A STUDY COMPARING THE HYPNOTIC EFFICACIES AND RESIDUAL EFFECTS ON ACTUAL DRIVING PERFORMANCE OF MIDAZOLAM 15 MG, TRIAZOLAM 0.5 MG, TEMAZEPAM 20 MG AND PLACEBO IN SHIFTWORKERS ON NIGHT DUTY

WJ Riedel
R Quasten
C Hausen
JF O'Hanlon

Institute for Drugs, Safety and Behavior
University of Limburg
P.O. Box 616
6200 MD Maastricht
The Netherlands

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University of Limburg
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CONTENTS

SUMMARY

The purpose of the study was to determine the hypnotic efficacy and residual effects of three hypnotics administered for the treatment of transient insomnia in the day-sleep of rotating shift workers. The average duration of day-sleep in rotating shift workers is 5 to 6 hours. Midazolam, triazolam and temazepam all possess short elimination half-lives, i.e. 2, 4 and 8 hours, respectively. This suggests that these drugs should be largely free from residual effects and therefore not impair performance in real-life tasks.

Four treatments were administered over five consecutive days in the morning after night duty to 14 rotating shift workers. The treatment conditions were midazolam 15 mg, triazolam 0.5 mg, temazepam 20 mg and placebo. Treatments were administered double-blind according to a balanced cross-over design. On the first and the fifth day of treatment subjects slept in the laboratory for a maximum of 5.5 hours. On the intermediate days, subjects slept at home as they normally would. Sleep duration, latency and activity during sleep were recorded using wrist-worn activity meters. Subjective sleep quality and subjective arousal were measured by questionnaire. Subjective arousal was also measured in the evening at the subjects' homes and at night during their work.
After sleeping in the laboratory, the subjects performed two driving tests (6.5 - 8.5 hours post-administration). The first was a city driving test in which an expert rated the subjects' driving behavior and recorded visual inspection using eye movement measurement. The second was a highway driving test in which the lateral position of the vehicle, speed and steering wheel angle were measured continuously, yielding measures of tracking error, steering angle error, speed and time to line crossing.

Midazolam significantly prolonged day-sleep duration at home and also improved subjective sleep quality relative to placebo. Triazolam decreased activity during sleep, presumably indicating increased sleep depth. However, triazolam greatly impaired driving performance both in city and highway driving tests, whereas midazolam did so to a very limited extent on the fifth day of treatment during highway driving only. Temazepam did not influence any of the sleep parameters, nor was there any influence of temazepam upon driving performance. Triazolam improved subjective activation during night-duty relative to placebo, just as did midazolam and temazepam, but to a lesser extent.

It was concluded that midazolam 15 mg can be recommended for use by rotating shift workers in order to cope with transient insomnia caused by poor adaptation to night-shift, and that in general no residual effects will be present 6.5 hours after ingestion.
Temazepam 20 mg is less likely to improve day-sleep, but is absolutely free from residual sedative effects.
Triazolam 0.5 mg can not be recommended because it is less likely to improve day-sleep and is unsafe to drive with 6.5-8.5 hrs after ingestion.

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1. INTRODUCTION

The study described here concerns the effects of benzodiazepine hypnotics on the day-sleep and subsequent performance of rotating shift workers on night duty. Some premises of this study are the following.

- Rotating shift work, either on an 8-hour or 12-hour schedule, causes shorter sleep time, more awakenings and more changes in sleep stages (Kales & Kales,1984), fatigue, tiredness, irritation and strain (Akerstedt & Gillberg, 1981; Akerstedt et al., 1987; Akerstedt, 1988; Anderson & Bremer, 1987; Ruthenfranz et al., 1977; 1981; Tilley et al., 1982)

- The underlying cause is the disturbance of the circadian cycle, which normally determines the duration and organization of sleep to a great extent (Czeisler et al., 1980; Adam, 1984).

- The consequences of chronically disturbed sleep can constitute a health hazard for individuals working in rotating shifts for long periods (Frese & Semmer, 1986).

Diverse solutions to this problem have been suggested:

- Selecting permanent night-shift workers. Permanent night work as opposed to rotating shift work would probably cause less health problems and would also improve work performance at night. However, few people choose to work on such a schedule (Wilkinson, 1971).

- Selecting individuals who readily adapt to rotating shift work. The so-called evening types and, to a lesser extent, extroverts, are said to suffer less from the transition to a reversed sleep-wake cycle, than morning types (Kerkhof 1985). This "advantage", however marginal, seems to be determined by both amplitude and phase differences in their twenty-four-hour rhythms (Vidacek et al., 1988).

- Limiting the duration of the night shift to two or three consecutive periods of twelve hours, the so-called twelve hour shift, instead of the typically five- or seven-day periods of eight-hour shifts, in order to minimize the disruption of the circadian cycle (Ruthenfranz et al., 1975). Though workers favor the twelve-hour shift, its advantages in terms of psychosocial health could not be proved by Frese and Semmer (1986).

- Treating the shift workers' transient insomnia pharmacologically is advocated by a number of authors (Scollo-Lavizzarri, 1983; Nicholson & Stone, 1983ab; Dement et al., 1984; Seidel et al., 1984; Kales & Kales, 1984; Nicholson, 1986), although the only empirical verification of this claim with real shift workers using triazolam (Walsh et al., 1984) led to a negative recommendation, due to rebound insomnia.
  During day-sleep the threshold for external stimulation relative to that during night-sleep is greatly decreased both because of its circadian phase and environmental causes (Hartmann, 1973). Pharmacological treatment would be useful to increase the threshold for external stimulation which would otherwise cause early awakenings and account for restless sleep. Pharmacological treatment would have to be evaluated with respect to a number of factors: objective and subjective sleep parameters, residual performance effects, tolerance and withdrawal effects (Gottfries, 1981).

The study described here is concerned with the latter solution. The aim is to answer the question: "If rotating shift workers suffering from insomnia after night shift are treated with hypnotics, what are the consequences in terms of sleep, residual performance effects and subjective feelings?".

1.1 Transient insomnia induced by shift work

Man has evolved and been trained for a twenty-four-hour cycle of work during the day and sleep at night, whereas modern technological systems increasingly demand that machines be manned twenty-four hours a day. Overall, the view is taken that although alternating shift systems are accepted (probably because they provide more pay and more free time), the effects of these routines upon health and efficiency may nevertheless be harmful. Judging from the twenty-four-

hour rhythms of body temperature and performance, which are closely related, some adaptation to night work is always observed, although the degree and speed of adaptation varies. Much depends upon the world around and whether it is geared to the new time routine (as when one crosses a time zone, flying from Europe to USA) or not (as in night shift work). With regard to performance, the kind of work and its duration are also important, suggesting that loss of sleep may be at least as influential as body rhythms in causing ill effects associated with abnormal working hours (Wilkinson, 1971). Czeisler et al. (1980) showed that sleep duration can reliably be predicted as a function of the phase of the body temperature curve at the moment of falling asleep. Usually we go to sleep late in the evening soon after body temperature begins to decline and wake up in the morning just after it begins to rise (Graeber, 1988). This relationship explains the fact that although shift workers are more fatigued after the first night of work when going to sleep, they won't necessarily sleep well.

The sleep problems of shift workers can mainly be characterized by:

- decreased total sleep time
- poor subjective sleep quality and subsequent (chronic) fatigue
- increased frequency of awakenings during sleep
- decreased proportion of deep sleep (slow wave sleep)
- increased daytime sleepiness

Dahlgren (1981) reported sleep durations of 5, 5.5 and 5.75 hours respectively after the first three night shifts of six rotating shift workers. Tilley et al. (1982) reported an average sleep duration of 5.25 hour in 12 rotating shift workers when on night duty whereas these workers slept 7 hours on average after day duty.

1.2 Pharmacological treatment of shift workers' transient insomnia

Benzodiazepine hypnotics would be particularly suited for "quieting the brain" by enhancing the endogenous inhibitory GABA-ergic activity (Kelly, 1985). As Dement et al. (1984) point out: "At the present time, the single most appropriate use of hypnotics is for transient insomnia. This includes situational insomnia due to acute stress, jet lag and acute shift work change." Furthermore, they state that toxicity, tolerance and rebound insomnia should not be a problem in the treatment of transient insomnia, whereas sleep induction, sleep maintenance and daytime alertness should be the issues of study in this problem area. Treatment with hypnotic drugs should prolong sleep duration, increase subjective sleep quality, increase sleep depth and decrease the frequency of awakenings during sleep. However, treatment with hypnotic drugs should not impose a new burden on the shift worker, namely that of residual sedation. Benzodiazepine hypnotics with rapid onset of action have been recommended for use by shift workers because they are assumed to induce phase-shifts in the circadian cycle (Turek & Losee-Olson, 1986), which would enhance adaptation to a changed work cycle. Three benzodiazepine hypnotics have been specifically advocated for the treatment of shift workers; midazolam 15 mg (Scollo-Lavizzari, 1983; Nicholson & Stone 1983a), triazolam 0.5 mg (Dement et al., 1984; Seidel et al., 1984) and temazepam 20 mg (Nicholson, 1984b).
In table 1.1 an overview of sleep and performance studies with midazolam, triazolam and temazepam are given. A description of the drugs and the major findings with these drugs are discussed below.
Midazolam and triazolam are categorized as ultrashort-acting hypnotics. After oral administration plasma concentrations of both drugs reach maximum values in about 45 minutes. From there, the pharmacokinetic profiles of the two differ in that midazolam's is biphasic and triazolam's monophasic. The former possesses a definite alpha- or distribution phase with a half-life of 0.25 hr. Thereafter midazolam's beta- or elimination phase dominates with a half-life of about 1.5 hrs, which is about one hour less than the 2.5 hrs half-life of triazolam. The final result after six hours is a plasma concentration of midazolam which is about 12 %, and of triazolam, about 34 %, of maximum. Both drugs are entirely excreted in urine as hydroxy metabolites conjugated with glucuronic acid. The alpha-hydroxy metabolites of both drugs are pharmacologically active but less so than their respective parents and are eliminated more rapidly (Ziegler et al., 1983).
Temazepam is absorbed rapidly after oral administration in the soft gelatine capsule formulation. Peak plasma concentration is reached in about one hour. Fall in concentration is biphasic ($t_{½\alpha}$, about 1 hour; $t_{½\beta}$, about 8 hours). About 25 % of administered temazepam is metabolized into

oxazepam, having about the same elimination half-life. The remainder is conjugated with glucuronic acid and excreted in urine.

Midazolam

Scollo-Lavizzari (1983) reported a study in which 12 sleep-deprived healthy volunteers were treated with midazolam 15 mg, oxazepam 15 mg and placebo. Midazolam shortened sleep latency, reduced the frequency of nocturnal awakenings and increased the length of sleep stages 3 and 4. Both midazolam and oxazepam reduced the total waking time and prolonged the total sleep time. No residual performance effects were found. On the basis of these results midazolam was recommended for the treatment of insomnia in shift workers or other transient sleep disturbances, like jet-lag. However, in this study total sleep time was limited to 5 hours so that no inferences about sleep maintenance could be made.

Nicholson & Stone (1983a) report shortened sleep onset and increased duration of stage 2 sleep induced in middle-aged men by midazolam 10 mg, whereas midazolam 20 and 30 mg shortened sleep onset, prolonged total sleep time and stage 2 sleep and reduced the occurrence of drowsy sleep. Performance effects nine hours after administration of midazolam 10, 20 and 30 mg were absent. On the basis of these results Nicholson & Stone recommended midazolam as a particularly useful hypnotic for shift workers whose rest periods tend to be shorter than in those who have a regular nocturnal sleep pattern.

Gudgeon & Hindmarch (1983), using performance tests, demonstrated the potent sedative effects of midazolam 15 and 20 mg at one hour after administration, which had dissipated seven hours after treatment. Loew et al. (1988) showed midazolam 15 mg to be efficacious in elderly patients without the occurrence of severe side effects or rebound insomnia after withdrawal. Hegelbach-Feller et al. (1988) found good efficacy and no side-effects for midazolam 15 mg and triazolam 0.5 mg. The two drugs had an identical effect on sleep latency, but under midazolam the patients woke more frequently during the night and slightly earlier in the morning, suggesting that the duration of action is shorter than that for triazolam. Both drugs had a rebound effect upon withdrawal, that of triazolam being stronger. Hauri et al. (1983) report decreased sleep latency and stage 1 sleep, increased stage 2 sleep, and delayed onset of the first REM period induced by midazolam 20 mg when compared with placebo. Nine hours after administration, no performance effects of midazolam 5 and 10 mg and a slight performance impairment of midazolam 20 mg were found. Borbély et. al (1983a) report no performance impairment nine hours after the administration of midazolam 15 mg, whereas nighttime motor activity was reduced compared with placebo.

Triazolam

Walsh et al. (1984) showed that triazolam 0.5 mg was efficacious in maintaining day-sleep in rotating shift workers. However, upon withdrawal of the drug after two days while night shift was continued, rebound insomnia was apparent.

Seidel et al. (1984) showed that triazolam 0.5 mg was efficacious in prolonging the day-sleep of healthy volunteers relative to placebo. At the same time triazolam treatment didn't impair wakefulness during waking hours as demonstrated by the multiple sleep latency test and performance tests applied repeatedly starting ten hours after administration. Therefore, Seidel et al. recommended the use of triazolam 0.5 mg for adaptation to changed work-rest cycles imposed by rotating shift work or transmeridian travel.

Hindmarch & Clyde (1980) found no severe performance impairment on the morning after triazolam 0.5 mg, but they failed to mention at what time after administration the measurements were taken. Triazolam 0.5 mg produced residual effects on performance nine hours after administration (Borbély et al., 1983a) but no evidence for rebound insomnia, whereas Soldatos & Kales (1981), Hegelbach-Feller (1988) and Borbély et al. (1983b) did. Nicholson and Stone (1980) found some impairing effects of triazolam 0.5 mg ten hours after administration. They reported an increase of total sleep time, a decrease of awake time and drowsy activity and increased latency to the first period of REM under the influence of triazolam 0.5 mg relative to placebo. However, after partial sleep deprivation, when subjects were only allowed to sleep from 2 to 5 a.m, Wickstrom et al. (1988) found impairing performance effects of triazolam 0.5 mg relative to placebo at 4 and 6 hours but not at 10 hours after administration.

Temazepam

Temazepam 20 mg administered orally in the soft gelatine capsule formulation has been studied at least 9 times to determine whether it exerts any residual effect on performance (Nicholson et

Table 1.1 Overview of studies investigating effects of midazolam, triazolam and temazepam on sleep quality, tolerance, rebounds, psychomotor performance, memory and subjective feelings.

