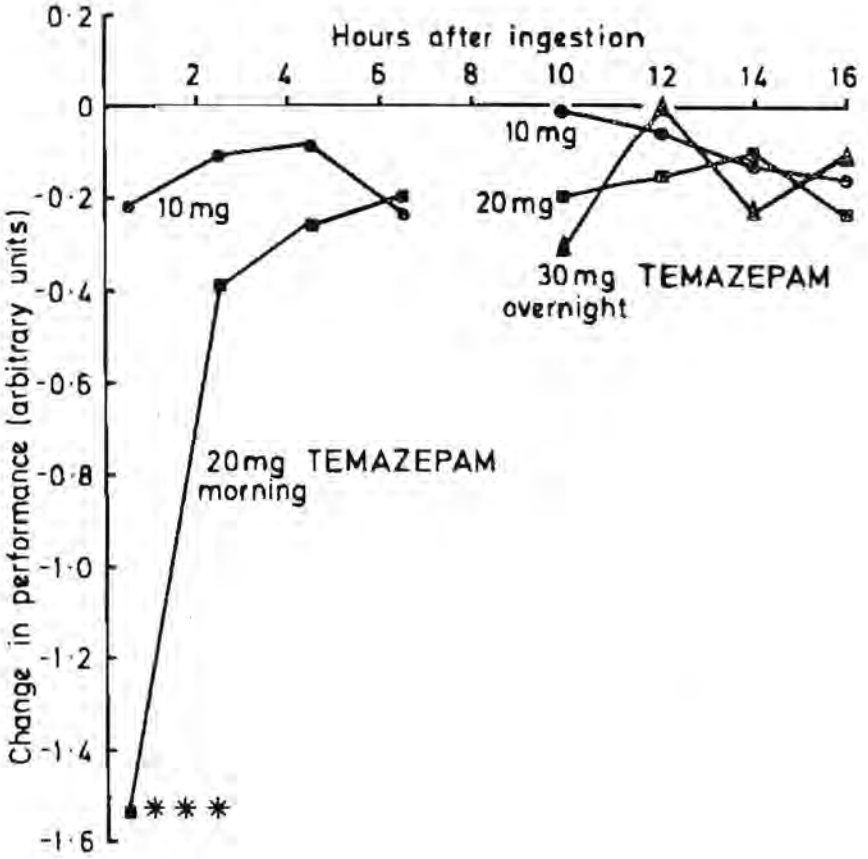

Figure 7. Effect of 10 & 20 mg temazepam ingested in the morning, and 10, 20, & 30 mg temazepam ingested overnight on visuo-motor coordination (arbitrary units). Significance level: *** $p < .001$.

