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Does the Sedation Resulting from Sleep Deprivation and Lorazepam Cause Similar Cognitive Deficits?

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FLUCK, E. J., S. E. FILE, J. SPRINGETT, M. D. KOPELMAN, J. REES AND J. ORGILL. *Does the sedation resulting from chronic sleep deprivation and lorazepam cause similar cognitive deficits?* PHARMACOL BIOCHEM BEHAV **59**(4) 909–915, 1998.—It is notoriously difficult to assess the contribution of the sedative effects of benzodiazepines to the cognitive impairments that they produce. The purpose of the present experiment was to determine whether a similar pattern of cognitive impairment would be seen in conditions when subjects felt equally sleepy as the result of sleep deprivation. The effects of a sedative dose of lorazepam (2.5 mg) in healthy volunteers was therefore compared with the effects of acute sleep deprivation (a night on-call) in a group of junior doctors and the effects of chronically disturbed sleep due to snoring. Lorazepam, acute sleep deprivation, and chronic sleep disturbance all significantly increased subjective sedation. In addition, lorazepam significantly impaired performance in two tests of psychomotor speed and caused significant anterograde amnesia. Semantic and short-term memory were not impaired by lorazepam, nor was there any impairment in executive function. The only deficit found following acute sleep deprivation was in a test of semantic memory, generating examples from a difficult category. The only significant deficit in the group suffering from chronically disturbed sleep, compared with age-matched controls, was in executive function, and there was a nearly significant impairment in sustained attention. These results suggest that, despite the common factor of increased subjective sedation, the profile of cognitive impairment in the two sleep deprivation groups are neither similar to each other nor to that seen following an acute dose of lorazepam. © 1998 Elsevier Science Inc.

Benzodiazepine Sleep deprivation Sedation Memory

BENZODIAZEPINES cause marked sedation, and this effect is likely to contribute to the benzodiazepine-induced deficits on a number of tasks of attention and memory, as well as those measuring psychomotor speed (2,20). It has been difficult to separate benzodiazepine-induced sedation and cognitive impairments because, firstly, tasks that purely measure memory, attention, or psychomotor speeds do not exist and, secondly, it is very difficult to find an acutely nonsedative dose of a benzodiazepine that affects memory. However, a dissociation between the benzodiazepine-induced sedation and amnesia is evident in patients chronically using benzodiazepines, who remain amnesic despite both subjective and objective tolerance to sedation (12). It is apparent that benzodiazepine receptor modulation of GABA transmission produces a more potent amnesia than that induced by other drugs potentiating GABA transmission such as barbiturates, at doses producing similar levels of subjective sedation (18) and, furthermore, Roth et al. (19) demonstrated that 200 mg of quinalbarbitone produced greater sedation but was less amnesic than 30 mg flurazepam. In addition, Girdler et al. (6) demonstrated that at equivalent sedative doses midazolam was more amnesic than temazepam, thus demonstrating dissociation between sedation and amnesia within benzodiazepine effects.

Sleep deprivation causes both subjective and objective sedation and deficits in episodic memory (13,15). Although

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there have been no direct measurements of endogenous ligands for the benzodiazepine receptor, there is indirect evidence that they may be elevated in sleep deprivation because the benzodiazepine receptor antagonist, flumazenil, reverses the subjective sedation due to sleep deprivation (9,10). It is also possible, but so far untested, that the cognitive decline following sleep deprivation is at least partly modulated through the GABA benzodiazepine receptor complex.

The purpose of this study was to compare the cognitive profile seen in three separate experiments where the common factor is an increase in subjective sedation. Thus, the effects of an acute sedative dose of lorazepam was compared with that seen after a night of acute sleep deprivation in junior doctors, and a sleep deprivation of a more chronic nature, resulting from excessive snoring in a group of middle aged men who sought medical help due to their concern about excessive daytime sleepiness.

METHOD

Subjects

These studies were all conducted with approval of UMDS academic board and the local ethics committees; all subjects gave written informed consent prior to participation in the study. All subjects were healthy and medication free at the time of testing. The details of the subjects are given in Table 1.

Mood Rating Scale

A visual analogue scale with 16 items (1) measuring present mood state was given pretreatment (for the lorazepam study) and at the beginning and end of testing. Subjects had to indicate how they felt at the time by placing a perpendicular mark along a 100-mm horizontal line. From nine of the items a factor of sedation was derived.