authors	type of study	sleep site	adm. time	drug	dose (mg)	# of days	# of Ss.	sample popul.	age group	contr. cond.	sleep param.	improvem. found in	tole-rance	rebound	perform. tests	after # hrs	impair ment	subj. tests	after # hrs	type of change
Lupolover et al. (1981)	dose finding	clinic	night	mida-zolam	5 10 15 20	3-7	75	insomnia patients	20-80 yrs	no	clin. rating	sleep onset # of awakenings	absent	absent				alert ness	upon waking	0
Helcl et al. (1981)	efficacy tolerance	clinic	night	mida-zolam	15	5	40	insomnia patients	50.3 yrs	oxazepam	clin. rating	sleep onset # of awakenings	absent	absent				alert ness	upon waking	+
Gudgeon & Hind march (1983)	efficacy safety		day	mida-zolam	5 10 15 20	1	12	healthy volunt.	?	placebo					CRT, CFF	4 7	yes no	alert ness	4 7	- 0
Nicholson & Stone (1983)	efficacy safety	lab	night	mida-zolam	10 20 30	1	6	healthy volunt.	47-53 yrs	placebo brotiz.	EEG subj.	sleep onset, -time sleep efficiency			DSST	9	no			
Hauri et al. (1983)	dose finding	lab	night	mida-zolam	5 10 20 30	2	17	insomnia patients	25-45 yrs	placebo fluraz	EEG subj.	sleep onset, subj. more stage 2,			DSST memory	9 9	yes yes			
Borbely et al. (1983)	efficacy safety	home	night	mida-zolam	7.5 15	1	15	healthy volunt.	25-36 yrs	placebo triazol.	actim. subj.	motor activity subj.sl.qual.		absent	typing	9-10	no			
Scollo-Laviz-zari (1983)	efficacy safety	lab	day	mida-zolam	15	1	12	shift-wokers	22-27 yrs	placebo oxazepam	EEG subj.	# of awakenings more stages 3 & 4			Vienna RT others	5-6	no	alert ness	5-6	0
Allen et al. (1986)	efficacy tolerance	clinic	night	mida-zolam	15	28-84	175	insomnia patients	18-65 yrs	tema-zepam	clin. rating	sleep onset # of awakenings	inverse	absent						
Castleden et al. (1987)	effect of age	lab	day	mida-zolam	15	1	12 12	old & young healthy	65-80 22-37 yrs	placebo	EEG	sleep efficiency		wake-fulness	CFF RT sway	4 4 4	no no no	alert ness	8	+
Loew et al. (1988)	efficacy safety	clinic	night	mida-zolam	15	5	61	old in-somniacs	69-96 yrs	oxa-zepam	clin. rating	sleep onset, -time # of awakenings		absent						
Borbely et al. (1988)	amnesia	lab	night	mida-zolam	7.5 15	1	10	healthy volunt.	22-29 yrs	placebo	actim. subj.	motor activity activity periods			episodes words	8 8	yes no	alert ness	8	0
Hegelbach et al. (1988)	efficacy rebounds	home	night	mida-zolam	15	3	30	insomnia patients	21-75 yrs	placebo triazol.	subj. rating	sleep onset # of awakenings		insomnia				alert ness	upon waking	0

authors	type of study	sleep site	adm. time	drug	dose (mg)	# of days	# of Ss.	sample popul.	age group	contr. cond.	sleep param.	improvem. found in	tole-rance	rebound	perform. tests	after # hrs	impair ment	subj. tests	after # hrs	type of change
Hindmarch & Clyde (1980)	efficacy safety	?	night	tria-zolam	0.5	4	20	healthy volunt.	20 yrs avg.	baseline nitraz.	subj. rating	sleep onset sleep quality			CRT, CFF other	? ?	no yes	alert ness	upon waking	0
Nicholson & Stone (1980)	efficacy safety	lab	night	tria-zolam	0.25 0.5		6	healthy volunt.	20-30 yrs	placebo flunit.	EEG subj.	total sleep time sleep efficiency			tracking	10	yes	alert ness	10	0
Borbely et al. (1983a)	efficacy safety	home	night	tria-zolam	0.25 0.5	1	15	healthy volunt.	25-36 yrs	placebo midazol.	actim. subj.	motor activity subj.sl.qual.		absent	typing	9-10	yes			
Borbely et al. (1983b)	efficacy withdrawal	lab	night zolam	tria-	0.5	1	8 volunt.	healthy	23-30 yrs	pla flur flunitr.	EEG	less act. in 1-9Hz more 9-14 Hz		present						
Walsh et al. (1984)	efficacy safety	lab	day	tria-zolam	0.5	2	10	rotating shiftw.	21-49 yrs	placebo baseline	EEG SSQ	total sleep time subj. sleep qual.		insomnia	DSST card sort	7 7	yes no			
Seidel et al. (1984)	efficacy safety	lab	day	tria-zolam	0.5	3	24	healthy volunt.	20-33 yrs	placebo fluraz.	EEG MSLT	sleep maintenance sleep onset			DSST tracking	8 8	no no	alert ness	8	0/+
Wickstrom et al. (1988)	safety sl.depr.	lab	night 2-5 am	tria-zolam	0.25 0.5	1	16	healthy volunt.	21-31 yrs	placebo ethanol	MSLT	sleep onset			percept. motor	6 6	yes yes	alert ness	8	0
Wickstrom et al. (1988)	safety	lab	day	tria-zolam	0.25	1	8	healthy volunt.	19-24	placebo ethanol	MSLT	sleep onset			percept. motor	4	yes	alert ness	4	0
Scharf et al. (1988)	amnesia	lab	night	tria-zolam	0.5	1	22	healthy volunt.	21-37 yrs	placebo					word-list	8	yes			
Hegelbach et al. (1988)	efficacy rebounds	home	night	tria-zolam	0.5	3	30	insomnia patients	21-75 yrs	placebo midazol.	subj. rating	sleep onset # of awakenings		insomnia				alert ness	upon waking	0
Nicholson (1984)	safety efficacy	army	night	tema-zepam	20	2	?	combat air crew	?		clin. rating	sleep quality			subj.work perform.	6-8	no	alert ness	6-8	0
Borbely et al. (1984)	efficacy safety	home	night	tema-zepam	20 30	1	14	healthy volunt.	23-43 yrs	placebo	actim. subj.	motor activity subj.sl.qual.		absent				alert ness	upon waking	0 20mg - 30mg
Volkerts & O' Hanlon (1985)	safety efficacy	home	night	tema-zepam	20	8	11	former insomniacs	26-38 yrs	baseline nitraz.	subj. rating	sleep time subj.sl.quality	present		driving perform.	10 16	no no			
Allen et al. (1986)	efficacy tolerance	clinic	night	tema-zepam	20	28-84	175	insomnia patients	18-65 yrs	mida-zolam	clin. rating	sleep onset # of awakenings	inverse	absent						

al., 1978; Nicholson, 1984a). No residual effect has ever been observed in laboratory tests 9 - 12 hours after ingestion when the intervening period included night sleep (O'Hanlon et al., 1985). The absence of a residual effect of temazepam 20 mg in a more realistic task which depends upon sustained attention and perceptual-motor coordination was demonstrated in an investigation of temazepam's effect upon driving performance by O'Hanlon and Volkerts (1986).
Nicholson (1984b) was responsible to some extent for supervising the treatment of transient insomnia in military aircrews during the Falklands War. The British military relied heavily upon temazepam 20mg (soft gelatine capsule formulation) and according to Nicholson this hypnotic was efficacious and without residual effects upon combat flying performance after 8- or even 6 hours.

1.3 Measuring sleep efficacy and residual effects of hypnotics

Borbély (1984) showed that sleep depth as reflected by the proportion of slow wave sleep can also be monitored by means of measuring gross bodily movement during sleep. Using this method, Borbély demonstrated that different hypnotic drugs produce different profiles of motor activity. Hypnotics with a long elimination half-life (i.e. flurazepam and flunitrazepam) induced a long-lasting reduction of motor-activity, whereas compounds with a short half-life (triazolam and midazolam) had only a short-lasting effect. The duration of temazepam's effects upon motor activity were between those induced by long- and short-lasting hypnotics respectively. According to Borbély (1984) the time profile of the observed motor activity under the influence of these hypnotics is predictable by the duration of their elimination half-lives. It is unknown however, whether the reduction in gross bodily movement during sleep as described by Borbély is mainly determined by reduced muscle tone, reduced cortical activity, or both. Therefore one has to be cautious when relying on this activity measurement as an indicator of the duration of action of a particular hypnotic. Performance studies have proved very sensitive for the residual sedative action of these hypnotics and should perhaps be combined with activity measurement as indicators of action of a substance. For example, Borbély et al. (1983a, 1984) reported similar motor activity reduction time courses for flunitrazepam 2 mg, flurazepam 30 mg and temazepam 20 mg, the effects of the flunitrazepam being somewhat stronger and the effects in the second half of the night of temazepam-treated sleep somewhat weaker. In studies of the residual performance effects of these drugs upon driving performance 10 and 16 hours after administration respectively, O'Hanlon et al. (1986), reported a number of comparative studies in which flunitrazepam 2 mg and flurazepam 30 mg impaired driving performance 10 and 16 hours after administration. The driving impairment after flurazepam 30 mg measured 10 hours after administration was two to three times worse than after flunitrazepam 2 mg. The impairment 16 hours after administration was still bigger after flurazepam, although less pronounced. Temazepam 20 mg did not impair driving performance at all. Thus, it appears that hypnotic drugs producing similar motor activity reduction profiles during sleep, can have strikingly different residual effects on performance.
As Dettli (1983) explains the terminal half-life is by no means a generally valid classification criterion by which to separate short-acting from long-acting benzodiazepines. Taking into consideration the absorption and distribution rate parameters and receptor binding affinity would greatly improve the accuracy of predictions.

1.4 Operational hypotheses

The purpose of the study reported here was to study the efficacy of midazolam 15 mg, triazolam 0.5 mg and temazepam 20 mg for promoting day-sleep in rotating shift workers using Borbély's activity measurement technique, and to test for residual sedation effects using both de Gier's (1980) and O'Hanlon's (1984) city driving and highway driving tests respectively. The hypotheses were tested as follows:

1. The unmedicated sleep of rotating shift workers after night shift is characterized by restless sleep with higher motor activity during sleep and too early awakening leading to a short day-sleep period (6 hours average). An increased number of sleep complaints will result as well as fatigue throughout the subsequent waking period. These effects will be more pronounced at the beginning of the nightshift period than at the end of the nightshift period.

2. Hypnotic drugs have the following effects: motor activity will be reduced during sleep; sleep period will be prolonged; sleep complaints and fatigue throughout the day will diminish. However, residual sedation effects may differ between drugs, resulting in a differential car driving impairment.

2. METHOD

2.1 Subjects

Eighteen (15 men and 3 women) rotating shift workers participated as subjects in this study. Two subjects dropped out before completion of all treatment conditions because they were able to acquire new jobs which did not include shift work. One subject dropped out because he suffered from a severe overreaction and could not continue medication (see Appendix A). Another subject did not complete one treatment condition because she suffered from an adverse reaction (see Appendix B). Thus, the results described concern the remaining fourteen (12 male and 2 female) subjects. They ranged in age from 24 to 50 years (mean $\pm$ SD = 35.3 $\pm$ 8.3) and all had held a drivers licence for at least 5 years and were experienced drivers. They had driven at least 5000 km/yr (mean $\pm$ SD = 35,000 $\pm$ 30,000 km/yr). Exclusion criteria were history of alcohol or drug abuse, cardiovascular, neurological or psychiatric disorders, and excessive smoking. Before the trial, the subjects gave informed consent and upon completion of all tests they were paid Hfl. 750.-
Five subjects were taxi drivers whose night work hours were generally 21.30h-7.00h, three were working in a hospital as nurses at 23.00-8.00h, two were receptionists and four were working as operators in industrial plants at 22.00-6.00h. All subjects fulfilled at least two of the following criteria with respect to day-sleep after night work:

1. Latency to sleep exceeding 30 min.
2. Two or more spontaneous awakenings per major period of day sleep.
3. A total sleep duration of six hours or less during the major day sleep (The necessity of resorting to naps for supplementing the major day sleep is viewed as a sign of broken or disturbed sleep, interfering with practical and leisure activities, even when the total duration of all day sleep exceeds six hours).
4. Chronic feelings of fatigue or unusual drowsiness upon awakening, during the remainder of the day or during night duty.
5. The need for recovery sleep on the first free day after night duty exceeding 10 hours in duration.

2.2 Drugs

Agents administered orally each day for five days during the treatment conditions were as follows: Midazolam 15 mg OD p.o. (MID), Triazolam 0.5 mg OD p.o. (TRI), Temazepam 20 mg OD p.o. (TEM) and Placebo (PLA). These were administered double blind, using a double dummy technique.

2.3 Design

The study was conducted according to a cross-over design. The first within (cross-over) factor was Treatment Condition. Each comprised the administration of a drug or placebo in a subchronic series lasting five days. The second within factor was Day of Treatment. Sleep data were acquired on each of the five days during the treatment. On the 1st and the 5th day of treatment the subjects slept in the laboratory, on the intervening days they slept at their homes. Driving performance was measured on the 1st and the 5th days in the treatment period.

2.4 Procedure

Separate treatments were administered at least one week apart and no other internal medication was allowed between successive treatments. During the week before the first treatment each subject performed a "dress-rehearsal" of the procedure, which included sleeping in the laboratory and performing the driving tests.

In figure 2.1 a time course of one full treatment period is drawn so that the relevant activities can be seen in time perspective. On the 1st and the 5th days of treatment subjects slept in the laboratory. They were picked up after night duty from their work or at home in the morning and were transported to the laboratory. They were given medication and went to bed at the scheduled time, which as much as possible matched the end of the subjects' working hours. The scheduled times were either 6.30, 7.30 or 8.30 AM and in a few exceptional cases 5.30 or 9.30 AM.

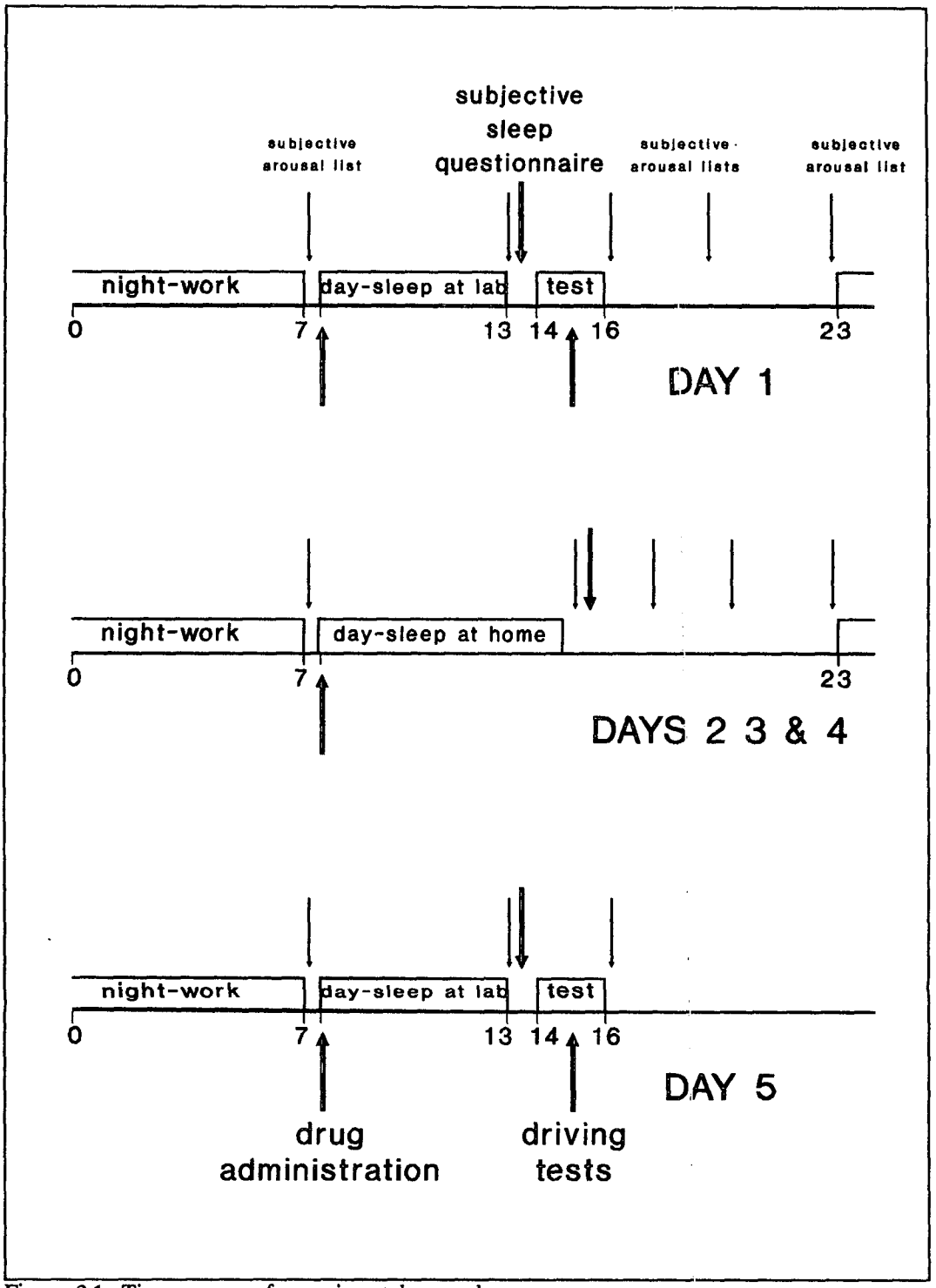

Figure 2.1 Time course of experimental procedures

To measure sleep depth and in order to accurately determine sleep latency and total sleep time, subjects wore a wrist activity meter (ZAK). In the laboratory, the total sleep time was limited to 5.5 hours. If the subjects were still sleeping at that time, they were woken and given time to shower and dress. A light meal was then served. Subjects were not allowed to drink coffee but could drink one cup of tea. After consuming breakfast, they completed a sleep quality questionnaire and a 10-item subjective arousal questionnaire. The driving tests always took place between 6.5 and 8.5 hours after drug ingestion. The city driving test started 6.5 hours after administration and lasted 30 minutes. The highway driving test started 7.25 hours after administration and lasted one hour. Subjects returned to the laboratory 8.5 hours after drug administration. After the driving test, the subjective arousal questionnaire was again administered and the subjects were transported home by the experimenter. On the 1st day of treatment subjects received their medication for the following three days. On the 2nd, 3rd and 4th days of

treatment, the subjects slept at their homes as they normally would. They were instructed to take their medication immediately before going to bed, to put the actimeter device on at that time and remove it upon awakening. They were also instructed to score the subjective arousal questionnaire prior to going to bed and upon awakening. Further, subjects wore a Seiko RC-1000 or RC-4000 wrist watch which was programmed to beep at several times in the afternoon, in the evening and at night, during their work. At these times subjects had to score the subjective arousal questionnaire.

2.5 Sleep registration

Subjects slept in our sleep laboratory on the 1st and the 5th days of each treatment series. The two sleeping rooms were windowless, ventilated and sound-isolated. During sleep, subjects wore a wrist actimeter (ZAK) that essentially consisted of a piëzo-electric accelerometer. The device was calibrated in such a way that after each two-minute period, the relative amount of movement, denominated by a number on a scale ranging from 0 to 100, was stored in the device's 8 Kbyte memory. In this way sleep parameters could easily be measured both in the laboratory and at the subjects' homes. After the 5-day treatment period the actimeter's memory was read by and stored in an Olivetti PC.
Subjective sleep quality was scored by the subjects immediately after awakening. Subjects scored a 14-item questionnaire (Mulder-Hajonides, 1981; appendix C).