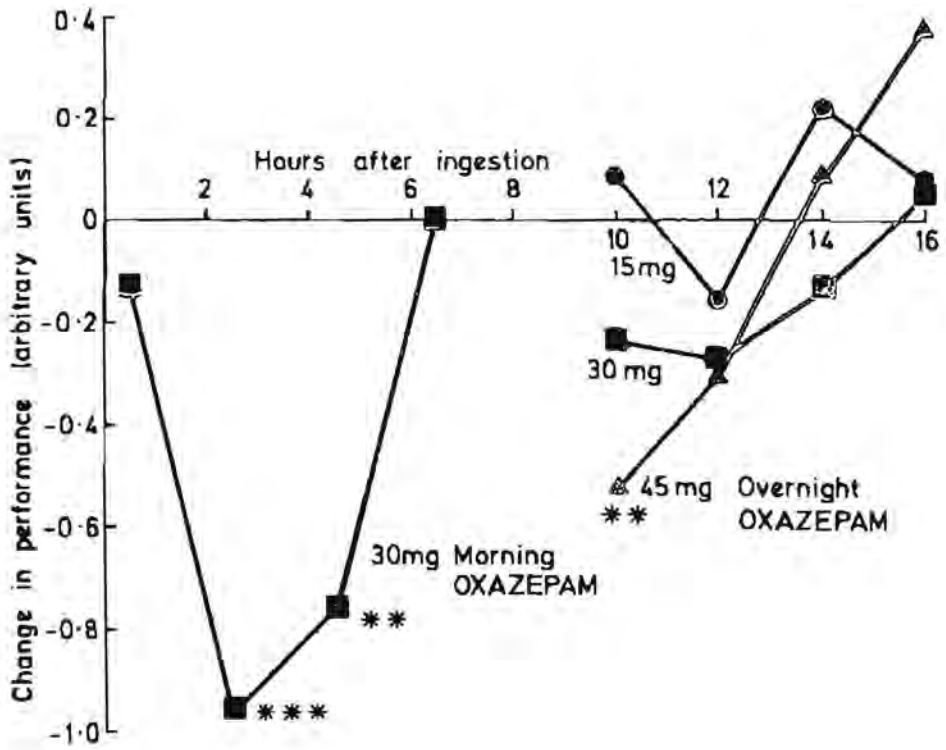

Figure 8. Effect of 30 mg oxazepam ingested in the morning, and 15, 30, & 45 mg oxazepam ingested overnight on visuo-motor coordination (arbitrary units). Significance levels: ** $p < .01$: *** $p < .001$.

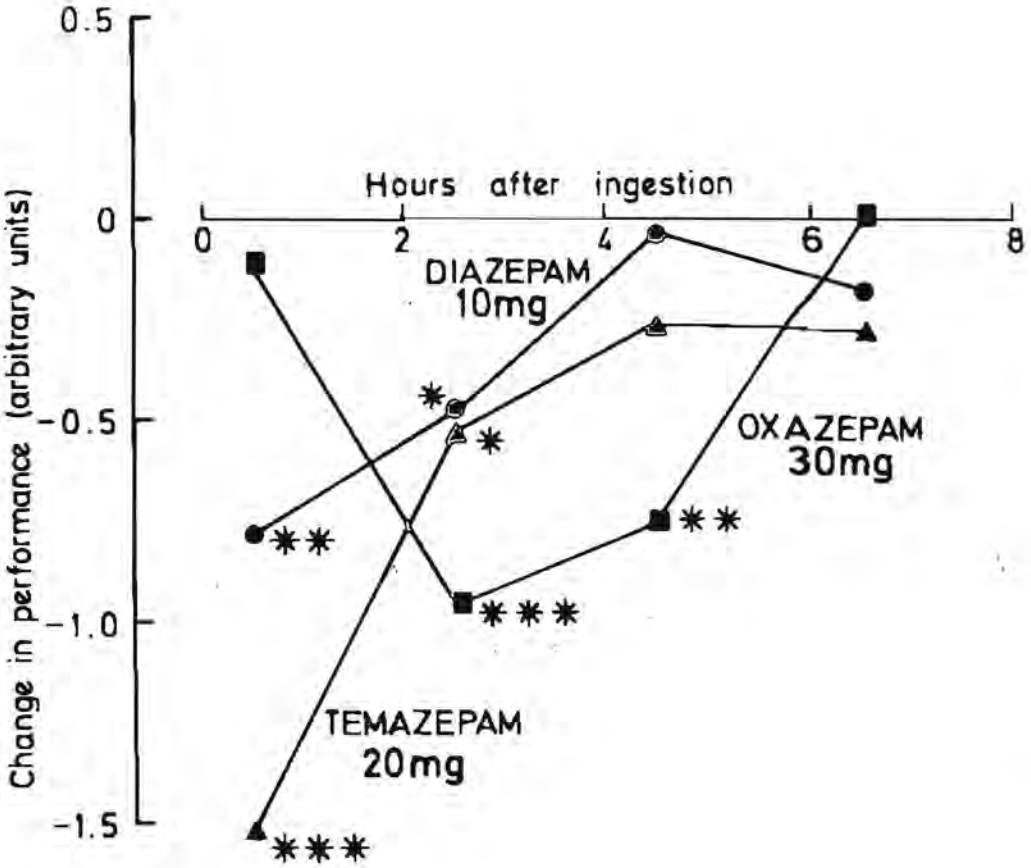

Figure 9. Effect of 10 mg diazepam, 20 mg temazepam, and 30 mg oxazepam ingested in the morning on visuo-motor coordination (arbitrary units). Significance levels: * $p < .05$; ** $p < .01$; *** $p < .001$.