Cognitive Tests

There were two matched versions (A and B) of all the cognitive tests.

Episodic Memory

Prose recall of two short stories was taken from the logical memory subtest of the Wechsler Memory Scale—Revised (25). Subjects heard a tape of the stories and were told that their memory would be tested later. Recall was tested 30 min later. Each story had 25 units of information and 1 point was scored for perfect recall or an exact synonym.

A total of 25 pictures were presented to the subjects for 3 s each at 1-s intervals, with the instructions that memory would be tested for them later. To ensure that the subject was attending to the task, he/she was asked to name each line drawing as it was presented. Recall was again 45 min later.

Semantic Memory

A category fluency test was used to assess semantic memory. Subjects were asked to generate as many words as possible in 60 s from the supermarket category and from an easy animal category (animals found in the house) and from a difficult category (animals found in the jungle). The category difficulty was based on a student volunteer study carried out by File et al. (4). Twenty seconds was allowed for each category.

Short-Term Memory

The Digit Span test from the subtest of the Weschler Adult Intelligence Scale—Revised (24) was used to assess short-term memory. In the first part of the test subjects had to repeat the sequence of digits read out by the experimenter. Each digit was read out at a rate of 1 per second and the number of digits progressed from three to nine. In the second test, the sequences had to be repeated by the subject in the reverse order; these sequences progressed from two to eight digits.

Tests of Psychomotor Speed

The Digit Cancellation test was used to assess psychomotor speed. The subject was given 30 s to cross out all occurrences of a specific digit from a sheet of random numbers. The Digit Symbol Substitution test is a subtest of the WAIS-R (24). Subjects had 90 s to complete this task.

Paced Auditory Serial Addition Test (PASAT)

The PASAT (7) was used to assess sustained attention and involved adding together pairs of single digit numbers read from a tape recorder. There were four tapes in total, with increasing rates of digit presentation (2.4–1.2/s). A correct response was a correct answer by the subject before the next number in the taped sequence was read out.

Trails Test

This test assesses attention and executive function (17) and is comprised of two trails, A and B. Trails A requires the subject to serially connect 25 encircled numbers with a continuous line. Trails B requires the alternate connection of 25 encircled numbers and letters (1-A-2-B-3-C, etc.). The time taken to complete both trails was recorded. The time taken to complete the trails A test was a measure of attention and motor function, and the difference between the time taken to complete trails A and B is a measure of executive function.

TABLE 1

CHARACTERISTICS OF SUBJECT GROUPS IN EXPERIMENTS 1–3

	Subjects	♀:♂	Age (years)	NART-R IQ	WAIS-R Verbal
Experiment 1	Preclinical medical students from UMDS				
	Placebo ($n = 10$)	4:6	20.3 ± 0.2	114.0 ± 2.3	not available
	Lorazepam 2.5 mg ($n = 10$)	3:7	20.5 ± 0.2	112.7 ± 3.0	not available
Experiment 2	Clinical medical students from UMDS ($n = 6$)	2:4	20.8 ± 0.2	114.3 ± 3.5	not available
Experiment 3	Matched control group ($n = 7$)	0:7	53.3 ± 2.1	116.6 ± 3.7	120.3 ± 4.0
	Snorers referred to Sleep Laboratory, St Thomas' Hospital ($n = 7$)	0:7	48.4 ± 1.4	110.3 ± 5.4	121.4 ± 6.4

Scores are mean ± SEM.

Rey Figure

This test measures executive function. Subjects were given a complicated design (made up of 18 units) and instructed to copy it as accurately as possible. Of particular interest was the strategy adopted on copying the design and drawing it from memory 30 s later. Scoring was 1 to 7, with each successive number indicating a more disorganized strategy (11). The times taken to complete the drawing and the number of units drawn were recorded.

Drug

Lorazepam (Ativan) and identical placebo tablets were generously donated by Wyeh Pharmaceuticals (Taplow, Maidenhead, Berks, UK)

Experimental Designs

Experiment 1. The subjects were randomly allocated, 10 each to the placebo and lorazepam (2.5 mg) groups. The placebo was an identical looking tablet and testing was double-blind. Mood ratings were taken predrug immediately before testing (1.5 h after drug administration) and at the end of testing (1 h later). Half the subjects in each group received version A of the tests and half received version B.