2.6 Driving tests

The test vehicle was an extensively modified 1986 Volvo 240 GL station wagon (see figure 2.2). Redundant controls were mounted at the front passenger seat, for use, if necessary, by one of the accompanying experimenters (a licensed driving instructor) in the case of emergency.

2.6.1 City-driving test

The city driving test involved operating the test vehicle over a preselected urban circuit. The circuit contained 49 intersections in which traffic coming from the right had priority. There were 53 other intersections with traffic coming from the right and 76 from the left respectively. A schematic map of the test route is shown in Appendix D. The length of the circuit was 9.3 km and approximately 30 minutes were required to complete it. The subjects were requested to drive according to the instructions given by the instructor and commonly accepted safety standards. Driving behavior was scored by the instructor using a 111-item checklist developed by the Royal Dutch Organization of Motorists (ANWB). Summation of the error scores on 22 safety-related items comprised the final dependent variable (de Gier, 1979; de Gier et al., 1981; 1986).
Eye movements were recorded from subjects not wearing glasses (N = 10). Subjects wore a helmet-mounted eye-movement registration system (NAK 4 eyemarker). A cyclope-lens, recording the visual scene as seen by the subject, was mounted in front of the eyemarker. A glassfiber cable connected the eyemarker to a video camera (Bauer) and -recorder (Sharp). Using the cornea reflection technique, the mirror-image of a lamp which was pointed at the right eyeball of the subject was calibrated as the fixation point and was as such, mixed into the visual scene and recorded on video tape. The video recordings were observed systematically with respect to location and duration of visual inspection of the intersection, and the behavior of the driver in all situations concerning the above described intersections was scored in a dichotomy as sufficient / erroneous. This scoring procedure was originally developed by Buikhuisen & Jongman (1970) and proved sensitive to the influence of alcohol. All registrations were observed double-blind with regard to drug-treatment and were scored at least twice.

2.6.2 Highway-driving test

The highway-driving test involved operating a specially instrumented automobile over a 100 km segment of the primary highway (A2) running east-west between the Belgian cities of Maasmechelen and Diest. The subject drove in the right traffic lane, attempting to maintain a constant speed (85-100 km/h) and steady lateral position between delineated (paint-stripe) lane boundaries, except while engaged in passing manoeuvres, which he was instructed to keep to a minimum.
External modifications to the test vehicle consisted of an electro-optical device ("Lanetracker" Human Factors Research Inc.) for measuring the vehicle's lateral position relative to the painted

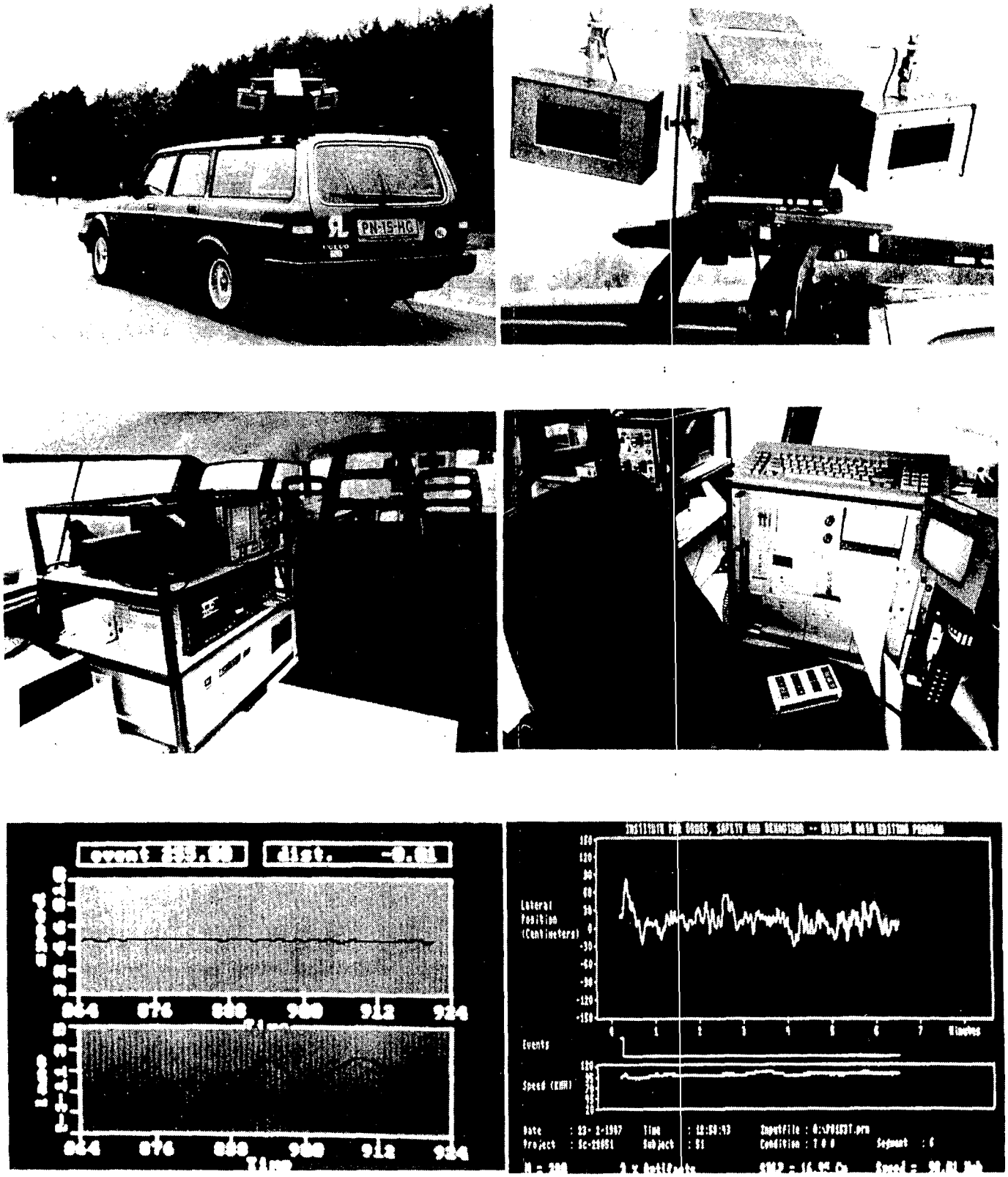

Figure 2.2 a) The instrumented test vehicle on the road. b) The lane-tracker flanked by infra red lights. c) Oscilloscope, data-recorder and PC-AT rack-mounted inside the car. d) Computer- keyboard and screen, paper-recorder and event-keyboard. e) On-line representation of real-time sampling of speed and lateral position. f) Off-line graphical editor screen displaying lateral position and speed.

stripe road delineation. The lanetracker was mounted in protective housing over the left rear corner of the vehicle and oriented so that its lens acquired an image over the road surface directly behind the vehicle. A band of this image corresponding to a 3 m line on the road at right angles to the direction of the vehicle's travel was focussed on a linear array of 256 capacitor-coupled photo-diodes. Luminance from the white line was normally the greatest falling upon the array, thus causing the most rapid discharge of a particular diode capacitor. The position of that diode was determined relative to a calibrated null-point in rapid (>100 Hz, depending upon ambient illumination) electronic scanning. This difference was then used to generate an analog voltage, proportional to the distance of the vehicle from the line. The null-point was set so that the system's output would be 0 volts when the vehicle was in the exact centre of the traffic lane. Full-scale values (± 5 volts) were obtained when the vehicle moved 1.5 m to the left or right. Taking into account both the asymmetric location of the device and the vehicle's width (1.6 m), the maximum readings were obtained when the vehicle's left wheels were about 0.38 m into the adjacent traffic lane and when the vehicle's right wheels were about 0.38 m onto the road shoulder.
Speed was measured from a pulse generator triggered by magnetic induction at a rate proportional to the revolutions of the drive wheels. Pulses were counted and subsequently converted into an analog signal with a dynamic range from 0 to 10 Volts.
Steering wheel angle was measured by linking the steering axis to an 11-bits optical absolute encoder, which converts mechanical shaft rotation to an accurate electrical output in binary format. The digital signal was calibrated in such a way that the 2048 bits of measurement space was equally distributed over a 108° steering angle range. Measurement of the steering angle was thus accomplished from 0° to 54° either to the left or right, with a precision of 0.0527°.
The analog signals from lateral position and speed sensors were A/D converted (Burr-Brown data-acquisition hardware with Labtech Notebook Software) and were simultaneously sampled on-line together with the digital steering angle signal, at a rate of 4 Hz by an IBM-compatible AT computer aboard the test vehicle. The analog signals of lateral position and speed and the D/A converted steering angle signal were recorded on an FM tape recorder (TEAC). An experimenter, riding in the vehicle's right rear passenger seat, had access to an 8 button keyboard. Separate or combined key inputs generated corresponding pulse codes that were registered by the computer to indicate the beginning and end of passing manoeuvres or transient conditions that could influence the driver.

2.6.3 Time to line crossing

Additionally, a measure developed by Godthelp (1984), called time to line crossing (TLC) was calculated for each data-sample. Basically, TLC represents the time available for a driver to neglect path errors until the moment at which any part of the vehicle reaches one of the lane boundaries (Godthelp, 1988). The TLC values at each sampled measurement moment were calculated applying the basic formula in an algorithm (see appendix E).
Godthelp et al. (1984) state that TLC can be used as a descriptor of driving performance concerned with lane keeping on the basis of an integration of speed, lateral position, heading angle and steering-wheel angle data. As such, TLC appears to be an integrated quantitative measure of driving performance, and also a descriptor of that parameter which the driver is actually trying to control. In this way, TLC may also provide insight into the probability of lane exceedance during a particular run. Furthermore, individual differences in TLC might reflect differences in risk taking behavior.
TLC distributions over time are obtained for lane crossings to the left and right respectively. These distributions are characterized by a high degree of skew. Therefore the median rather than the mean is taken to indicate the central tendency. Medians for both the left and right TLC's as well as their 85th percentile points were chosen as the dependent variables.

2.7 Subjective measures

2.7.1. Subjective rating of driving performance and side-effects

Four types of retrospective self-rating scales were administered to the subjects after each driving test. These provided separate measures of the following: 1) mental activation, 2) perceived effort, 3) perceived driving quality and 4) presence and severity of drug side-effects. Mental activation was measured using Bartenwerfer's Scale (Bartenwerfer, 1969; Appendix F). The subject marked a point along an activation continuum in relation to reference points identifying activation states

that he could expect to experience in various situations. The latter were described by short sentences (e.g. "I am reading a newspaper while resting on a couch") set at the psychophysically calibrated points. Scores, or the measured distances from individual marks to the end of the scale, are, according to the scale's theory of construction, assumed to lie on an interval scale. Effort experienced while performing the driving task and driving quality were also measured subjectively using corresponding visual-analog scales (Appendices G & H, respectively). Presence of drug side-effects were assessed using an 8-item questionnaire (Appendix I). Each item was related to a specific complaint (e.g. "Dry mouth"). Responses to an item could be made on a 3-level ordinal scale ("None", "Some", "Severe").

2.7.2 Subjective mood scales

A 10-item subjective mood scale was administered after waking. Subjects had to rate their subjective state on an absolute scale. The same items were repeatedly scored throughout the day and night, however all later scores were relative (Fahrenberg et al., 1979); i.e. subjects now had to rate how much their mood had changed relative to their perceived state after awakening. This part of the study will be reported in more detail elsewhere (Hausen, 1988).

2.8 Data reduction and analysis

Sleep

Activity data were time-stamped numbers in a 0-100 range compiled at two minute intervals. The moments of mounting and removing the activity meters were marked by the appearance or disappea-rance of an asterisk attached to the numerical code. Sleep latency was calculated as the time elapsed between the moment of mounting and the moment of onset of the first four consecutive 2-minute periods of zero-activity. Taking the latter as a starting point of the total sleep period, the moment of awakening was taken as the last 2-minute period that showed zero-activity before removing the activity meter. The relative amount of still sleep was the percentage of time in the total sleep period that consisted of zero-activity readings. The frequency of nocturnal movement periods was the number of consecutive periods of nonzero-activity per hour of sleep. The amount of movement consisted of the summated activity readings per hour of sleep. The amount of early movement was the percentage of movement that occurred during the first half of the total sleep period.

Highway driving

Data obtained from highway driving tests were edited off-line by means of an interactive computer-program. All disturbing manoeuvres, such as overtaking, or any other artefacts were removed from the data by the experimenter. Descriptive statistics were calculated for every successive 5 km segment in each test. These were mean, standard deviation, skew and kurtosis of lateral position, speed and steering angle and the medians and 85th percentile points of the TLC distribution to the left and to the right, as well as the percentage of time driven out of the lane. Averages of each parameter across all 20 segments were also calculated as the representative measure for the entire test. With respect to the latter summary statistics, variance between segments was removed in the calculation of the parameters of lateral position, speed, steering wheel angle and TLC.
All data were analyzed using multivariate analysis of variance (Horton, 1978). This was accomplished using the MANOVA module (Norusis, 1985) of the SPSSX program series within a VAX 8650 (DEC) computer. Multivariate overall effects were tested as well as main effects of treatment condition and day of treatment.

3. RESULTS

3.1 Sleep

Data loss from actimeter devices was considerable in some cases. Occasionally subjects forgot to wear the actimeter at home. Some data loss could be attributed to experimenter errors. However, the most severe form of data loss was equipment failure which accounted for the loss of three entire conditions in the respective three subjects. Thus, data from these subjects could not be included in the statistical analyses. Therefore, all statistical analyses pertaining the sleep data were performed on eleven subjects. Occasional missing data from the aforementioned subjects concerning nights slept at home were replaced by the average values of the other nights slept at home in the same condition. Data concerning the analysis of subjective sleep quality were performed upon thirteen subjects, since data from one subject were incomplete.

3.1.1 Subjective sleep quality

Subjects rated the absence/presence of 14 complaints shortly after awakening. Scores are presented as percentages of maximum (0 complaints = 100%). In table 3.1 the average percentage scores are listed. Subjective sleep quality for the two nights prior to night shift did not differ significantly between conditions. Multivariate analysis revealed an overall drug effect ($F = 5.59$; $df = 3,10$; $p < .01$).

Table 3.1 Subjective sleep quality (% of optimal score) of night-sleep before and after drug- and placebo treated night-shift period, and of day-sleep during a 5-day night-shift period. Means and standard deviations per treatment condition and day of treatment (N=13).

	Midazolam		Triazolam		Temazepam		Placebo		Sleep	
Day before treatment	Mean	SD	Mean	SD	Mean	SD	Mean	SD	at	during
1	76.37	29.22	86.26	26.32	78.57	22.59	80.22	27.53	Home	night
2	86.81	15.93	86.26	15.00	83.52	17.59	86.81	18.17	Home	night
Day of treatment										
1	72.53	14.24	76.37	14.40	50.55	25.16	62.09	29.79	Lab	day
2	79.12	20.51	74.18	18.79	71.98	28.19	68.13	26.82	Home	day
3	79.67	16.20	67.03	25.18	63.19	28.84	76.92	20.65	Home	day
4	84.07	27.69	85.16	17.61	79.12	16.87	75.82	29.96	Home	day
5	73.08	16.28	69.78	18.93	74.73	17.16	75.82	22.31	Lab	day
Day after treatment										
1	81.87	20.75	64.84	27.27	68.13	30.11	71.98	27.43	Home	night
2	82.97	26.97	75.27	31.89	68.68	30.38	78.02	21.12	Home	night

Subjective sleep quality after midazolam treatment is improved relative to placebo conditions, yielding a significant main effect of midazolam ($F = 4.53$; $df = 1,12$; $p < .05$). Improved subjective sleep quality after midazolam is most prominent when subjects slept at home on days 2, 3 and 4 of treatment and also on the first two normal nights when nightshift and treatment have ended. Under placebo conditions the influence of night shift work on subjective sleep quality is most prominent on days 1 and 2.
Summarized data from laboratory sleep and home sleep separately are shown in figures 3.1 and 3.2 respectively. In figure 3.1 it can be seen that in laboratory conditions, the subjective quality of unmedicated day-sleep after the first night-shift is significantly impaired relative to the subjective sleep quality on the fifth day ($F = 6.10$; $df = 12$; $p < .05$). The same pattern is also seen after temazepam treatment ($F = 5.76$; $df = 12$; $p < .05$), but not after treatment with midazolam or triazolam which apparently improved the subjective day-sleep quality after the first working night.

Figure 3.2 shows that subjective quality of day-sleep at home during the night shift period is worse after treatment with placebo, triazolam and temazepam ($F = 4.84$; $df = 12$; $p < .05$), but not after treatment with midazolam. Subjective sleep quality for the first two nights at home after the night-shift period treated with triazolam and temazepam had ended, was still lower. This tendency may point to a rebound insomnia effect. With respect to placebo, a tendency of improvement was observed after the night-shift period had ended.