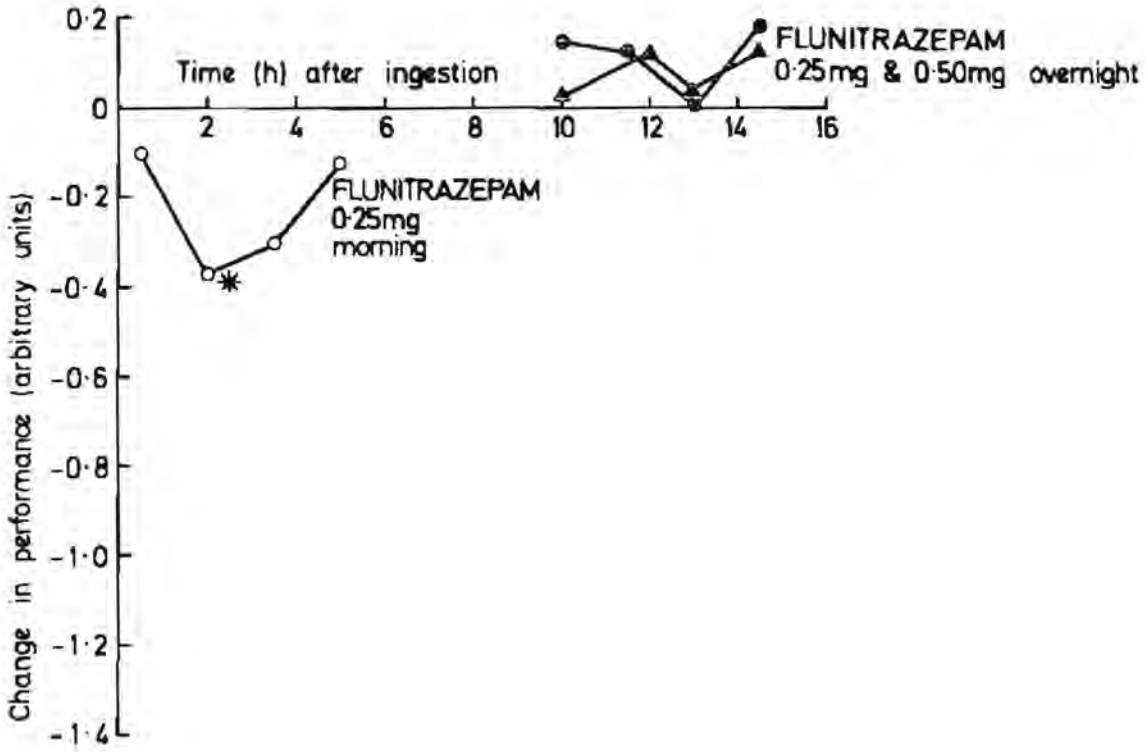

Figure 10. Effect of 0.25 mg flunitrazepam ingested in the morning, and 0.25 & 0.50 mg flunitrazepam ingested overnight on visuo-motor coordination. Significance level: * $p < .05$.

Triazolo-Benzodiazepines

A disadvantage of the use of diazepam is its long-acting metabolite, nordiazepam, and to avoid this pathway heterocyclic ring structures have been added across the 1- and 2-positions. Triazolam, which is an example of a triazolo-benzodiazepine with an ortho chlorophenyl group (Rudzik, Hester, Tang, Straw, & Friis, 1973), has relatively short half life (Eberts, Ko, & Thomas, 1978). However, triazolam around 1 mg has residual effects on performance (Veldkamp, Straw, Metzler, & Demissianos, 1974) and smaller doses may be more appropriate. Studies using visuo-motor coordination (Nicholson & Stone, 1980) have shown that with 0.25 mg triazolam performance is impaired for about 5.0 h after ingestion, but there are no residual effects with overnight ingestion. With 0.50 mg triazolam there are residual effects but these have disappeared within 11.5 h of ingestion (Figure 11).

Sleep Studies

Diazepam and its hydroxylated metabolites, as well as flunitrazepam and triazolam, may be appropriate hypnotics for persons involved in skilled activity, and so we have examined their effects on sleep. With diazepam and its metabolites the investigations have included observations in young adulthood (Nicholson & Stone, 1976, 1978) and in middle age (Nicholson & Stone, 1979a) and on their effectiveness for inducing sleep during the day (Nicholson & Stone, 1979b), which may be relevant to the management of sleep disturbance associated with irregular work. Studies with flunitrazepam and triazolam are less well advanced, but their effectiveness for sleep in young adults in doses free of residual effects has been studied (Nicholson & Stone, 1980).