Experiment 2. Six junior doctors were tested twice, once after a normal night's sleep and once after a night of acute sleep deprivation (average sleep length 169 ± 38 min in the previous 28 h). Half of the subjects were first tested after a normal night's sleep and half after a night on call; half of the subjects received version A on their first test. The mean interval between tests was 22.7 ± 6 days.

Experiment 3. The patients (n = 7) recruited from the Sleep Laboratory at St. Thomas's Hospital had sought help because of excessive day time sleepiness and concerns about their sleep. Their partners confirmed heavy snoring for >1 year, but an overnight sleep evaluation confirmed that they did not suffer from significant obstructive sleep apnoea (defined as >10 apnoeic episodes per hour). Apart from sleep disruption associated with snoring , none had any other cause for excessive daytime sleepiness. The control group (n = 7) was recruited from friends and colleagues at UMDS. Their partners also confirmed snoring for >1 year, but none had sought medical help for daytime sleepiness or poor sleep.

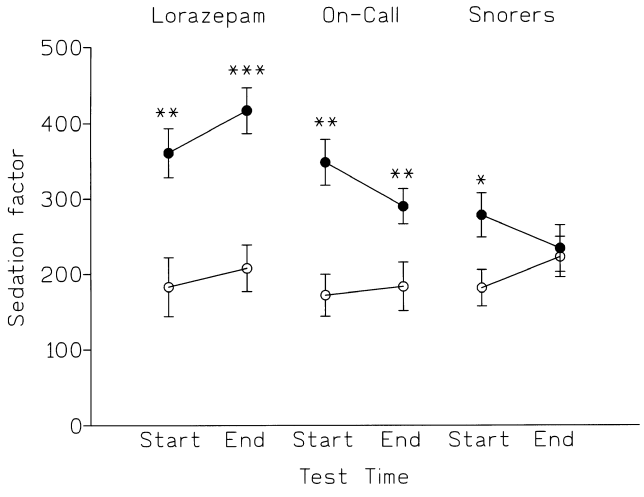

FIG. 1. Mean (±SEM) subjective sleepiness measured by the sedation factor assessed at the beginning and at the end of testing for the experimental groups (●) and control state (○) in all three experiments. *$p < 0.05$, **$p < 0.001$, ***$p < 0.0005$ compared with appropriate control group or state.

STATISTICS

In Experiments 1 and 3 the data were analyzed with one-way analyses of variance (ANOVA) with drug treatment or subject group as the independent factor. Where there were repeated tests (e.g., at more than one time) the data were analyzed with two-way ANOVAs. The data from Experiment 2 were analyzed with single or multifactor repeated measures ANOVAS, as appropriate. The drawing strategy used for the Rey figure was analyzed using the Mann–Whitney U-tests.

RESULTS

Ratings of Sedation

The placebo and lorazepam groups did not differ in their pretreatment mood ratings. However, as can be seen from Figure 1, by the start of testing the lorazepam group was significantly more sedated than the placebo group $F(1, 18) = 20.8$, $p < 0.001$. Although both groups felt more sedated at the end of testing, this increase did not reach significance $F(1, 18) = 0.6$.

The junior doctors felt significantly more sedated/sleepy after a night on call than after a normal night's sleep $F(1, 5) = 24.1$, $p < 0.005$. Interestingly, when they were tested after acute sleep deprivation they felt less sleepy at the end of testing than they had at the beginning, whereas this pattern was not seen after a normal night's sleep [sleep state × test time interaction $F(1, 5) = 3.4$, $p = 0.10$], (see Fig. 1).

The group of patients referred for daytime sleepiness did, indeed, feel more sleepy than their matched controls at the start of testing ($p < 0.05$) but by the end of testing their scores were the same, because the patients became less sleepy and the controls more sleepy as a result of testing [group × time interaction, $F(1, 12) = 9.8$, $p < 0.01$. It can be seen from Fig. 1 that, at the start of testing, this group of patients were not as sedated as the group suffering a night's acute sleep deprivation or the group treated with lorazepam.

Episodic Memory

Lorazepam significantly reduced the number of units recalled from the stories $F(1, 18) = 14.4$, $p < 0.001$, and the number of pictures recalled, $F(1, 18) = 5.4$, $p < 0.05$ (see Fig. 2).