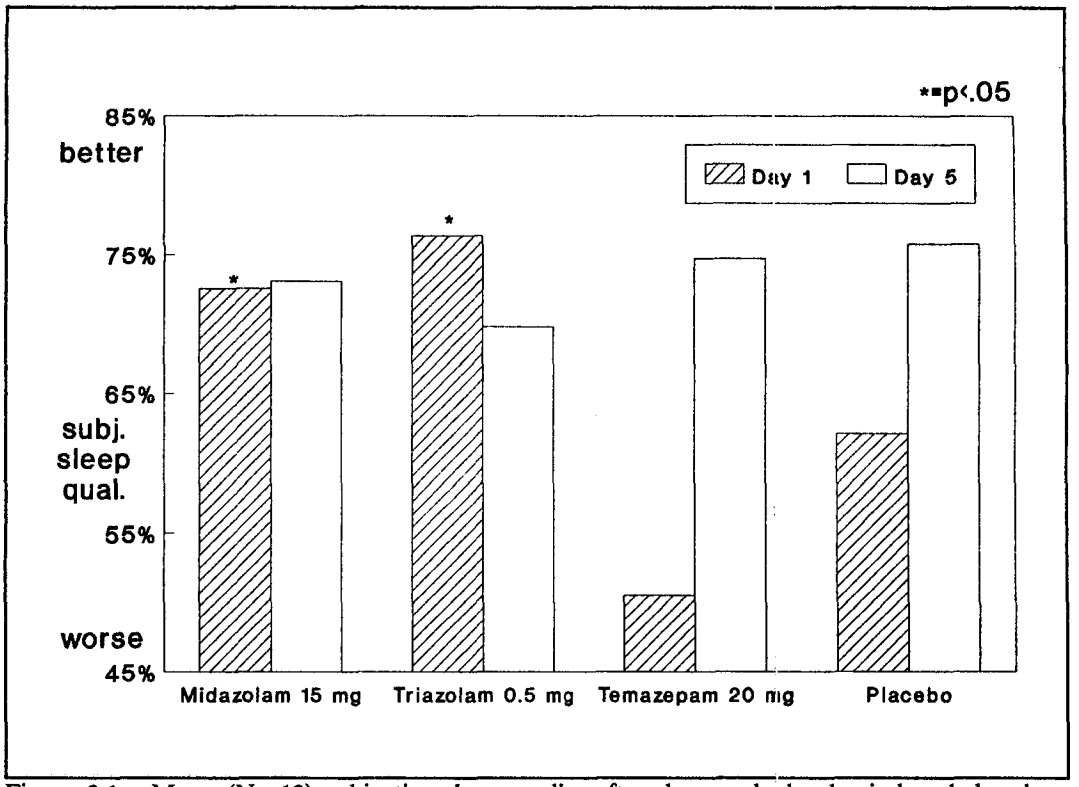

Figure 3.1 Mean (N = 13) subjective sleep quality after drug and placebo induced day-sleep in the laboratory on the 1st and the 5th day of treatment.

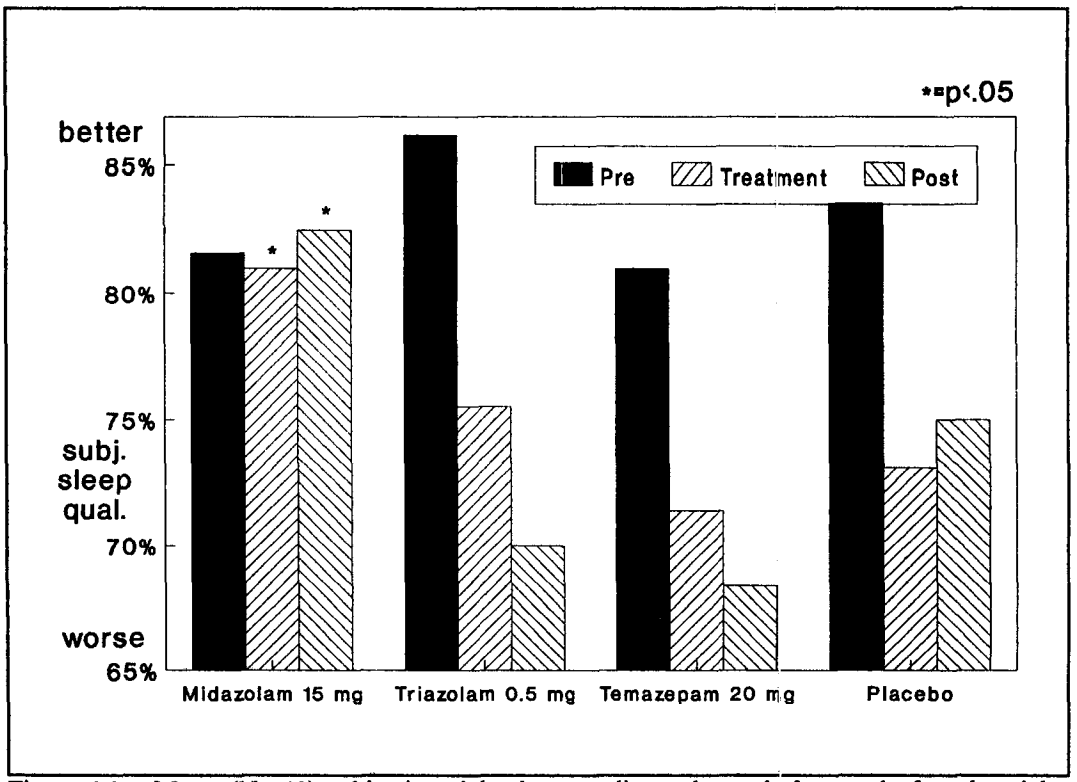

Figure 3.2 Mean (N = 13) subjective night-sleep quality at home before and after the night-shift period and drug and placebo induced subjective day-sleep quality within the night-shift period.

3.1.2 Total sleep time

Although sleep time was limited to 5.5 hours only on days 1 and 5 of treatment when subjects slept in the laboratory, considerable effects of drug treatment were found on total sleep time. Total sleep time increased after midazolam treatment on the first and the second day of treatment and on the first day of treatment with triazolam. The overall multivariate effect of drug treatment on total sleep time was significant ($F=5.12$; $df=3,8$; $p<.05$). This effect could be attributed mainly to an overall prolonged total sleep time under the influence of midazolam, as demonstrated by a significant main effect of midazolam ($F=7.94$; $df=1,10$; $p<.05$). At home, average total sleep time was longest under the influence of midazolam, whereas on the first day of treatment average total sleep time was significantly less in the laboratory under placebo conditions relative to triazolam ($F=12.96$; $df=10$; $p<.005$) and midazolam ($F=5.34$; $df=10$; $p<.05$). The same trend could be observed with regard to treatment with temazepam but the effect was not significant. Unmedicated total sleep time is also shortest at home on the second day of treatment with placebo, where sleep time is not limited to 5.5 hours; 5.53 hours turns out to be the average total sleep time on that day. From day 2 through day 4, total sleep time under placebo conditions gradually increases by 0.5 hour per day to 6.5 hours on the fourth day of treatment. Whereas the placebo condition shows a clear trend with respect to total sleep time over the days, there seems to be a compensation-effect for the short sleep period on the first day, on the second day of all drug treatment conditions, followed by a relapse on day 3. This striking effect can be seen to some extent in the subjective sleep quality data as well.

Table 3.2 Total day-sleep time (hours) after working at night. Means and standard deviations per treatment condition and day of treatment (N=11). The number of subjects who had to be woken by the experimenter in the laboratory is given in brackets.

Day of treatment	Midazolam		Triazolam		Temazepam		Placebo		Sleep at
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
1	5.42	.23 [10]	5.50	.21 [11]	5.29	.30 [10]	4.95	.55 [4]	Lab
2	7.22	.94	6.03	1.49	6.13	.97	5.53	1.31	Home
3	6.76	.59	5.95	2.00	5.75	1.24	6.03	1.41	Home
4	7.50	1.27	6.38	1.41	5.70	1.25	6.50	.88	Home
5	5.21	.39 [8]	5.30	.25 [6]	5.10	.66 [6]	5.28	.31 [8]	Lab

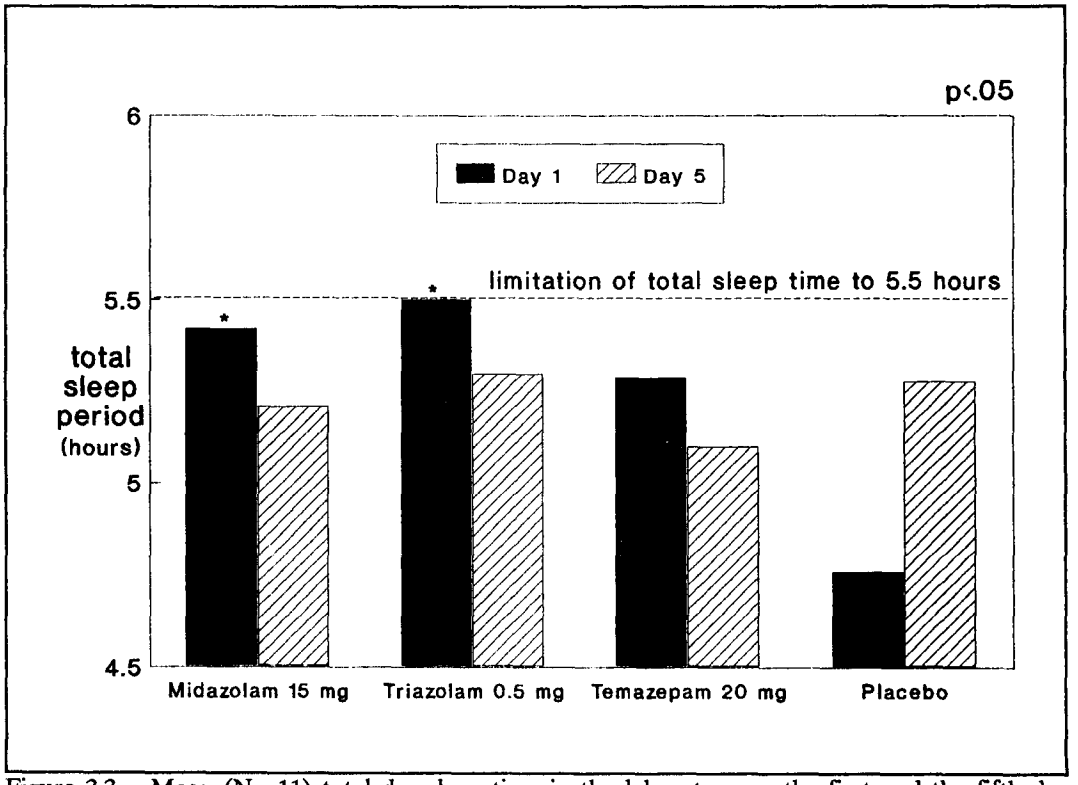

Figure 3.3 Mean (N=11) total day-sleep time in the laboratory on the first and the fifth day of treatment with drugs and placebo.

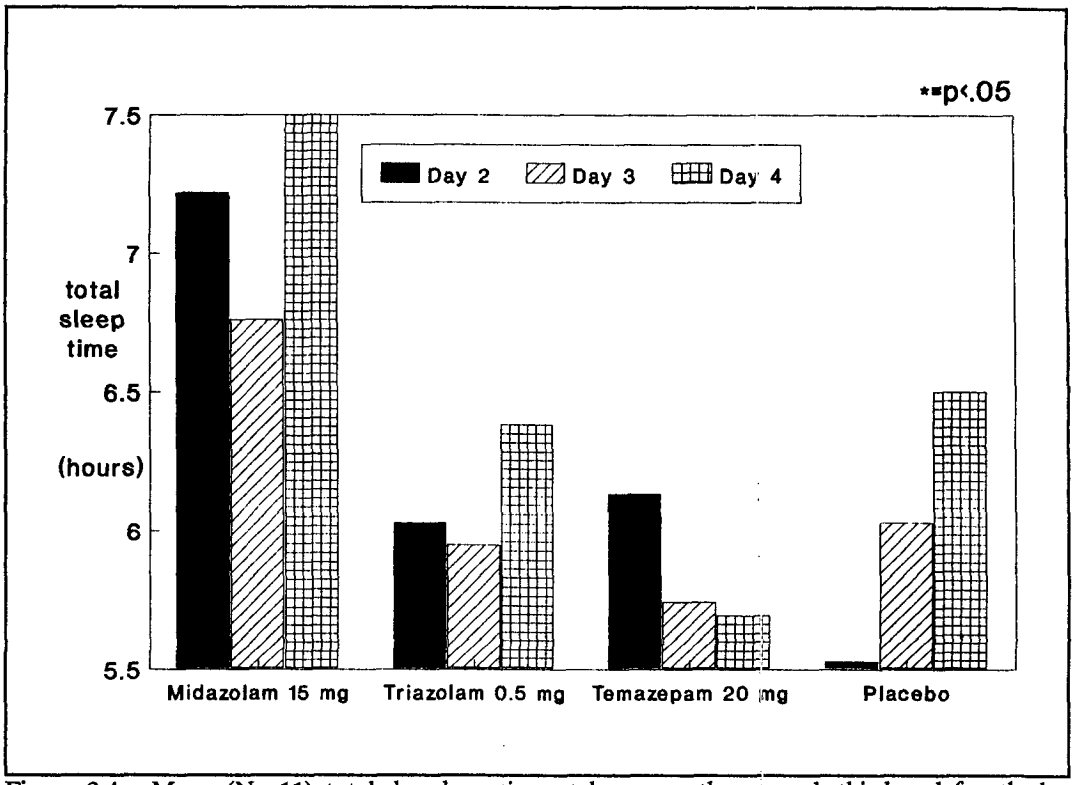

Figure 3.4 Mean (N=11) total day-sleep time at home on the second, third and fourth day of treatment with drugs and placebo.

Figures 3.3 and 3.4 depict the effects of treatment conditions on day-sleep in the laboratory and at home respectively. In figure 3.4 the adaptation to night-shift can best be seen in the placebo condition. The prolonged total sleep time on the fourth day with respect to that of the second day is significant ($F=9.00$; $df=10$; $p<.01$). Treatment with temazepam seems to produce the opposite of adaptation; i.e. a downward trend with respect to total sleep time can be observed, resulting on the fourth day of treatment in a temazepam induced sleep duration which is 0.8 hour shorter relative to placebo ($F=4.0$; $df=10$; $p<.10$). This result may reflect the consequences of an increased pharmacological tolerance of subjects to temazepam.

3.1.3 Still sleep time

Still sleep time refers to the sleep time during which absolutely no movement is registered. When correcting for the total sleep time, the percentage of still sleep time appears to be higher after treatment with triazolam when compared with midazolam. The multivariate overall effect is significant for laboratory sleep ($F=6.13$; $df=3,8$; $p<.05$). The triazolam - midazolam comparison yields a significant effect as well ($F=5.73$; $df=1,10$; $p<.05$).

Table 3.3 Percentage of still sleep time. Means and standard deviations per treatment condition and day of treatment (N=11).

Day of treatment	Midazolam		Triazolam		Temazepam		Placebo		Sleep at
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
1	82.31	15.17	86.08	12.00	83.80	6.96	83.82	6.35	Lab
2	81.51	9.80	88.09	7.74	83.28	8.60	84.92	8.73	Home
3	81.63	12.13	82.52	12.18	83.78	5.75	82.90	7.74	Home
4	80.08	8.29	87.00	9.68	78.54	10.62	82.98	7.22	Home
5	80.74	14.36	88.36	10.75	84.84	5.75	83.31	7.27	Lab

3.1.4 Sleep latency

Average sleep latency was 12 minutes. No effects of any treatment condition was found on sleep latency.

Table 3.4 Sleep latency (minutes). Means and standard deviations per treatment condition and day of treatment (N=11).

Day of treatment	Midazolam		Triazolam		Temazepam		Placebo		Sleep at
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
1	10.00	4.9	9.82	9.6	15.64	10.5	12.00	9.3	Lab
2	11.64	14.1	12.64	10.0	12.64	9.7	10.36	8.9	Home
3	12.18	11.9	11.64	5.7	10.82	8.2	11.09	7.9	Home
4	13.64	11.1	10.64	7.1	11.73	7.7	13.09	9.6	Home
5	12.91	6.3	10.36	10.0	21.45	32.6	13.09	13.1	Lab

3.1.5 Frequency of periods of movement.

The frequency of periods of movement per hour under the influence of triazolam appears to be somewhat less relative to placebo in the laboratory sleep periods. The multivariate effect approaches significance ($F=3.10$; $df=3,8$; $p<.10$) whereas the main effect of triazolam relative to placebo is significant ($F=4.86$; $df=1,10$; $p<.05$).

Table 3.5 Frequency of periods of movement per hour. Means and standard deviations per treatment condition and day of treatment (N=11).