The subjects were healthy male volunteers familiar with the labratory and with the techniques used in sleep recording. They were required to refrain from napping and undue exercise, and to abstain from caffeine and alcohol after mid-day on the days with overnight sleep recordings and during the whole day for day-time recordings. The laboratory was sound attenuated and temperature and humidity were controlled. Recordings were made with silver-silver chloride electrodes placed according to the 10:20 system. Electroencephalographic activity was recorded from the F_1-F_7 or C_4-A_1, P_1-T_5 and O_2P_z-O_3 positions. The electromyogram was recorded from the right eye-mastoid or nasion and the left eye-mastoid or nasion. Each sleep record was scored in 30 s epochs according to the scheme of Rechtschaffen and Kales (1968) and each night's sleep was then analysed for various measures.

The subjects completed assessments of sleep and well-being related to a 100 mm analogue scale 0.5 h after awakening. The assessments and the extremes of the scales were, I slept, Very poorly - Very well, Now I feel, Very sleepy - Wide awake, I fell asleep, Never - Immediately and After I fell asleep I slept, Very badly - Very well.

Studies in Young Adulthood
(Figure 12)

Investigations with diazepam (5 & 10 mg), temazepam (10 & 20 mg) and oxazepam (15, 30 & 45 mg) were each carried out in six males aged between 19 & 43 years (Nicholson & Stone, 1976, 1978). Total sleep time was increased with 10

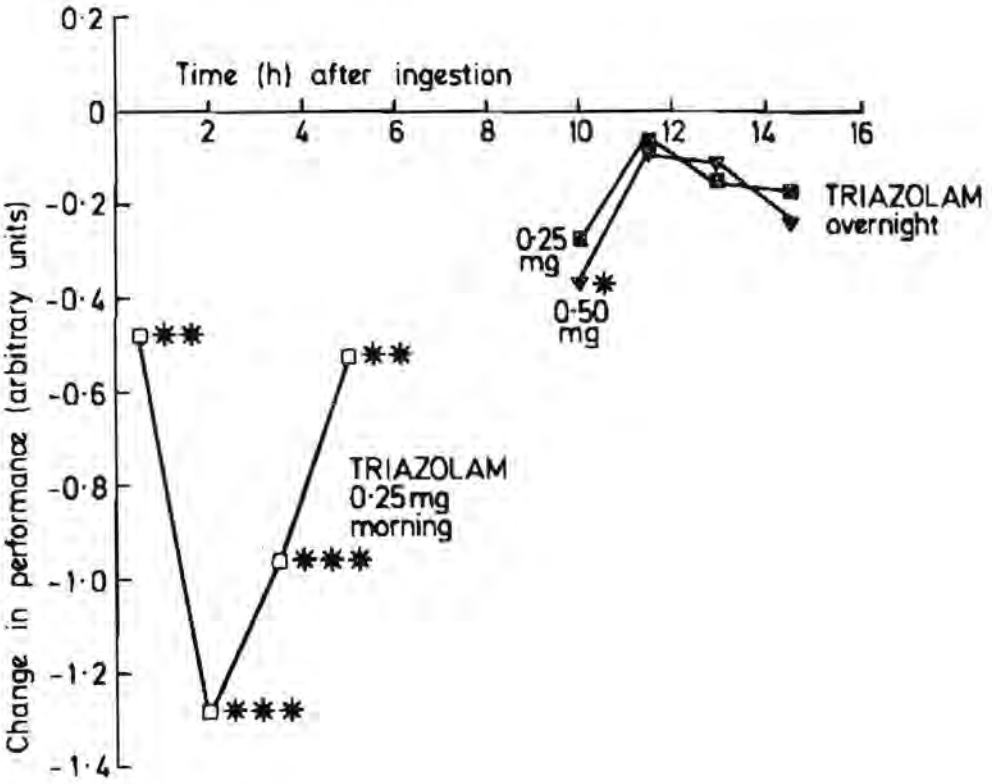

Figure 11. Effect of 0.25 mg triazolam ingested in the morning and 0.25 & 0.50 mg triazolam ingested overnight on visuo-motor coordination. Significance levels: * $p < .05$; ** $p < .01$; *** $p < .001$.