The junior doctors recalled as many units from the stories after the night of sleep deprivation as they did after a normal night's sleep $F(1, 5) = 0.1$, and there was no difference in the number of pictures recalled on the two occasions $F(1, 5) = 1.7$, (see Fig. 2).

The patients referred to the sleep laboratory did not differ from their matched controls in their prose recall, $F(1, 12) = 1.2$, or in the number of pictures recalled, $F(1, 12) < 1.0$ (see Fig. 2).

Semantic Memory

Lorazepam had no effect on the number of words generated for the supermarket category [mean ± SEM: controls 28.9 ± 1.7, lorazepam 26.2 ± 2.6, $F(1, 18) < 1.0$] or for the number of animals, $F(1, 18) < 1.0$. There was a significant effect of animal category with all subjects generating fewer words for the difficult category $F(1, 18) = 79.5$, $p < 0.001$; the

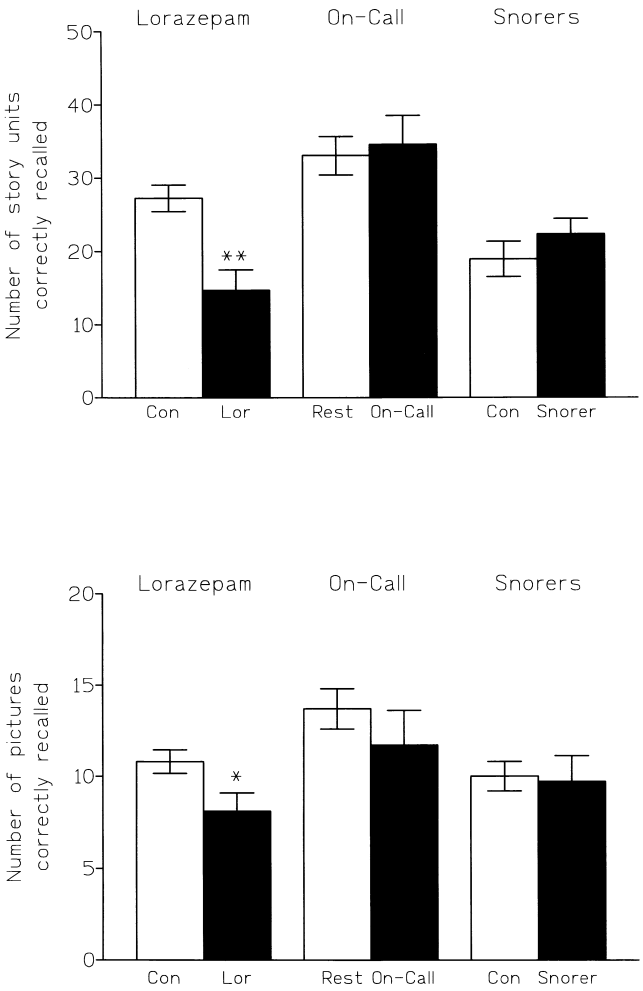

FIG. 2. Mean (±SEM) number of story units (upper panel) and pictures (lower panel) correctly recalled for both the experimental (■) groups and control state (□) in all three experiments. *$p < 0.05$, **$p < 0.001$ compared with appropriate control.

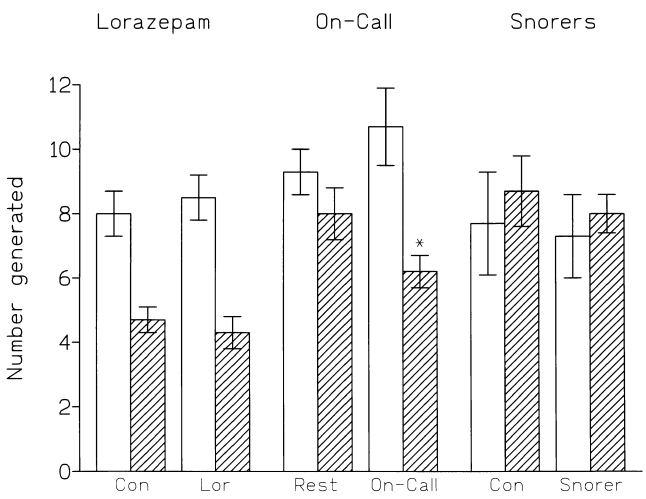

FIG. 3. Mean (±SEM) number of exemplars generated from an easy (□) and hard animal category (▨) for all three experiments.

drug treatment × category interaction was not significant $F(1, 18) = 1.1$ (see Fig. 3).