Day of treatment	Midazolam		Triazolam		Temazepam		Placebo		Sleep at
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
1	2.74	1.56	2.11	1.13	2.85	1.16	2.81	1.18	Lab
2	3.33	1.08	2.36	1.48	2.84	1.11	3.01	1.69	Home
3	3.29	1.13	3.21	1.65	3.37	1.30	3.43	1.45	Home
4	3.66	1.07	2.36	1.45	3.21	1.40	3.36	1.33	Home
5	3.16	1.07	1.79	.95	2.76	.79	3.33	1.32	Lab

3.1.6 Amount of movement

The percentage of movement per hour under the influence of triazolam was significantly lower relative to placebo conditions when subjects slept in the laboratory. The multivariate effect was significant ($F=9.59$; $df=3,8$; $p<.01$). The main effect of triazolam was also significant ($F=4.61$; $df=1,10$; $p<.05$).

Table 3.6 Percentage of movement per hour. Means and standard deviations per treatment condition and day of treatment (N=11)

Day of treatment	Midazolam		Triazolam		Temazepam		Placebo		Sleep at
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
1	1.26	1.07	1.00	.95	1.64	.90	1.67	1.07	Lab
2	1.17	.71	.93	.75	1.13	.54	1.13	.89	Home
3	1.18	1.02	1.12	1.00	1.36	.65	1.36	.99	Home
4	1.18	.71	.82	.72	1.39	.66	1.45	1.10	Home
5	1.22	.80	.87	.58	1.35	1.04	1.23	.81	Lab

3.1.7 Amount of early movement

When the amount of registered movement was divided between the first and the second half of

the night for the respective treatment conditions, no difference between treatment conditions was found.

Table 3.7 Percentage of movement during the 1st half of total sleep time compared to the second half of the night. Means and standard deviations per treatment condition and day of treatment (N=11).

Day of treatment	Midazolam		Triazolam		Temazepam		Placebo		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Sleep at
1	48.06	23.6	44.77	27.5	40.43	30.2	43.98	34.1	Lab
2	44.48	15.5	33.16	18.4	34.04	15.9	42.46	10.8	Home
3	49.10	26.4	44.50	12.0	41.39	15.7	56.18	12.9	Home
4	36.61	15.8	46.96	19.4	38.97	19.9	51.16	15.3	Home
5	43.45	22.2	37.83	16.6	43.16	24.8	45.69	16.9	Lab

3.1.8 Summary of sleep-results

Under placebo conditions the day-sleep disturbances caused by night-shift can be mainly characterized by a too-short sleep duration and a decreased subjective sleep quality, especially at the beginning of the night-shift period. Adaptation in terms of sleep duration could be seen at days 2 through 4 when sleep duration progressed from 5.5 hours to 6.5 hours in three days. Subjective sleep quality was especially poor on days 1 & 2, stabilized on days 3, 4 & 5, but was still decreased relative to the pre-nightshift level. No effects were found in terms of sleep latency or activity pattern.

The results clearly show a beneficial effect of midazolam which can be characterized by a prolonged day-sleep time, better subjective day-sleep quality and no changes in sleep latency and the amount and patterns of activity during sleep time. Triazolam diminished activity during sleep and reduced early awakenings in the first day-sleep period in the laboratory, whereas temazepam didn't show any beneficial effect on sleep parameters.

3.2 Driving tests

3.2.1 City driving test

3.2.1.1 Eye movements

Due to data loss, data obtained on days 1 and 5 had to be combined. Data loss could be solely attributed to technical difficulties with calibrating the eye marker. In figure 3.5 the eye-movement data concerning the subjects visual inspection of streets on the right with priority are plotted. There is an overall effect of drug treatment ($F=10.74$; $df=3,6$; $p<.01$). This is entirely due to the effect of triazolam ($F=10.8$; $df=7$; $p<.01$).
Thus, residual effects of triazolam, but not of either midazolam or temazepam impair visual search behavior in city driving, 6.5 hours after drug ingestion.

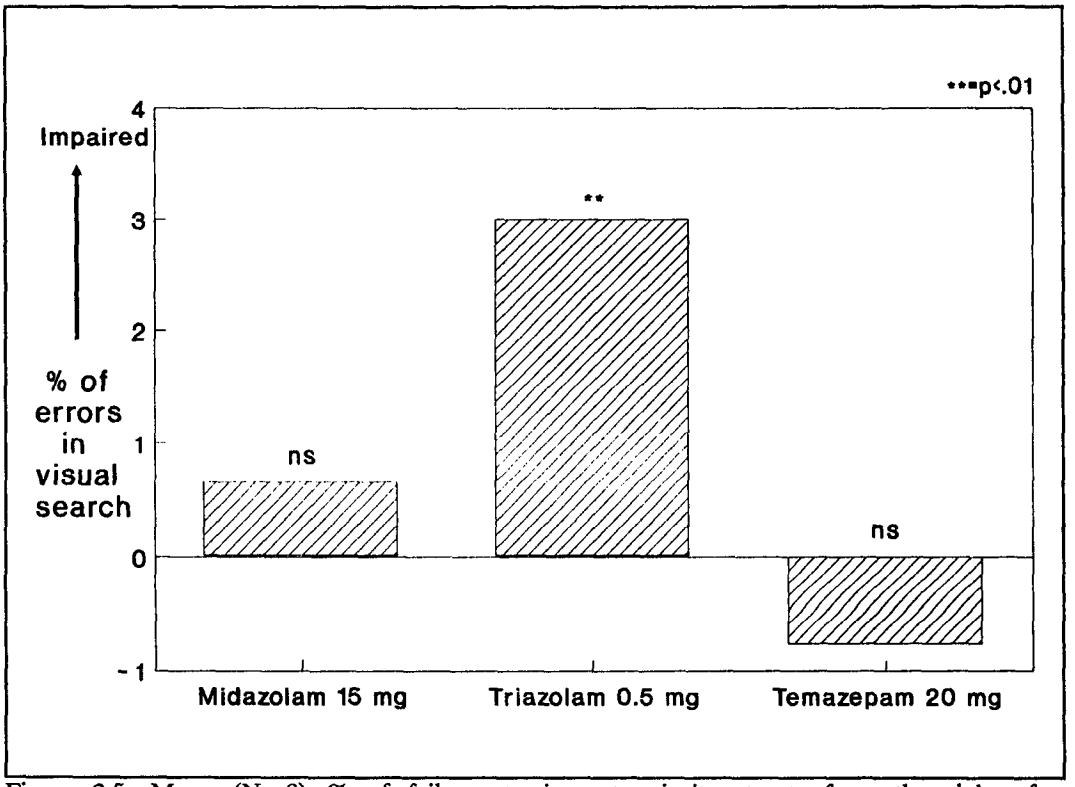

Figure 3.5 Mean (N=8) % of failures to inspect priority streets from the right after treatment with drug or placebo.

In table 3.8 the results of visual search behavior and speed are presented. The data concerning visual inspection of streets on the right and left not having priority show the same trend as the visual inspection of streets on the right with priority, but the differences are not significant. No differences between conditions in terms of speed were found.

Table 3.8 Means and standard deviations (N=8) of percentage of side-streets that were not visually inspected and speed (mean and SD), broken down by treatment condition. The results of days 1 and 5 are combined.

	Midazolam		Triazolam		Temazepam		Placebo	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Right + priority	4.63	4.10	6.88	3.23	3.25	2.87	4.00	2.88
Right no priority	11.69	4.29	14.38	3.48	12.44	4.47	12.31	4.74
Left	32.81	8.35	36.88	9.56	34.94	7.20	31.75	13.13
Speed (Kmh)	30.76	1.91	30.85	2.25	30.59	2.69	30.61	2.32

3.2.1.2 Expert ratings

Expert-ratings of the subjects traffic-behavior during the city test yielded the same pattern of results, however the differences are less marked. However, on the first day of treatment with triazolam, expert-ratings were significantly less, relative to placebo ($F=5.38$; $df=13$; $p<.05$). In table 3.9 the results are presented. In figure 3.6 the results are plotted.

Table 3.9 Means and standard deviations (N=14) of expert rater's percentage score broken down by treatment condition and day of treatment.

	Midazolam		Triazolam		Temazepam		Placebo	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Day 1	77.76	16.33	64.90	19.03	74.95	16.68	77.62	19.63
Day 5	76.84	11.56	70.38	17.96	71.94	21.71	73.43	18.67

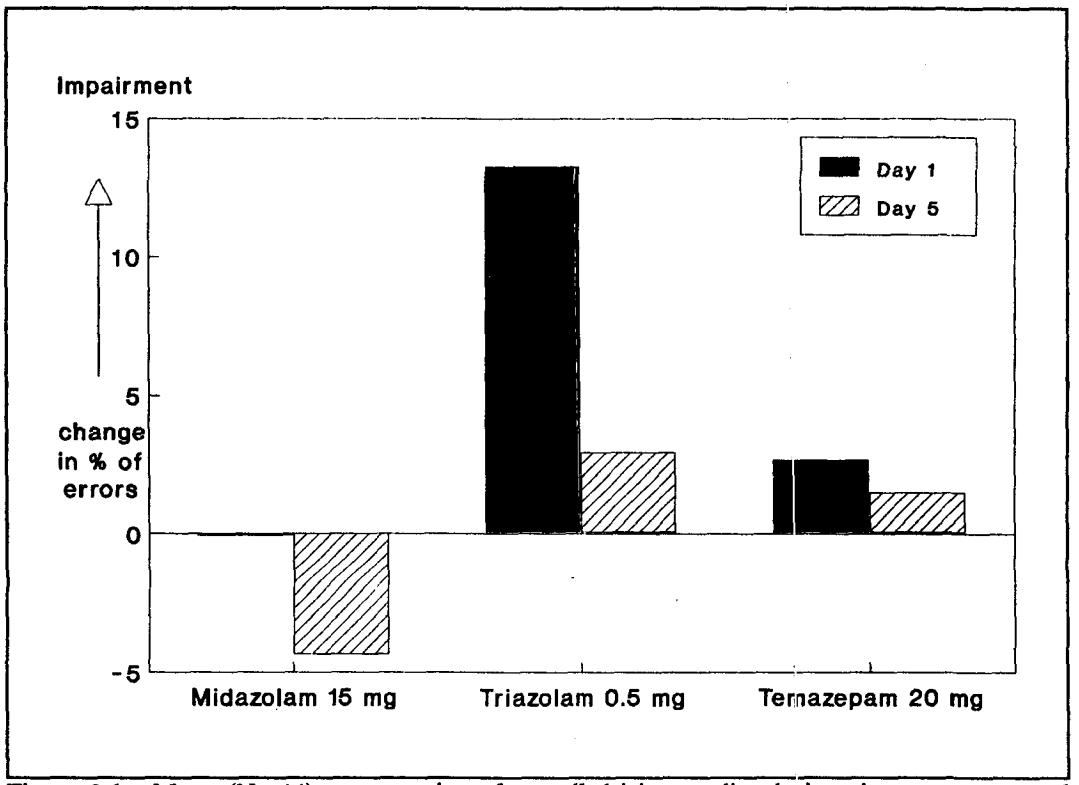

Figure 3.6 Mean (N=14) expert rating of overall driving quality during city test on 1st and 5th days of treatment with drug or placebo.

3.2.2 Highway driving test

In two cases, data obtained from the steering wheel were lost due to technical failure. Thus data analyses concerning steering wheel and TLC data are performed using the 12 remaining complete cases. Careful inspection of the average steering wheel angle data over the course of the experiment showed a trend over time indicating a shift of the average steering wheel angle of about 0.5° to the left. In this way, the calculated TLC distributions were biased to one side.
Means and standard deviations of all dependent variables were calculated over all 5 km measurements obtained from each subject in each test. These were partitioned by groups and treatment conditions. Means and standard deviations were calculated and the results are as shown in Table 3.11.

Table 3.11 Means and standard deviations of dependent variables in highway driving broken down by treatment condition and day of treatment.

	Midazolam				Triazolam				Temazepam				Placebo			
	Day 1		Day 5		Day 1		Day 5		Day 1		Day 5		Day 1		Day 5	
dep vars	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
(N=14):																
Mn_LP	1.46	17.29	.97	17.52	1.11	19.93	-.53	16.98	-3.21	16.63	-1.71	16.48	2.35	25.55	-2.59	16.58
SD_LP	25.44	4.70	24.87	4.59	30.74	6.01	27.78	4.97	23.79	4.55	23.23	3.77	24.17	4.97	23.04	4.14
Mn_SP	94.98	3.23	95.43	3.10	96.23	3.81	95.82	2.74	96.51	3.31	94.73	1.46	96.38	3.41	96.54	3.67
SD_SP	3.44	.88	3.68	1.24	3.78	.78	4.18	1.02	3.45	1.06	3.35	1.12	3.53	.99	4.05	1.10
(N=12):																
SD_ST	1.00	.07	.99	.14	1.03	.13	1.07	.15	1.00	.10	.96	.10	.98	.09	.96	.13
TOL	*.14*	*.23*	*.06*	*.09*	*.99*	*1.60*	*.22*	*.28*	*.16*	*.23*	*.14*	*.17*	*.49*	*1.29*	*.05*	*.09*
TLC50(L+R)	4.68	.22	4.69	.38	4.54	.22	4.30	.46	4.64	.32	4.77	.36	4.69	.31	4.82	.45
TLC50(L)	4.38	.63	4.37	.74	4.32	.61	4.18	.69	4.24	.60	4.37	.70	4.45	.79	4.45	.78
TLC50(R)	4.98	.50	5.02	.43	4.76	.75	4.90	.58	5.03	.29	5.17	.42	4.93	.76	5.18	.55
TLC85(L+R)	3.04	.17	3.06	.23	2.86	.25	2.97	.22	3.03	.18	3.11	.17	3.05	.22	3.12	.25
TLC85(L)	3.09	.45	3.11	.51	3.01	.29	3.00	.43	3.02	.42	3.13	.44	3.18	.52	3.18	.51
TLC85(R)	2.98	.37	3.02	.26	2.71	.69	2.95	.36	3.04	.24	3.09	.31	2.92	.60	3.08	.33

Mn_LP = mean lateral position in cm.
SD_LP = standard deviation of lateral position in cm
Mn_SP = mean speed in km/h
SD_SP = standard deviation of speed in km/h
SD_ST = standard deviation of steering wheel angle in degrees
TOL = time out of lane in percentage of total driving time
TLC50 = median of the TLC distribution in seconds either to the left, right or both
TLC85 = TLC in seconds that is exceeded 85% of the time either to left, right or both

3.2.2.1 Failure to complete tests

One subject in the PLA condition requested to stop at the 50 km turning point because he was experiencing adverse subjective feelings. His objective performance before that decision was relatively normal, however. Twelve test rides were stopped by the licensed driving instructor. The terminated tests per treatment condition, day of treatment and distance travelled are listed in Table 3.10. Some aspects of driving performance prior to the terminated tests are plotted in figures 3.7, 3.8 and 3.9.

Table 3.10 Failure to complete tests broken down by treatment condition, day of treatment and distance (Km) driven before the test was terminated.

Subject	Treatment	Day	Distance
3	Triazolam	1	44
7	Triazolam	1	41
7	Triazolam	5	26
7	Temazepam	5	32
7	Midazolam	5	84
7*	Placebo	1	58
8	Placebo	1	69
8	Triazolam	1	84
10	Triazolam	1	14
10	Triazolam	5	45
16	Triazolam	1	81

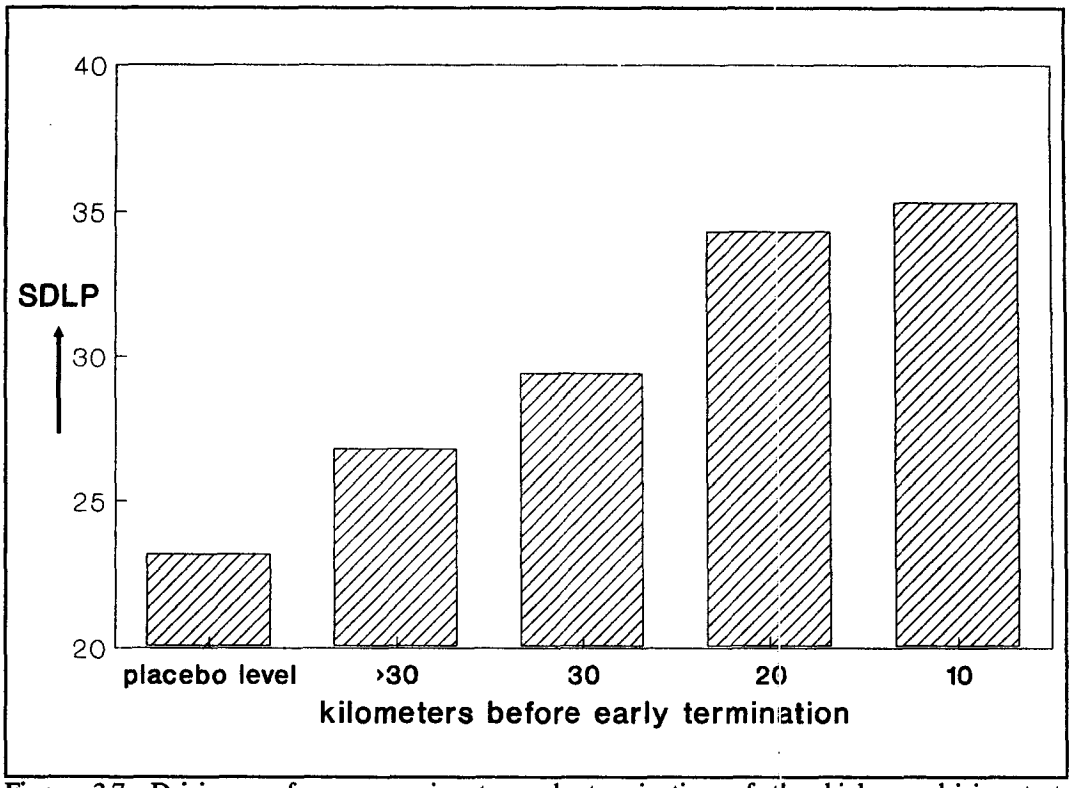

Figure 3.7 Driving performance prior to early termination of the highway driving test. Standard deviation of lateral position.