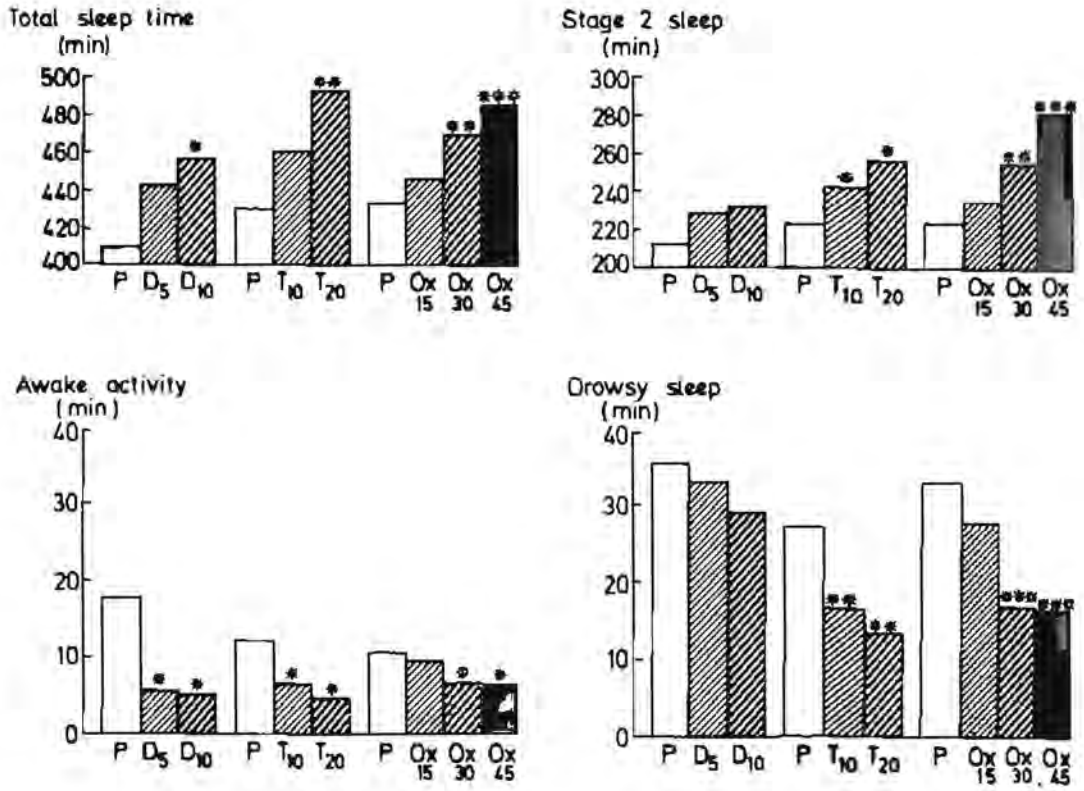

Figure 12. Some effects of diazepam (5 & 10 mg), temazepam (10 & 20 mg) and oxazepam (15, 30, & 45 mg) on night-time sleep in young adults compared with placebo. P - placebo, D - diazepam, T - temazepam, and Ox - oxazepam. Significance levels: * $p < .05$; ** $p < .01$; *** $p < .001$.

mg diazepam, and sleep onset latencies were shortened and awakenings were reduced. With 10 mg temazepam there was no change in total sleep time, though with 20 mg total sleep time was increased. Temazepam shortened sleep onset latencies, and reduced awake activity and drowsy sleep, and the effect on drowsy sleep was seen during each two hourly interval of the sleep period. The subjects reported improved sleep with temazepam, but subjective assessments of well-being were not altered. Oxazepam (30 & 45 mg) increased total sleep time and reduced awake activity and drowsy sleep, but it was not possible to establish an effect on sleep onset latencies. The subjects did not report changes in their quality of sleep or well-being with 15 & 30 mg oxazepam, but reported impaired wakefulness after the overnight ingestion of 45 mg. With these drugs no changes were observed in stages 3, 4 or REM sleep, except that the first REM period was delayed with 20 mg temazepam.

The potential for flunitrazepam is uncertain. With 0.25 mg there is little, if any, effect, though the higher dose (0.50 mg) may be useful when residual sequelae are to be avoided. With the higher dose total sleep time is increased and awake activity and drowsy sleep decreased without any adverse effects on the sleep process (Figure 13). With 0.25 & 0.50 mg triazolam total sleep time is increased and awake activity and drowsy sleep decreased (Figure 13). There are no changes in slow wave sleep, though the first period of rapid eye movement sleep is delayed with the higher dose. However, though triazolam reduces the duration and percentage of REM sleep during the early part of the night, REM sleep over the whole night is not changed. There is no clear evidence of a greater hypnotic effect in the healthy individual with the higher dose of triazolam.