There was no effect of sleep deprivation on the number of supermarket items generated [mean ± SEM: normal sleep 34.6 ± 2.6, sleep deprived 34.2 ± 1.9, $F(1, 5) < 1.0$]. However, there was a sleep state × category interaction for the number of animals recalled $F(1, 5) = 7.7$, $p < 0.05$, because there were fewer items recalled from the difficult category after sleep deprivation than after a normal night's sleep (see Fig. 3).

The patients referred to the sleep laboratory did not differ from their matched controls in the numbers of words generated for supermarket items [mean ± SEM: controls 22.6 ± 2.8, snorers 29.1 ± 3.7, $F(1, 12) = 2.0$] or animals, $F(1, 12) = 0.1$. Interestingly, in these subjects there was no difference between the number of farm and jungle animals generated, $F(1, 12) = 2.2$, suggesting that for this older group of subjects the categories did not differ in difficulty (see Fig. 3).

Short-Term Memory

There was no effect of lorazepam on the digit span test for sequences repeated forwards $F(1, 18) = 0.1$. There was, however, a nonsignificant difference between the groups for sequences repeated backwards with the lorazepam group reaching a smaller number span than controls, $F(1, 18) = 3.7$, $p = 0.07$ (see Table 2). To determine whether this deficit was due to impaired attention, the digit span scores were analyzed with analysis of covariance using the scores from the PASAT test (see later section) as the covariates, $F(1, 17) < 1.1$, for all tape speeds. This showed that when impaired attention was accounted for, there was no longer an impairment in digit span.

For the junior hospital doctors there was no effect of sleep state on the digit span test for sequences repeated forwards, $F(1, 5) = 0.8$, or backwards, $F(1, 5) = 0.2$ (see Table 2).

The patients with daytime sleepiness were significantly better than the controls in the number of digits repeated forwards, $F(1, 12) = 4.9$, $p < 0.05$, and backwards, $F(1, 12) = 6.1$, $p < 0.05$ (see Table 2).

Digit Cancellation and Digit Symbol Substitution

Lorazepam significantly reduced the number of digits correctly cancelled, $F(1, 18) = 12.0$, $p < 0.01$, and the number of correct substitutions in the digit symbol substitution test, $F(1, 18) = 14.8$, $p < 0.01$ (see Table 2).

There was no effect of acute sleep deprivation in the digit cancellation, $F(1, 5) = 0$, or digit symbol substitution tests, $F(1, 5) = 0.9$ (see Table 2).

There was no effect of chronic sleep disturbance on the number of digits correctly cancelled, $F(1, 12) = 0.9$, or symbols substituted, $F(1, 12) = 1.1$ (see Table 2).

Paced Auditory Serial Addition Test (PASAT)

There was a very significant overall effect of tape speed in PASAT, $F(3, 54) = 92.4$, $p < 0.001$, and lorazepam significantly impaired performance, $F(1, 18) = 42.1$, $p < 0.001$; there was no drug × tape speed interaction $F(3, 54) = 0.3$, indicating that the rate of decline in performance as the test became more difficult was parallel in both groups, see Figure 4.

A night of sleep deprivation did not impair the overall performance on PASAT, $F(1, 5) = 0.4$, or the deterioration in performance with tape speed, $F(1, 5) = 0.1$ (see Fig. 4).

TABLE 2

MEAN (±SEM) DIGIT SPAN TEST AND NUMBER OF CORRECT SCORES IN THE DIGIT SYMBOL SUBSTITUTION (DSS) AND DIGIT CANCELLATION (DC) TESTS

		Digits Forward	Digits Backward	DSS	DC
Experiment 1	Preclinical medical students from UMDS				
	Placebo ($n = 10$)	7.7 ± 0.4	6.6 ± 0.3	72.0 ± 3.1	13.5 ± 1.1
	Lorazepam 2.5 mg ($n = 10$)	7.7 ± 0.4	5.4 ± 0.5	57.2 ± 2.2†	8.4 ± 0.9†
Experiment 2	Clinical medical students from UMDS				
	Normal night ($n = 6$)	8.2 ± 0.5	6.0 ± 0.7	71.2 ± 2.7	17.5 ± 1.1
	Sleep deprived ($n = 6$)	8.0 ± 0.4	5.5 ± 0.5	68.0 ± 2.5	17.5 ± 1.7
Experiment 3	Matched control ($n = 7$)	5.6 ± 0.5	4.1 ± 0.3	59.9 ± 3.6	12.5 ± 0.3
	Snorers referred to Sleep Laboratory, St Thomas' Hospital ($n = 7$)	7.4 ± 0.6*	6.1 ± 0.7*	53.9 ± 4.4	14.5 ± 1.3