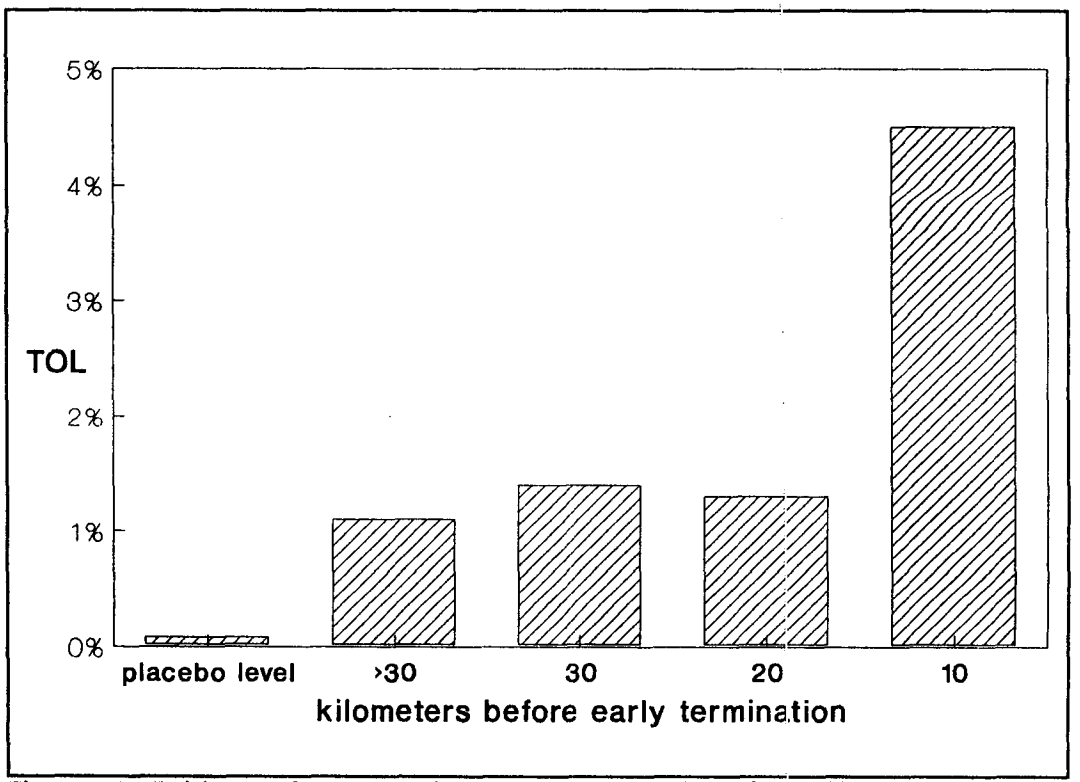

Figure 3.8 Driving performance prior to early termination of the highway driving test. Percentage of time driven out of lane.

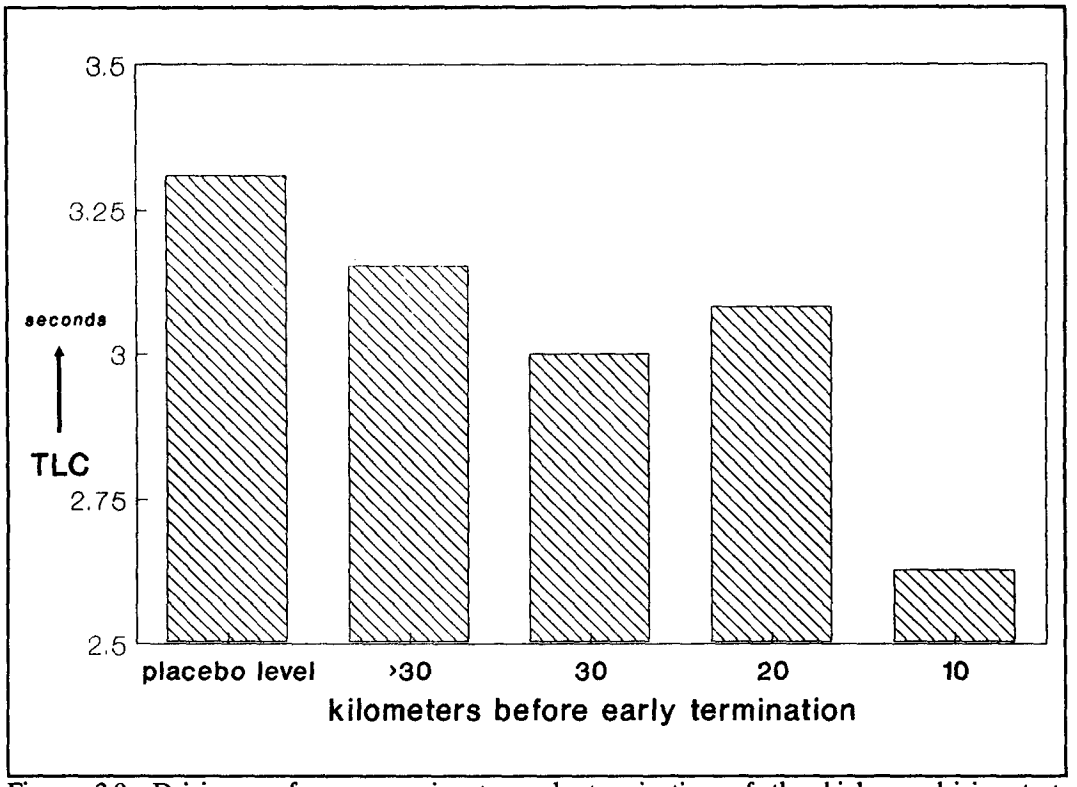

Figure 3.9 Driving performance prior to early termination of the highway driving test. Average values of TLC that are exceeded 85% of the time. Eighty-fifth percentiles of TLC distribution, left and right TLC's are combined.

3.2.2.2 Lateral Position

Mean lateral position

No effects of either treatment condition on mean lateral position were found. Mean lateral position didn't differ significantly from zero, indicating that subjects drove in the middle of the lane, as instructed.

Standard deviation of lateral position

There are significant overall effects on SDLP of drug treatment ($F=8.53$; $df=3,11$; $p<.005$). Inspection of drug treatment effects reveals that the main effect of triazolam is significant ($F=26.6$; $df=1,13$ $p<.0001$). The SDLP is bigger on the first day of treatment than on the fifth day of treatment, yielding a significant main effect ($F=13.37$; $df=1,13$; $p<.005$). The significant drug by day interaction ($F=3.9$; $df=3,11$; $p<.05$) is perhaps best explained by the observation that the triazolam-placebo difference is far bigger on the first day of treatment. Furthermore, the slight increase in SDLP on day 5 of midazolam treatment, relative to placebo, is also significant ($F=1.84$; $df=13$; $p<.05$).

3.2.2.3 Speed

No significant effects of either treatment conditions on mean speed and standard deviation of speed were found.

3.2.2.4 Steering angle error

Standard deviation of steering wheel angle was slightly increased under the influence of triazolam. A main effect was approaching significance ($F=3.47$; $df=1,11$; $p<.10$). On the fifth day of treatment the triazolam-placebo difference was significant ($F=4.71$; $df=12$; $p<.05$).

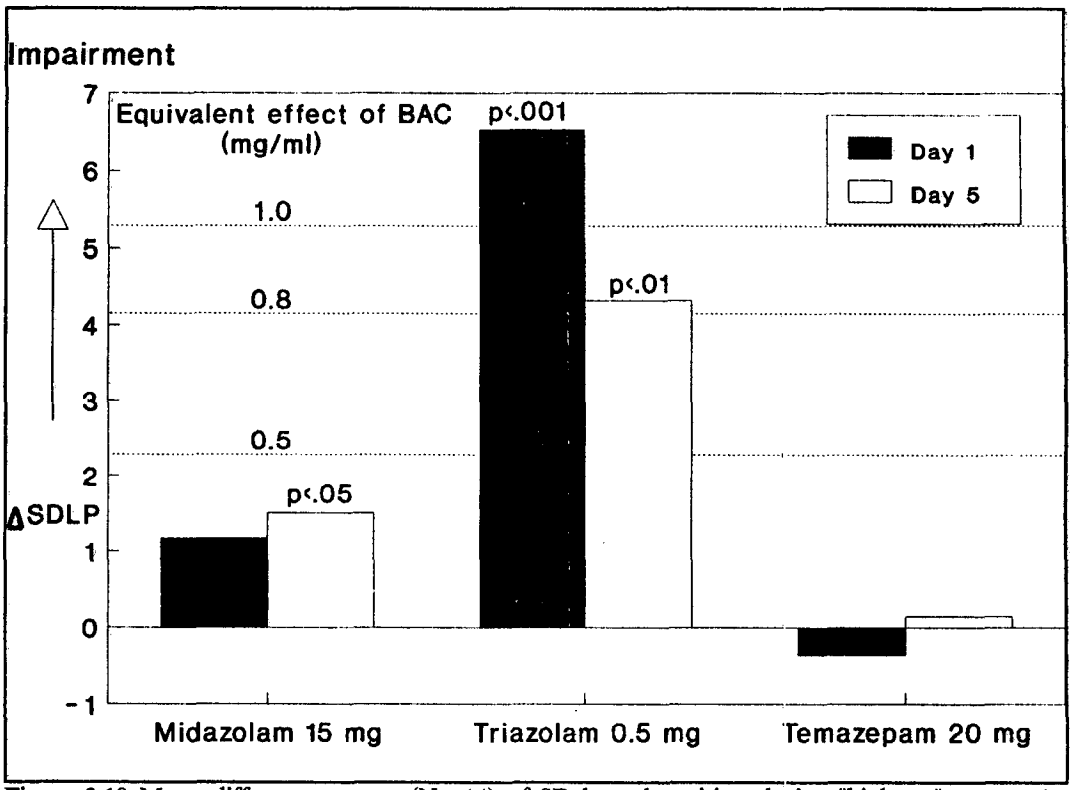

Figure 3.10 Mean difference scores (N = 14) of SD lateral position during "highway" test on 1st and 5th days of drug treatment relative to placebo

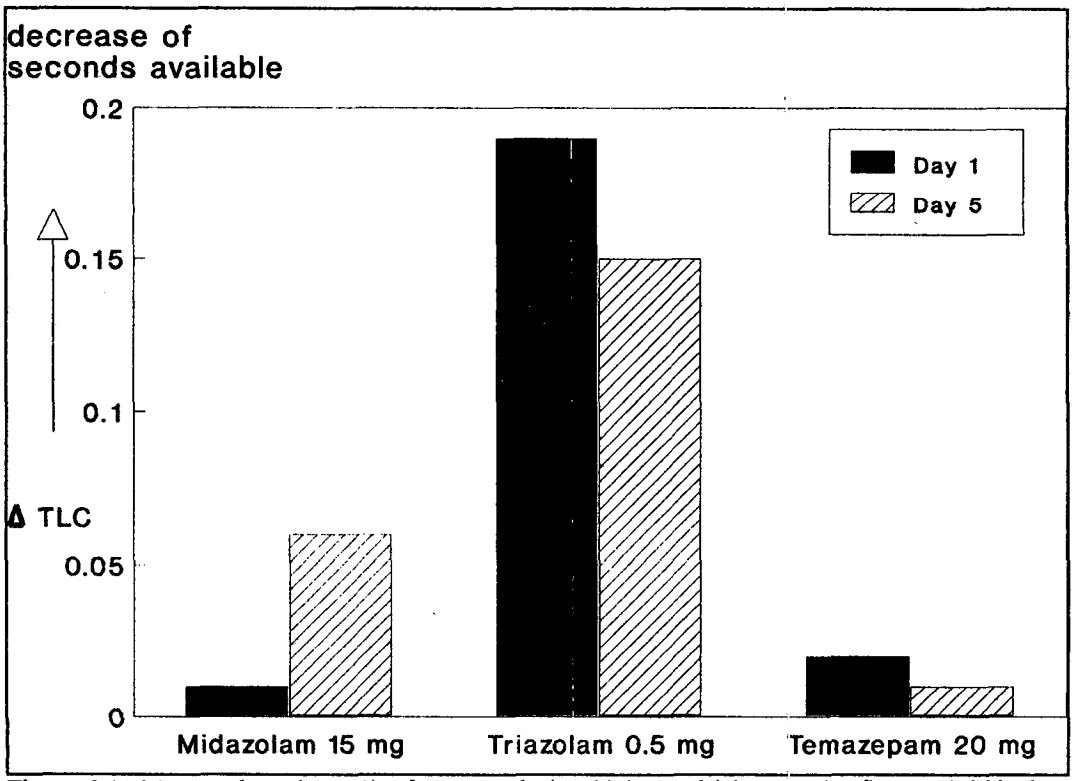

Figure 3.11 Mean values (N = 12) of TLC85 during highway driving on the first and fifth days of treatment with drugs or placebo.

3.2.2.5 Time to line crossing

TLC-data for left and right were combined and thus three major dependent variables were derived: time out of lane, median TLC and 85th percentile TLC.

Time out of lane(TOL)
The percentage of time that subjects exceeded the lane boundaries during the highway driving test was slightly elevated when driving under the influence of triazolam ($F=3.24$; $df=1,11$; $p<.10$). This was especially the case on the fifth day of treatment ($F=5.24$; $df=11$; $p<.05$).

Median TLC (TLC50)
TLC50 was lower after treatment with triazolam. The multivariate treatment effect approached significance ($F=3.13$; $df=3,9$; $p<.10$). The main effect of triazolam was significant ($F=7.89$; $df=1,11$; $p<.01$).

85th percentile TLC (TLC85)
TLC85 was lower after treatment with triazolam. The multivariate treatment effect was significant ($F=3.88$; $df=3,9$; $p<.05$). The main effect of triazolam was significant ($F=12.02$; $df=1,11$; $p<.005$). See also figure 3.11.

3.2.2.6 Test-retest reliabilities.

In table 3.12 the correlations between the test-values observed on days 1 and 5 of each treatment are listed. The good test-retest reliability of SDLP is confirmed again. The mean lateral position appears to be a very reliable individual measure of lane position but is, as shown above, insensitive to drug treatment effects.

Table 3.12 Test-retest reliability of dependent variables in city and highway driving

dep vars	Midazolam	Triazolam	Temazepam	Placebo
(N=14):				
Exp_rating	.6567*	.7951***	.6568*	.5492
Mn_LP	.9093***	.8416***	.9644***	.9050***
SD_LP	.9467***	.8173***	.8920***	.9015***
Mn_SP	.5298	.6705*	.5434	.5215
SD_SP	.5978*	.4328	.6039*	.4449
(N=12):				
SD_ST	.3015	.4850	.4631	.5135
TOL	.3825	.4182	.7376*	-.0061
TLC50(L)	.9034***	.6632*	.9039***	.8834***
TLC50(R)	.4916	.5928	.0919	.6021*
TLC85(L)	.8979***	.3468	.8948***	.8719***
TLC85(R)	.6212*	.8009**	.6250*	.7184*
TLC50(L+R)	.6165	.0448	.6500*	.5571
TLC85(L+R)	.5321	-.2781	.3393	.3813

The left TLC values appear to be reliable as well. The left-right differences in TLC's reliability probably cannot be explained by any trends in the steering-wheel data, since the correlated measures were taken only four days apart. However, the leftward trend in the steering wheel angle data might have corroborated the reliability of the TLC_right values per se. Despite problems of a technical nature that remain to be overcome, the TLC seems to be a useful new dependent variable to be used in the highway driving test.

3.2.3 Summary of driving test results

Triazolam affected visual search behavior in the city driving test. Besides that, behaviour of subjects under the influence of triazolam was rated as less safe after the first night shift.
In the highway driving test, triazolam affected standard deviation of lateral position, steering behavior, time out of lane and time to line crossing. Midazolam slightly affected SDLP on day 5. No substantial effects were found on mean lateral position, speed or standard deviation of speed. Test-retest reliabilities as measured on days 1 and 5 of treatment conditions were generally high for mean and standard deviation of lateral position and also for the TLC values related to line crossings to the left.