Studies in Middle Age
(Figure 14)

The effect of diazepam (5 & 10 mg) and temazepam (10, 20 & 30 mg) were examined in six healthy middle aged (45-55 years) males. The sleep of the group was also compared with that of young adults (20-29 years) (Nicholson & Stone, 1979a). Control studies showed that there was a marked reduction in total sleep time, an increase in latency to Stage 3 and an increase in percentage of drowsy and Stage 2 sleep in the older group, but there were no changes in REM sleep. Diazepam and temazepam did not increase total sleep time. Sleep onset latencies were shortened by diazepam, but were unchanged with temazepam, and awake activity was reduced by both drugs. The subjects assessed their sleep as improved with both drugs without residual effects on well-being.

Studies on Day-Time Sleep
(Figure 15)

An investigation of the effects of diazepam (5, 10 & 15 mg), temazepam (10 & 20 mg) and oxazepam (15, 30 & 45 mg) on day-time sleep was carried out in six healthy males aged 19-28 years. The subjects slept normally the preceding night, and were required to sleep for a 6 h period beginning at 1400 h the next day (Nicholson & Stone, 1979b). Total sleep time was increased by 10 & 15 mg diazepam and by 30 & 45 mg oxazepam, but it was not possible to establish an increase in total sleep time with temazepam. Sleep onset latencies were decreased by diazepam, though such an effect was not observed with tema-

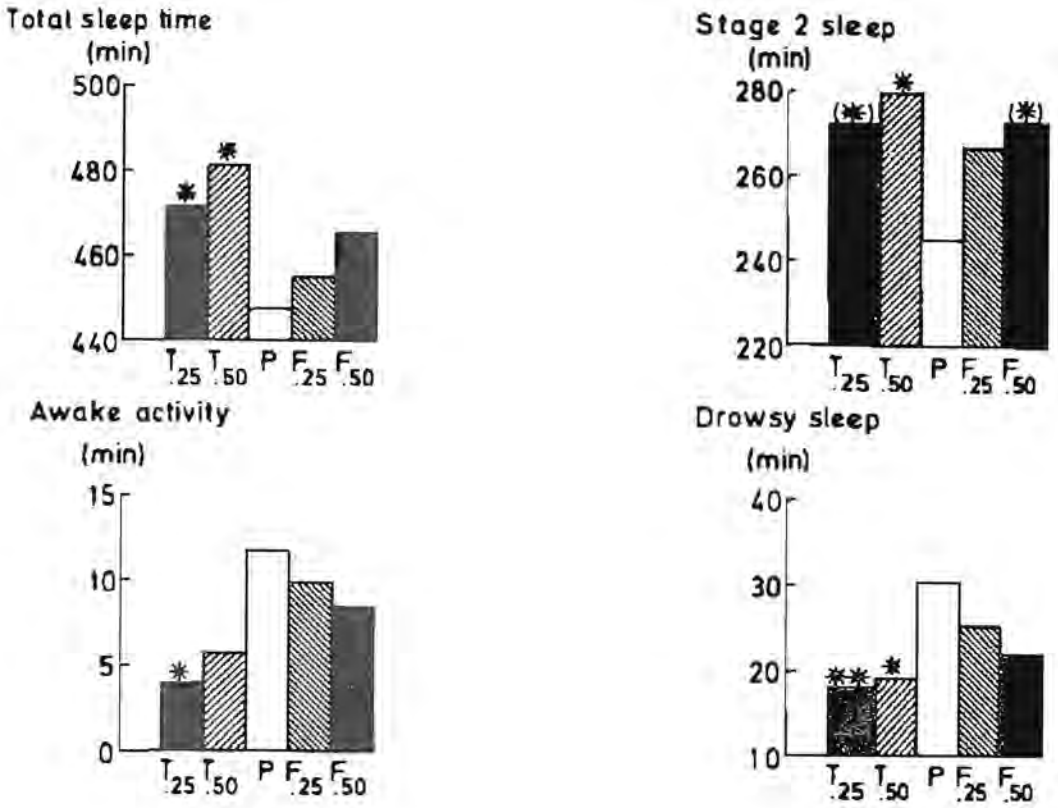

Figure 13. Some effects of triazolam (0.25 & 0.50 mg) and flunitrazepam (0.25 & 0.50 mg) on night-time sleep in young adults compared with placebo. P - placebo, T - triazolam, and F - flunitrazepam. Significance levels: * $p < .05$; ** $p < .01$.