*$p < 0.05$, †$p < 0.001$ compared with the appropriate control group.

The patients with daytime sleepiness did not differ from their controls in performance of the PASAT, $F(1, 12) = 1.0$, but there was a group × tape speed interaction that just failed to reach significance, $F(3, 36) = 2.4$, $p = 0.09$; this was due to the patients performing worse than controls on the second tape only (see Fig. 4).

Trails

Lorazepam did not impair performance in this task, $F(1, 18) = 0.5$. All subjects took longer to complete trails B than A, $F(1, 18) = 33.9$, $p < 0.001$, but there was no group × trail interaction, $F(1, 18) = 1.1$. After a night of acute sleep deprivation the junior doctors were slower at completing the trails task, $F(1, 5) = 3.8$, $p = 0.1$, and this effect was more marked on trails B than A [state × trail interaction, $F(1, 5) = 3.5$, $p = 0.1$].

The patients with chronic sleep difficulties did not differ from the controls in time taken to complete the trails tests (group and group × trail, $F < 2.0$).

Rey Figure

There were no differences between the lorazepam and placebo groups in the strategies used when copying or drawing from memory the Rey figure (in all cases, $Z < 0.6$). Both groups copied the same number of units, $F(1, 18) = 0.3$ and drew fewer units from memory 30 s later [time, $F(1, 18) = 101.5$, $p < 0.001$], but the proportion of the units drawn from memory did not differ between the groups [drug × time, $F(1, 18) = 1.4$. However, the lorazepam group took longer both to copy and draw the diagram from memory, $F(1, 18) = 12.2$, $p < 0.001$ (see Table 3).

Acute sleep deprivation did not affect the strategy used in the Rey task ($Z = 0$), the number of units, $F(1, 5) = 0.7$, nor the time taken to draw the figure, $F(1, 5) = 0.3$. Once again, subjects recalled fewer units from memory, $F(1, 5) = 24.3$, $p < 0.01$, than had been copied (see Table 3).

Although both groups drew fewer units from memory than they had copied, $F(2, 24) = 78.0$, $p < 0.001$, there were no differences between the patients with chronic sleeping difficulties and the controls on the number of units copied or drawn from memory, $F(1, 12) = 0.8$. The groups did not differ on the time taken to copy the Rey figure, $F(1, 12) = 1.5$, and there was no significant difference between the groups on the strategy adopted to copy the Rey figure, ($Z = 1.7$). However, the groups significantly differed in the strategy adopted when drawing the figure from memory ($Z = 3.7$, $p = 0.5$); this was due to subjects with chronic sleeping difficulties using a more disorganised strategy, but despite this, these patients took less time the draw the diagram from memory than did the controls, $F(1, 12) = 4.8$, $p < 0.05$ (see Table 3).

DISCUSSION

The common factor for all the experimental groups was that before testing began all were subjectively more sleepy than the control groups or states. However, what was most striking was that despite the lorazepam group becoming more sleepy as testing progressed, the two sleep-deprived groups became more alert. Although the on-call doctors still remained significantly more sleepy than after their normal night's sleep, the chronic snorers were no different from their controls by the end of testing; it thus appears that the sleep-deprived groups were able to overcome their subjective sleepiness. The total testing time was 1.5 h, and although it is not known how subjects would have rated themselves if left alone for that time, it is likely that performing the cognitive tasks increased their alertness. This result contrasts to that seen in the lorazepam group, who could not overcome sleepiness when given challenging cognitive tasks and actually became more sleepy as testing progressed. Thus, sedation as a result of sleep deprivation differs in at least one important way from that caused by benzodiazepine action at the GABA receptor complex. Lavie