3.3 Subjective effects

3.3.1 Subjective rating of driving performance and side-effects

In table 3.13 the results of subjective ratings as scored immediately following the highway driving test or 8.5 hours after drug administration, on visual analog scales of driving quality (SDQ), effort (EFF) and mental activation SMA are listed. SDQ is significantly less after midazolam ($F=4.41$; $df=13$; $p<.05$) and triazolam ($F=6.86$; $df=13$; $p<.05$), both on the 5th day of treatment. There was a significant main effect of triazolam on effort ($F=5.84$; $df=1,13$; $p<.05$) indicating that subjects invested more effort in the driving task under the influence of triazolam.

Table 3.13 Means and standard deviations of subjective ratings and frequency of occurrence of side-effects after highway driving (8.5 hours after drug administration) broken down by treatment condition and day of treatment.

	Midazolam				Triazolam				Temazepam				Placebo			
	Day 1		Day 5		Day 1		Day 5		Day 1		Day 5		Day 1		Day 5	
dep vars	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
SDQ	47.0	11.1	43.1	16.3	38.0	15.3	43.7	15.9	48.9	12.1	49.2	15.6	45.5	21.1	52.8	13.3
EFF	23.7	8.6	28.0	21.4	31.8	14.9	35.6	21.7	24.3	18.8	30.4	16.8	26.7	18.2	25.2	14.6
SMA	57.3	9.8	54.1	14.3	55.7	13.0	54.9	16.6	58.8	10.2	52.9	15.3	55.1	15.2	56.8	6.4

In table 3.14 counts of frequency and severity of occurrence of complaints concerning side-effects of drugs are listed. Note that feelings of unreality was reported more often and more severe after triazolam treatment whereas forgetfulness was reported more often and more severe after midazolam.

Table 3.14 Counts of complaints about side-effects. Number of subjects reporting light or severe disturbance caused by: drowsiness, lack of concentration, feelings of unreality, forgetfulness, dizziness, nausea, itch and other complaints (mainly headaches).

	Midazolam				Triazolam				Temazepam				Placebo			
	Day 1		Day 5		Day 1		Day 5		Day 1		Day 5		Day 1		Day 5	
	Light	Severe	Light	Severe	Light	Severe	Light	Severe	Light	Severe	Light	Severe	Light	Severe	Light	Severe
DROWSY	6	1	2	3	6	4	5	3	5	0	3	2	4	4	7	1
UNCONC	8	0	5	4	8	3	5	3	4	1	6	3	7	2	2	4
UNREA	3	0	4	1	3	2	4	1	2	1	2	0	4	0	2	0
FORGET	5	0	3	1	1	0	3	1	5	0	2	0	2	0	3	0
DIZZY	2	0	1	0	0	0	3	0	0	0	0	0	0	1	1	0
NAUSEA	0	0	1	0	1	1	2	0	0	0	0	0	1	0	1	0
ITCH	0	0	0	0	2	0	2	0	1	0	0	0	1	0	0	0
OTHER	1	0	5	1	2	2	3	1	4	0	2	2	2	2	2	0

3.3.2 Subjective mood scales

Absolute ratings of mental activation, drowsiness and lethargy were taken immediately after awakening every day during the treatment period. Ratings of the same items, relative to the absolute scores upon awakening, were taken during night work at 1.00 AM and 4.00 AM.
A composite score "activity/lethargy", which was measured immediately after awakening, was constructed. The results are shown in figure 3.12. There is an overall effect on this score of drug treatment ($F=11.0$; $df=3,11$; $p<.001$). Contrast analyses reveal that scores at awakening in the laboratory show less activation after all drugs relative to placebo. When subjects slept at home, the same result was found after midazolam- and triazolam-induced sleep.

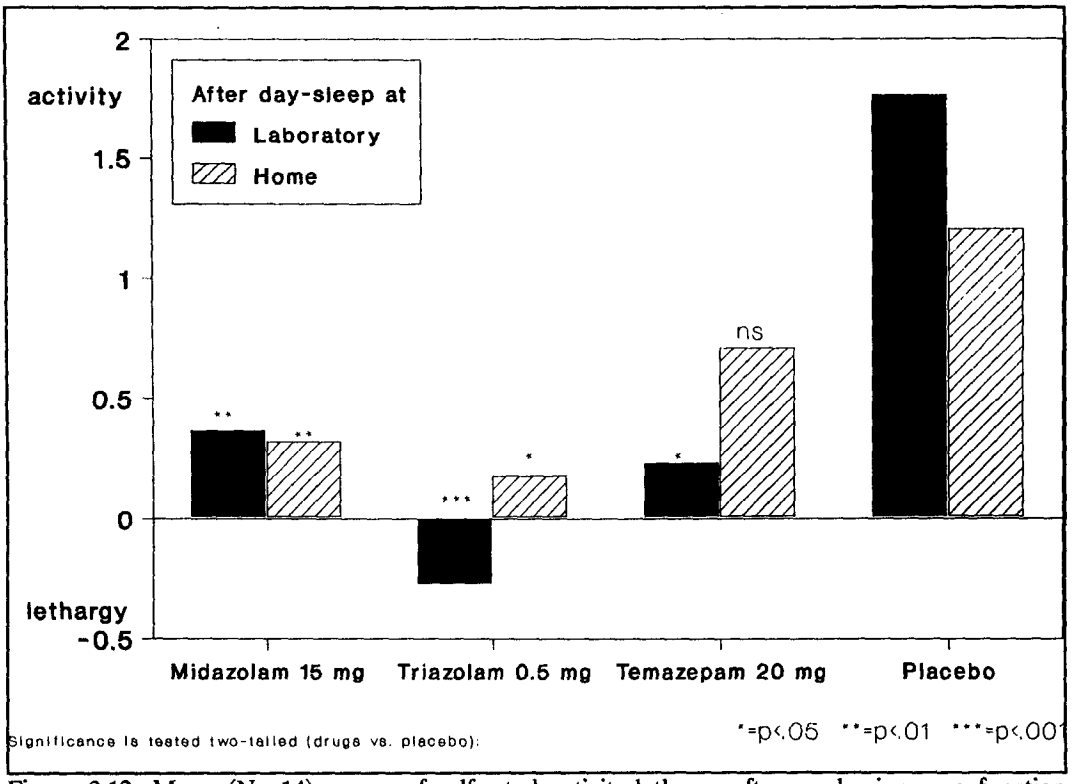

Figure 3.12 Mean (N = 14) scores of self-rated activity-lethargy after awakening as a function of preceding drug treatment and sleeping conditions.

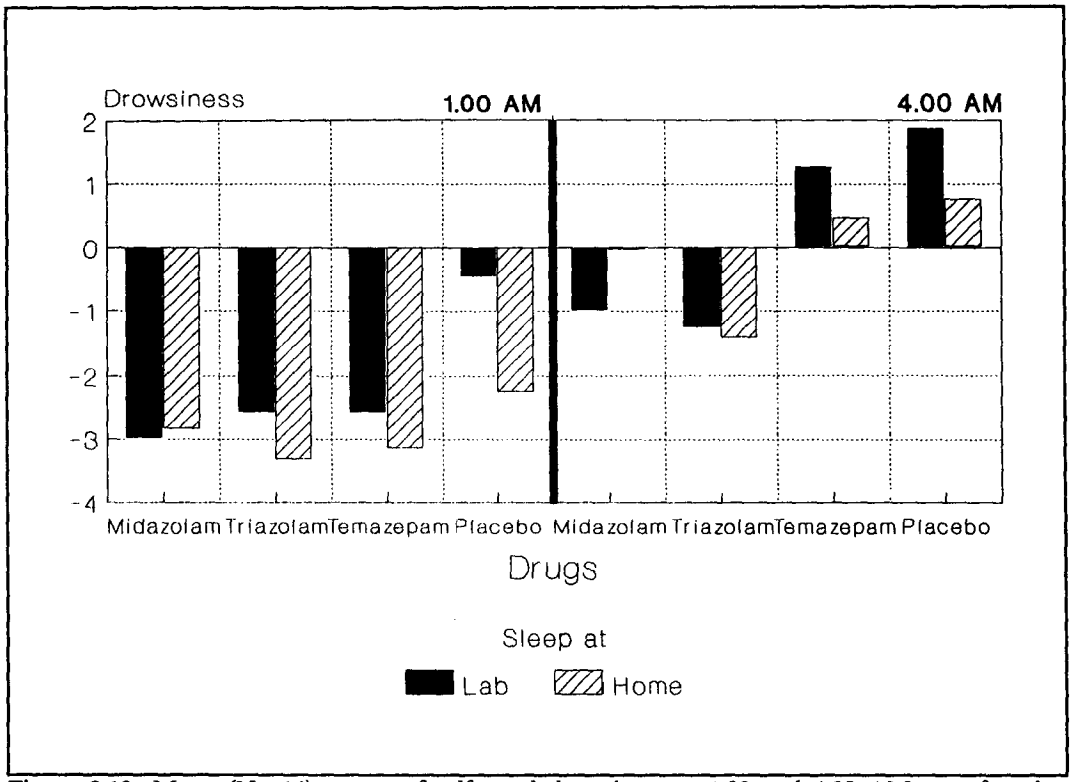

Figure 3.13 Mean (N = 14) scores of self-rated drowsiness at 1.00 and 4.00 AM as a function of preceding drug treatment and sleeping conditions.

Subjective ratings of drowsiness show no drug effect immediately after awakening. However, at both 1.00 and 4.00 AM (16 and 19 hours after drug administration), an overall effect of drug treatment on subjective drowsiness was found (1.00 AM: $F=4.07$; $df=3,11$; $p<.05$; 4.00 AM: $F=4.32$; $df=3,11$; $p<.05$). At 1.00 AM this effect is due to triazolam after sleeping either in the laboratory or at home and also to midazolam and temazepam after sleeping in the laboratory on the first day of treatment.
At 4.00 AM, drowsiness is also scored lower after midazolam on the first day (after day-sleep in the laboratory) and after triazolam both after day-sleep at home and in the laboratory. The results are shown in figure 3.13.
These results show, that subjective feelings of drowsiness at night-work are reduced, 16 and 19 hours after day-sleep induced by triazolam and also, but to a lesser extent, after midazolam and temazepam.

3.4 Summary of results

Adaptation to a night shift under placebo conditions could be seen in terms of progressive trends in subjective sleep quality and sleep duration. Midazolam substantially prolonged day-sleep duration and improved subjective sleep quality, whereas triazolam and temazepam did not. Triazolam however, reduced activity during sleep, presumably through increasing sleep depth.
Triazolam severely impaired driving performance in city and highway driving, both objectively and subjectively on a great number of dependent measures.
All three hypnotics reduced feelings of mental activation and increased feelings of lethargy, relative to placebo, immediately upon awakening from day sleep. That is, the hypnotics had equivalent residual sedative effect on the shift workers' subjective feelings. Feelings of drowsiness during nightwork were reduced, 16 and 19 hours after midazolam- and triazolam-, but not temazepam-induced sleep.

In figure 3.14 summarized results are displayed. Looking at these results it should be kept in mind that these are referring only to the most important tests described in this report. More evaluative drug testing that was not reported here (e.g. memory tests) should be included if the table was to be seen as a complete product evaluation.

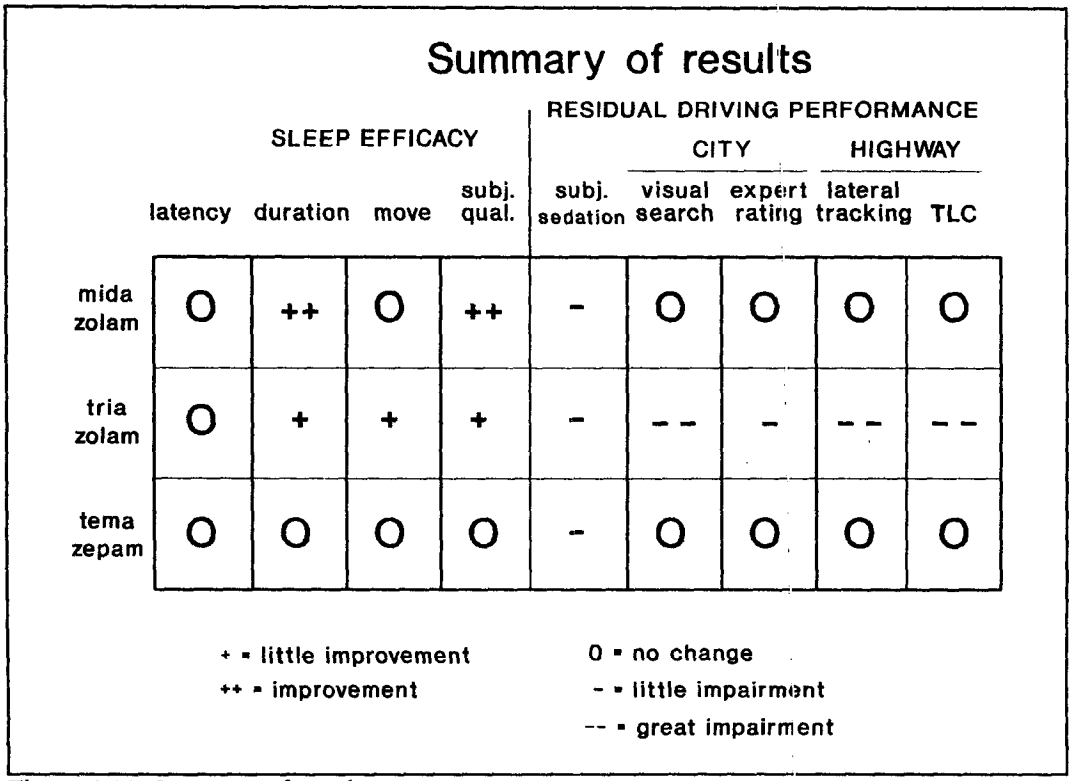

Figure 3.14 Summary of results

4. DISCUSSION

The unmedicated sleep of rotating shift workers on night duty

The average day-sleep durations of the rotating shift workers, when they slept at their homes, were as short as predicted on the basis of published data: 5.5, 6 and 6.5 hours after the 2nd, 3rd and 4th night of work. One could argue that these durations were also influenced by the restriction of the subjects' sleep time in the laboratory after the first night of work. However, this disturbance appeared to be limited in extent, since only four out of eleven subjects had to be awakened by the experimenter at the end of the first day-sleep period in the placebo condition. On the fifth day of placebo-treatment however, eight of eleven subjects had to be awakened.

With regard to subjective sleep quality we also observed an adaptation effect in terms of an increase in sleep quality from the first through the third day-sleep period. The third, fourth and fifth day-sleep periods were then rated equal, though still lower than night-sleep quality measured before the treatment period.

The short total sleep times of the subjects were the result of early awakenings, since their latencies to sleep onset were short on average and didn't change from the first through the third day-sleep period as did the other variables.

Thus, findings about the disturbed day-sleep of rotating shift workers reported in the literature were accurately replicated in terms of reduced sleep duration due to early awakenings and reduced subjective sleep quality, in both cases especially on the first two days.

However, no inferences could be made on the basis of activity data in the placebo condition, since they lacked any consistent trend.

Hypnotic efficacies

Midazolam 15 mg significantly prolonged the objectively measured day-sleep duration at the shift workers' homes and concomittantly improved subjective sleep quality relative to placebo. There was no sign of rebound insomnia in terms of subjective sleep quality after withdrawal of midazolam upon returning to night-sleep. Midazolam was especially effective on the first two days of treatment, although this cannot be stated firmly with regard to sleep duration on the first day, since subjects were awakened at a preset time. Therefore, midazolam's effect on sleep duration on the first day of treatment should be considered in conjunction with the number of subjects who had to be awakened by the experimenter. In the first day-sleep condition with midazolam, ten out of eleven subjects had to be awakened, versus only four in the placebo condition. It is of particular importance that midazolam improved sleep on the first two days since these days have been identified, as described above, as the core sleeping problem of rotating shift workers on night duty.

Midazolam didn't influence any of the motor activity measures, contrary to expectations based on findings with midazolam reported by Borbély (1983). However, midazolam appeared to be particularly efficacious on the first two days when the sleep-problems of rotating shift workers were most severe.

Triazolam 0.5 mg lacked the effects reported for midazolam, except for the first-day effect, which was strongest in triazolam. Though sleep time was restricted, subjects slept significantly longer with triazolam relative to placebo. All eleven subjects had to be awakened on the first day-sleep period under the influence of triazolam. However, when sleeping at home, triazolam didn't significantly prolong sleep duration relative to placebo. On the fifth day of treatment with triazolam, sleep duration was the same as for placebo while fewer subjects had to be awakened. Furthermore, the lower subjective sleep quality scores after the withdrawal of triazolam relative to placebo-withdrawal suggest that triazolam induced rebound insomnia.