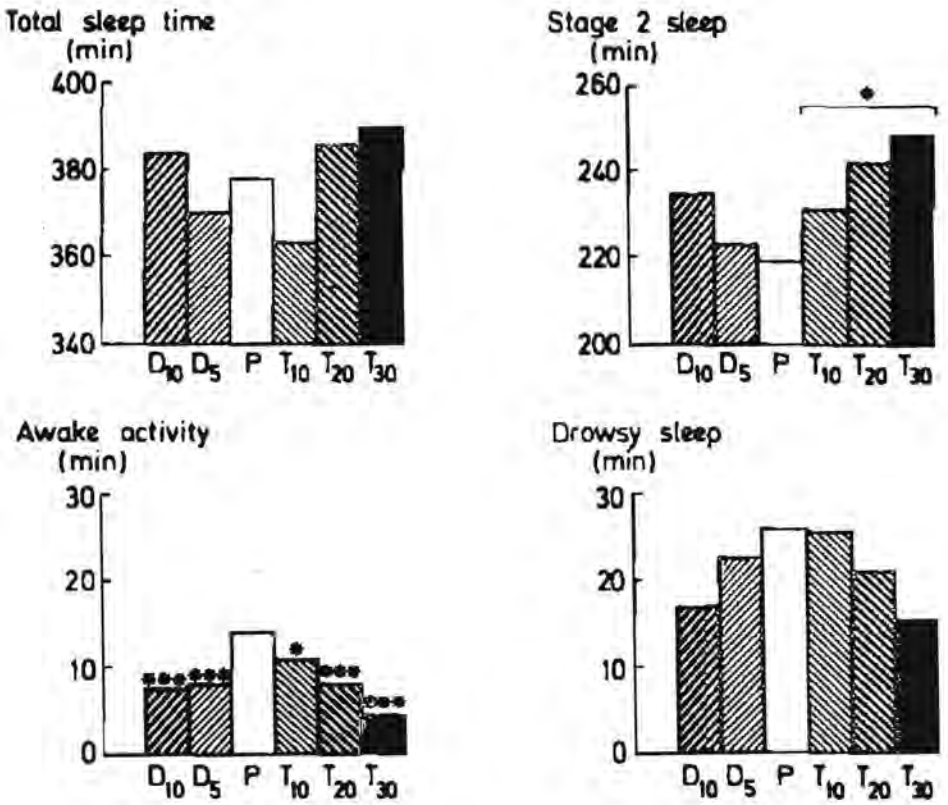

Figure 14. Some effects of diazepam (5 & 10 mg) and temazepam (10, 20, & 30 mg) on night-time sleep in middle age compared with placebo. D - diazepam and T - temazepam. Significance levels: * $p < .05$; *** $p < .001$.