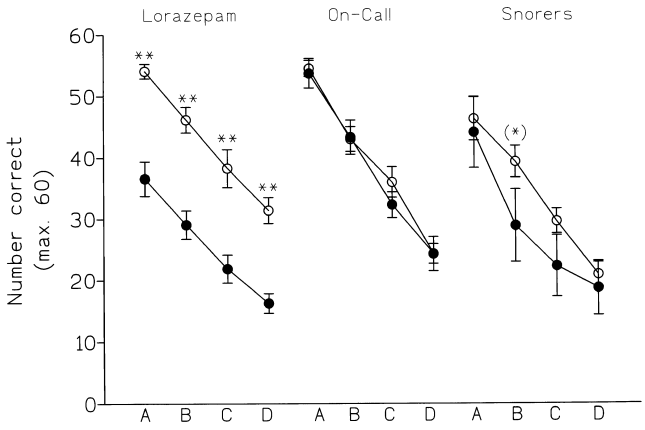

FIG. 4. Mean (±SEM) number of correct additions (max. 60) in the PASAT, at four tape speeds (A–D), for both the experimental groups (●) and the control state (○) in all three experiments. (*)$p = 0.07$, **$p < 0.001$ compared with appropriate control.

TABLE 3

MEAN (±SEM) TIME (s) TO COMPLETE TRAILS A AND B TIME TO COPY AND DRAW THE REY FIGURE, NUMBER OF UNITS COPIED AND DRAWN, AND MEAN (RANGE) OF SCORES OF STRATEGY USED

		Trails A	Trails B	Rey Copy (Time)	Rey Memory (Time)	Rey Copy (Units)	Rey Memory (Units)	Rey Strategy (Copy)	Rey Strategy (Memory)
Experiment 1	Preclinical medical students from UMDS								
	Placebo ($n = 10$)	30.9 ± 8.2	51.6 ± 4.1	127 ± 11.7	125.5 ± 12.6	35.1 ± 0.3	22.8 ± 2.3	1.9 (1–2)	2.3 (1–6)
	Lorazepam 2.5 mg ($n = 10$)	30.1 ± 2.8	60.0 ± 2.9	202 ± 14.3†	175.4 ± 17.9*	35.3 ± 0.3	19.7 ± 1.9	1.9 (1–2)	1.7 (1–2)
Experiment 2	Clinical medical students from UMDS								
	Normal night ($n = 6$)	17.3 ± 1.4	31.0 ± 2.3	54.3 ± 4.1	62.3 ± 4.5	36.0 ± 0	31.0 ± 1.6	1.0 (1)	1.0 (1)
	Sleep deprived ($n = 6$)	20.2 ± 2.5	38.5 ± 3.2	62.5 ± 5.3	62.3 ± 8.4	35.2 ± 3.2	31.2 ± 1.4	1.2 (1–2)	1.2 (1–2)
Experiment 3	Matched control group ($n = 7$)	37.0 ± 4.5	85.6 ± 9.3	99 ± 8.4	121 ± 18.9	35.1 ± 0.6	21.9 ± 2.5	1.4 (1–2)	1.1 (1–2)
	Snorers referred to Sleep Laboratory, St Thomas' Hospital ($n = 7$)	32.3 ± 4.9	67.7 ± 8.1	116 ± 10.7	77 ± 6.9*	34.4 ± 0.8	20.5 ± 2.3	2.1 (1–4)	2.4 (1–4)‡

*$p < 0.05$, †$p < 0.01$ compared with the appropriate control using single-factor ANOVA.
‡$p = 0.05$ compared with the matched control using the Mann–Whitney U-test.

(9,10) has demonstrated a role for the benzodiazepine system in subjective sedation seen following sleep deprivation because of its reversal by the benzodiazepine receptor antagonist, flumazenil. It therefore seems that an additional compensatory system is available in conditions of sleep deprivation.

The stimulation provided by the test conditions was sufficient to overcome the subjective sleepiness of the sleep-deprived subjects, and this may partly explain the lack of cognitive impairment found in these groups. This contrasts with the wide range of cognitive impairments found after lorazepam administration, which mirrored the classic profile found with benzodiazepines (2,5). Thus, there was decreased performance in the tests of psychomotor speed (digit cancellation, digit symbol substitution), sustained attention (PASAT), and episodic memory (picture and prose recall), but normal short-term (digit span forward) and semantic memory (category generation). Interestingly, benzodiazepines did not impair recall of the Rey figure, which was administered without explicit memory instructions, which would suggest that the automatic processing that accompanies incidental learning was spared following lorazepam. Indeed, Joyce and File (8) reported that, in contrast to benzodiazepine-induced impairment of effortful processing, automatic processing is left intact. In this study, lorazepam impaired performance in the digits backwards test, but when impaired attention was taken into consideration by covarying with the scores from the PASAT test there was no longer an effect.

It is unlikely that the impaired cognitive performance in the lorazepam group, compared with the sleep-deprived groups, resulted from differences in motivation, because increasing motivation is without effect on lorazepam-induced sedation or cognitive impairment (3). Although it is not clear why, it seems that sleep-deprived subjects are able to perform in effortful tasks when they are presented to them, whereas benzodiazepines impair effortful processing (8). After a night on-call, the junior doctors were impaired in generating words from a difficult category. Time of day has been shown to affect retrieval from semantic memory, and this has been related to circadian change in body temperature and arousal. Furthermore, when arousal is lowest there is a greater discrepancy between the classification of words to high- or low-dominance categories, and it is thought that this is due to low-dominance categories requiring greater powers of search which are hardest to apply when arousal is lowest (21). Although body temperature was not measured in this study, following a night of sleep deprivation body temperature is reported to be lowest between 0530 and 1330 h (16), and our study was carried out during this time span. The middle-aged groups showed no difference in the number of exemplars they generated for the two different categories, possibly due to greater elaboration of semantic memory.

There is evidence that the longer the sleep deprivation the greater the impairment in sustained attention (14). Our results suggest that after disrupted sleep caused by snoring only this aspect of performance was impaired and, on the contrary, the patients with chronic sleeping difficulties had a better short-term memory than the matched controls. The only other cognitive deficit in this group of patients suggest some executive dysfunction, evident from a more disorganised strategy used when drawing the Rey figure. No such executive dysfunction was seen following lorazepam administration, which would suggest that it is not under GABA–benzodiazepine control.

Although it was not the main purpose of this study, several interesting differences emerged between our young and middle-aged groups. The control groups were well matched in

terms of IQ and subjective sedation, yet the middle-aged group was markedly slower in the digit symbol substitution test, which is a test of divided attention based on speed of responding and in performance in the PASAT test of sustained attention. There were no age-related differences in the digit cancellation task, which tests selective attention, and is also based on the speed of responding. There were also no age-related differences in short-term memory or memory for the Rey figure or pictures, but the middle-aged group showed poorer memory for prose.

The aim of this study was to provide evidence for a dissociation between sedation and amnesia. To some extent this was achieved, as equal sedation ratings did not result in equal amnesia. In particular, benzodiazepines impaired effortful tasks, whereas sleep deprivation did not. However, the lack of cognitive decline in the sleep deprivation groups could be related to the fact that subjects became more alert during testing; this increased alertness could have arisen due to a compensatory system, which enabled the subjects to perform well in the tests. However, our results do not allow us to exclude the release of endogenous benzodiazepine ligands during conditions of sleep deprivation because these may cause sedation and cognitive impairments in unstimulating conditions. Furthermore, the release of endogenous ligands for the benzodiazepine receptor following sleep deprivation may be brain region specific, and indeed, Wu et al. (26) found a decrease in glucose metabolism only in discrete brain areas. This contrasts with the widespread brain distribution and global decrease in glucose metabolism following administration of lorazepam (22,23), which may prevent the compensatory alerting mechanism.

In conclusion, this study shows that feeling sleepy does not necessarily result in a similar cognitive decline. Indeed, although all three experimental groups experienced similar levels of subjective sedation, parallel changes in objective measures of sedation did not always occur. There were objective sedation deficits seen following lorazepam administration in medical students, but in contrast no corresponding deficit was seen in junior doctors following a night on call. Furthermore, the sleep-deprived junior doctors showed only one memory deficit, which was not benzodiazepine-like and would therefore seem unlikely to be mediated by the GABA–benzodiazepine receptor complex. Regarding the patients with chronic sleeping difficulties, no aspect of memory was impaired and in the short-term memory test, performance was actually better in these patients. They did, however, show a deficit in the organisation aspect of executive function, but again, this was not mirrored following lorazepam, suggesting it was not mediated by the GABA–benzodiazepine complex.

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