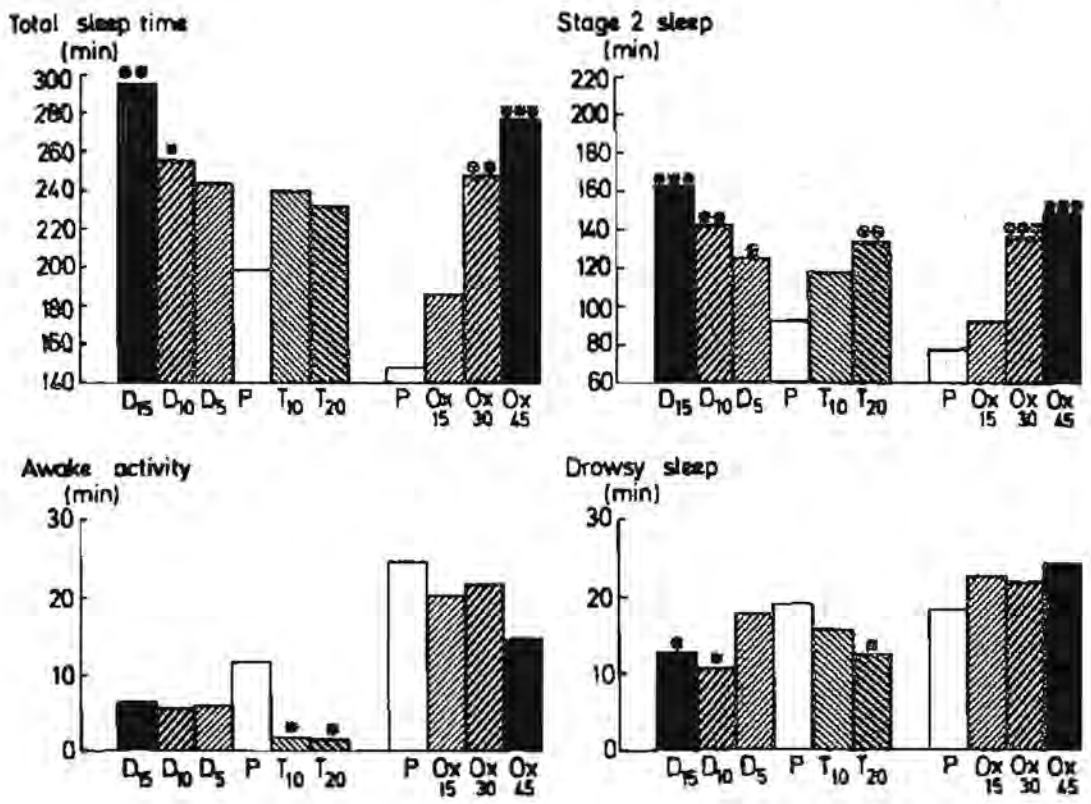

Figure 15. Some effects of diazepam (5, 10, & 15 mg), temazepam (10 & 20 mg), and oxazepam (15, 30, & 45 mg) on day-time sleep in young adults compared with placebo. P - placebo, D - diazepam, T - temazepam, O - oxazepam. Significance levels: * $p < .05$; ** $p < .01$; *** $P < .001$.

zepam or oxazepam. Awake activity was reduced by 10 & 20 mg temazepam. Drowsy sleep was decreased by 10 & 15 mg diazepam, and by 20 mg temazepam, but was not altered by oxazepam.

These results on three closely related benzodiazepines showed that very similar drugs may have different effects on sleep. In young adults, diazepam and temazepam reduced sleep onset latencies and awake activity and increased total sleep time, though temazepam also reduced drowsy sleep. The activity of oxazepam was similar to that of temazepam, although it has no effect on sleep onset latencies. In middle age, the effects of diazepam and temazepam were much less pronounced than would be expected from studies in the younger group. There was no increase in the total sleep time of middle age, even though both drugs increased the much longer sleep of young adults, and, though sleep onset latencies were similar between the two groups, it was only possible to establish an effect with diazepam, though temazepam shortens sleep onset latencies in early adulthood. Essentially, the effect of diazepam and temazepam in middle age was to reduce awake activity only.

The effects of these drugs on sleep during the day were unrelated to their relative effects on sleep during the night. Diazepam increased total sleep time during the day and reduced drowsy sleep, but temazepam and oxazepam had less activity during the day than would be expected from night-time studies. With temazepam there was no increase in total sleep time, though there was reduced awake activity and drowsy sleep, and with oxazepam total sleep time was increased.

Recommendations

It is considered that these findings provide a basis for the management of sleep disturbance in persons involved in skilled activity. The residual effects of nitrazepam (10 mg) and flurazepam hydrochloride (30 mg) within the currently accepted therapeutic dose ranges preclude their use in those involved in skilled activity the next day. However, diazepam (5-10 mg) is useful for both night-time and day-time sleep, though daily ingestion could lead to an accumulation of its long-acting metabolite with persistent behavioural effects. It may be wise to restrict the ingestion of diazepam to intervals not less than 48 hours and perhaps to not more than twice in a 7-day period. On the other hand, such restrictions are unlikely to be necessary with temazepam (10-20 mg) and oxazepam (15-30 mg). Temazepam (20 mg) may not be so effective for sleep as diazepam (10 mg) at times which do not coincide with the normal circadian desire to sleep and may be of less usefulness in shift workers, while oxazepam, at least in its present formulation, is unlikely to hasten sleep onset. Triazolam (0.125-0.25 mg) and flunitrazepam (0.50 mg) are without residual effects on performance and have useful hypnotic activity, but further experience with these drugs is required before any decision can be made as to their suitability in the present context.

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