In the laboratory day-sleep periods on days 1 and 5, triazolam reduced the frequency of awakenings, increased the amount of still sleep relative to total sleep time, and decreased the amount of movement during sleep. Although the same tendencies were seen in the data concerning day-sleep periods at home, these weren't significant. This finding may illustrate the advantage of having subjects sleep in the laboratory in order to eliminate sources of uncontrollable variance when subjects sleep at home. The suppression of activity reported by Borbély was confirmed, although we couldn't confirm the finding that this was only the case in the first half of the night.

Thus, the efficacy of triazolam seems to be restricted to the first day of treatment only. On the first day of treatment sleep duration, subjective sleep quality and activity pattern were all improved. On the fifth day of treatment the suppression of motor activity indicates the pharmacological activity of triazolam, but effects on sleep duration and subjective sleep quality relative to placebo are lacking.

Temazepam 20 mg slightly prolonged day-sleep in the laboratory on the first treatment day relative to placebo. Furthermore there is at least a suggestion of the effects of pharmacological tolerance to temazepam in the data since total sleep time decreased from day 2 through day 4 of treatment. Total sleep time under the influence of placebo showed the opposite trend which might be expected in the case of adaptation to night-shift. The lower scores on subjective sleep quality after withdrawal of temazepam suggest a rebound insomnia effect, just as described for triazolam.

Residual effects

There were no residual effects of temazepam upon driving performance, neither in the city-driving nor in the highway driving test. Midazolam didn't impair performance in the city driving test, but very slightly impaired highway driving on the fifth day of treatment. This effect can be explained in terms of a slight improvement that was observed in placebo condition from day 1 through day 5 of treatment. This placebo improvement probably reflects the subjects' adaptation, although far from complete, to the nightshift condition in the same period. This statement can be further justified by comparing the shift workers' placebo performance with that of other groups using the same test on the same road. Highway driving performance of the shift workers is worse than that of a group of healthy subjects tested under placebo condition during the same period (Schoenmakers et al., 1988). Moreover, the placebo values for the shift workers were the highest reported to date in studies using this method (O'Hanlon, 1986). Thus, one can interpret the absence of impairing effects of temazepam and midazolam upon highway driving after the first day-sleep period as "not making things worse." The midazolam-induced highway driving impairment after the fifth day-sleep period was less than that induced by .05 mg/ml blood-alcohol-concentration (Louwerens et al., 1985).
Triazolam 0.5 mg severely impaired driving performance both in city and highway tests. Impairment of highway driving on the first day of treatment was more severe than that induced by .10 mg/ml blood-alcohol-concentration, whereas impairment on the fifth day of treatment was still as high as that induced by a .08 blood-alcohol-concentration (Louwerens et al., 1985). The decrease in severity of impairment might reflect some behavioral tolerance to the residual effects of triazolam.

Subjective effects

Subjective alertness upon awakening after treatment with all three hypnotics was lowered relative to placebo, but was improved during night work to some extent, although this was observed more strongly after treatment with triazolam, and least after treatment with temazepam. It is tempting to say that the latter finding, taken in combination with the drugs' effects on sleep, indicate that the hypnotics might have facilitated a phase shift of the sleep-wake cycle.

Time to line crossing

In particular, the data obtained on test rides in which subjects were forced to stop because the experimenter decided it was unsafe to continue, shed some light on the relationship between SDLP, TLC and probability of lane exceedance. Allen & Stein (1987) describe the relationship between SDLP and the probability of lane exceedance: "This relationship that is depicted in figure 4.1, gives an interesting nonlinear interpretation to SDLP. For levels below 25 cm the lane exceedance probabilities are quite small, and virtually vanish in the region of 20 cm. This is a typical SDLP level for unimpaired drivers under good driving conditions (O'Hanlon, et al., 1986). When SDLP reaches levels of 25-30 cm the probability of lane exceedance increases quite rapidly, and this region represents significant driver impairment or seriously degraded driving conditions. There are many criticisms that can be made of the above traffic safety interpretation. The drivers probably do not maintain their average position in the center of the lane. The probability of lane edge exceedance metric does have a sensitivity that is representative of safety, however, and should be taken in this vein" (Allen & Stein, 1987).
This theoretical description of the relationship between SDLP and the probability of lane exceedance explains perfectly the phenomena described in paragraph 3.2.2.1 with respect to the trends in SDLP, time driven out of lane and TLC during the last 30 km prior to the decision to stop the test-ride. The data plotted in figure 3.8 seem to justify the decision of the experimenter to stop these particular test rides at these particular moments in time. Although SDLP had increased gradually as a function of the distance driven, during the last 10 km there was a sudden increase in time driven out of lane. The trend in the TLC data reflect both the former and the latter trend, suggesting that the TLC is an indicator of both the SDLP-related driving-skill and the probability of lane-exceedance safety-related processes.

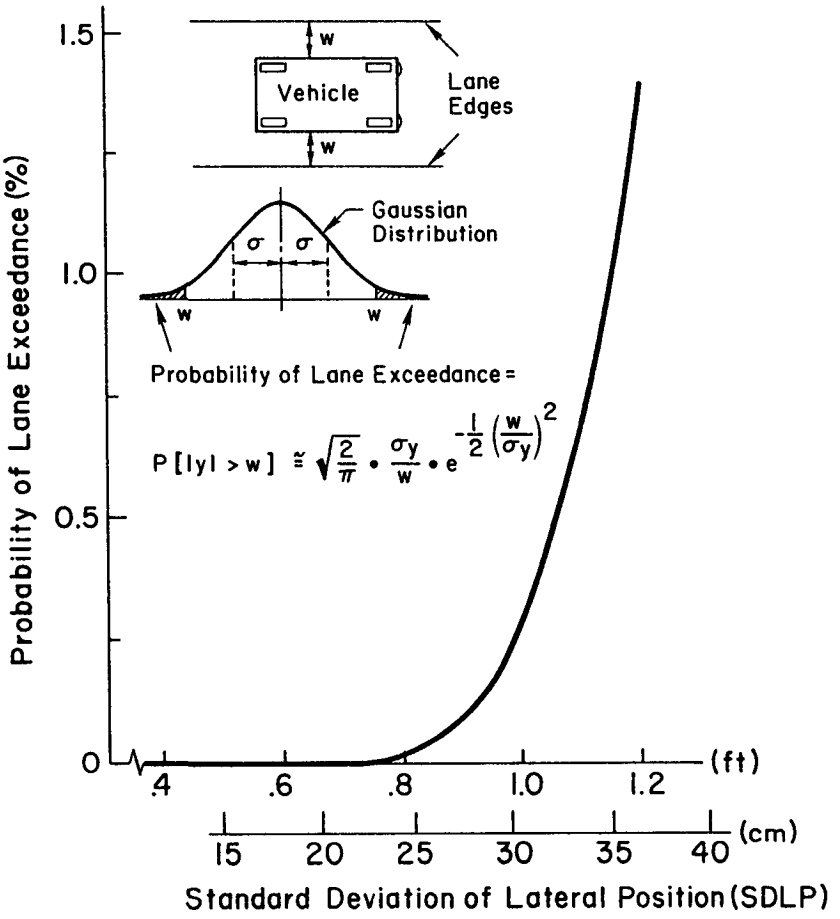

Figure 4.1A Traffic Safety Interpretation of the Standard Deviation of Lateral Lane Position Measure (from: Allen & Stein, 1987).

Concluding remarks

The results obtained with midazolam were most favorable with respect to improving the clearly demonstrated transient insomnia conditions of shift workers after changing to night-shift, demonstrating the almost complete lack of residual performance effects 6.5 - 8.5 hours after administration in real driving tasks, although subjective alertness was reduced before the driving test was undertaken. Improvement of the subjective state during night work is a beneficial effect but should be confirmed with objective performance data as well. The same need for confirmation with objective data exists with respect to the absence of any indication of a rebound insomnia effect of midazolam in terms of subjective sleep quality after withdrawal of the drug. This is particularly important since rebound-like effects were found after withdrawal of both triazolam and temazepam. Although we didn't measure memory functions, we did even find a subjective complaint of increased forgetfulness 8.5 hours after administration of midazolam on the first treatment day. This is in accord with other findings indicating the presence of memory impairing effects of midazolam and, to a lesser extent, triazolam (Van der Laan & Slangen, 1987; Borbély et al., 1988). There are ample reasons to assume that these effects would be absent when used for the treatment of day-sleep. Whatever its magnitude in the case of midazolam, the eventual residual memory impairment apparently did not incapacitate subjects' driving performance.

Triazolam shows very strong residual performance impairment at 6.5-8.5 hours after its administration. The practical implications of this finding would be less if it were always so that sleep after triazolam lasted longer than was allowed on test days. However, triazolam did not lengthen the subjects total sleep time when they slept at home. This result contradicts those obtained in previous investigations, including one where the same dose did increase the duration of day-sleep (Seidel et al., 1984). Still it seems necessary to address the apparent paradox of how a potent hypnotic might have failed to increase our subjects' total sleep time while at the same time leaving them with strong residual sedation. It seems just possible that something like a physiological rebound to triazolam's initial hypnotic activity began to occur after about 5-6 hours to awaken the subjects. Again referring to Triazolam 0.5 mg, Morgan & Oswald (1982) described this as "an adaptive change in the CNS, as if to counteract the drug". Despite the physiological rebound producing wakefulness, the drug's circulating concentration may have been close to the hypnotic treshold at the times the subjects awoke. Residual sedation could have been the result. Unless there is something very different about triazolam's pharmacodynamic activity as compared to other benzodiazepines, its tendency to produce a rebound in this study seems related both to the relatively high dose and the drug's rapid elimination. Possibly a lower dose might have allowed the subjects to sleep longer at home and awaken free from residual sedation. In any case there was no evidence that midazolam 15 mg had either of these adverse effects.
One interesting prediction that would logically follow from the above reasoning would be that the effects of triazolam 0.25 mg might be more like midazolam 15 mg and thus would perhaps prolong day-sleep in shiftworkers, even more than triazolam 0.5 mg.

The lack of performance impairment after temazepam is completely in accordance with previous findings after nocturnal administration of temazepam (Volkerts & O'Hanlon, 1986), however its lack of hypnotic efficacy is an argument against selecting the drug as most suited for use by shift workers (although this doesn't exclude that for some individuals the drug might be beneficial in overcoming adaptation to night-shift). However, one should be cautious with repeated administration of the drug since even in our relatively short-lasting period of repeated administration effects resembling pharmacological tolerance were found.

5. CONCLUSIONS

On the basis of the results reported in the previous sections, the following conclusions can be drawn:

1. **Poor adaptation to night shift work is particularly prominent with respect to the first two day-sleep periods of rotating shift workers after transition to the night shift.**

2. - Midazolam 15 mg is efficacious in improving subjective quality and maintaining duration of sleep that is normally disturbed by early awakenings caused by transition to night shift, particularly during the first two day-sleep periods when on night-shift.

   - Midazolam 15 mg in general did not cause impairment in driving a car either through city or highway traffic 6.5 hours after administration.

   - Subjective alertness during subsequent night work periods was improved 16-19 hours after the administration of midazolam 15 mg.

   Midazolam 15 mg can be recommended as a generally efficacious and safe hypnotic for use by rotating shift workers to cope with transient insomnia induced by poor adaptation to night shifts.

3. - Triazolam 0.5 mg was efficacious only for treating the first day-sleep period after transition to night shift.

   - The observed lack of efficacy of triazolam 0.5 mg in this study conflicts with findings in the literature.

   - Subjective alertness during subsequent night work periods is improved 16-19 hours after the administration of triazolam 0.5 mg.

   - It appears unsafe to drive a vehicle between 6.5 to 8.5 hours after administration of triazolam 0.5 mg.

   - The residual sedative effects found after triazolam 0.5 mg were much more severe than hitherto reported.

   Triazolam 0.5 mg can not be recommended as a safe hypnotic for rotating shift workers owing to its strong residual effects.

4. - Temazepam 20 mg was in general not efficacious for treating transient insomnia caused by transition to night shift work, although in some cases its use might improve the first day-sleep period after night work.

   - Subjective alertness during the first subsequent night work period was improved 16-19 hours after the administration of temazepam 20 mg.

   - It appears safe to drive a vehicle 6.5 hours after administration of temazepam 20 mg.

   Temazepam 20 mg can be recommended as a very safe, but not very efficacious hypnotic for rotating shift workers in order to cope with transient insomnia induced by poor adaptation to night shift.

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APPENDIX A **Adverse reaction to triazolam by subject # 1.**

REPORT OF AN UNUSUAL REACTION TO TREATMENTS ADMINISTERED AS PART OF AN INVESTIGATION OF HYPNOTIC DRUG EFFECTS ON SLEEP AND PERFORMANCE OF SHIFTWORKERS : E. Schoenmakers, M.D., Medical Supervisor, W. Riedel, Project Manager, J.F. O'Hanlon, Principle Investigator

A 25 year old, male subject (height: 1.75 m., weight: 65.4 kg.) suffered an unusual reaction consistent with the diagnosis of mild benzodiazepine intoxication in a double-blind, cross-over trial comprised of four separate 5-day series of the respective treatments, midazolam 15 mg, triazolam 0.5 mg, temazepam 20 mg and placebo d.d., p.o.

The incident occurred while this subject (code: 01) was in the first day of the second treatment series (code: B). The subject received medication at 7.30 am. and retired to sleep within laboratory facilities at the institute. He was awakened with great difficulty by an assistant at 1:00 pm. (5.5 hours after medication). After being awakened, he showered and received breakfast. At 1.30 pm. he completed sleep- and alertness questionnaires. At 1.45 pm. preparations began for the city-driving test, including the mounting of an eye-movement recording device on the subject's head. The experimenter experienced great difficulty in calibrating the eye-movement device because the subject could not hold his eyes open, despite repeated requests to do so. At 2:00 pm. he undertook the driving test but was soon stopped by an experienced driving instructor after appearing unable to proceed safely. He was returned to the institute and examined by the Medical Supervisor.

The subject exhibited disturbed equilibrium, impaired fine hand coordination, low muscle tension, disturbed speech and he reported difficulties in concentrating. Heart and lung functions were normal, as were blood pressure, vision and hearing.

After drinking coffee and conversing with stafff members, the subject became within a period more overtly alert. After one hour he was taken home, instructed to sleep and to avoid engaging in any activity which could be considered dangerous in his present condition.

The subject was phoned by the Medical Supervisor 6:00 hours pm. (10.5 hours after taking medication). His condition had improved; concentration and speech were better. The subject said that he still couldn't walk normally but his motor impairment was not as bad as before.

The subject was seen at home by the Medical Supervisor on same day, at 10.00 hours pm. (14.5 hours after medication) to determine if he were in a condition to go to work, as scheduled, later that night. At the time of the second examination, the subject appeared normal and his only reported symptom was "light headedness". Consequently he was permitted to go to work but was again advised to avoid situations which could be dangerous.

Finally, the subject was contacted by telephone the next day and it was determined that he had accomplished his night work without difficulty and felt normal.

Because of the subject's reaction it was considered essential to end his participation in the study. However, since the reaction did not require medical intervention, the code was not broken.

Previous experimental contacts with the subject had revealed fully normal sleeping behavior and driving performance during the unmedicated training session. However, during the first medication (code: A) condition on both days 1 and 5 while the subject had slept in our laboratory there had been informal reports to the project manager that this subject was the hardest one to awake. A written report by the experimenter reveals that the subject had told him that he slept at least twice through his clock at home on days 2, 3 and 4 and woke up one hour later while his clock was still on alarm. At night duty during this condition he said he had been easily irritated and that his colleauges had told him so as well. During the experiment there were overt signs of moderate to severe, but not abnormal drowsiness, which related to poor performance only during the highway driving tests on both days 1 and 5 of drug treatment. On day 1 the subject wrote that he had not been able to keep his speed constant and below 100 kmh. On day 5 the experimenter wrote that the subject had been driving very bad during his highway test.

Table 1 Performance scores related to city driving tests. All data are in percentages with 100% as maximum unless indicated otherwise.

City test: Condition	Looking to streets at the Right+ priority	Right	Left	Average speed (kmh)	Expert rater's score	Comments
Training	93	89	77	26.2	84	easy going, but attentive driver
A day 1	92	90	82	28.7	100	hesitates at crossings, misses a side street once and a while but still a good ride
A day 5	96	93	83	30.7	95	cuts off curves to the left, despite some minor errors in looking, a good ride

Table 2 Performance and subjective scores related to highway driving tests. SDLP is a test-score (weaving index) with a normal range of 18-30 cm. Time out of lane is a percentage score (Values in brackets are estimated on the basis of visual inspection of the polygraphic registration since training data were not computer-filed systematically).

Highway test:	objective				subjective scores			
	sdlp (cm)	speed (kmh)	time out of lane	sleepi-ness	lack of conc.	driving quality	effort	mental activation
Training	(<30)	(95)	(0)	none	none	good	little	high
A day 1	36.91	94.18	0.21	some	some	normal	much	moderate
A day 5	38.09	94.07	1.01	severe	severe	bad	very much	low

Medical history and physical examination of the subject before the beginning of the experiment revealed that the subject was a carrier of the hepatitis B virus. This had been discovered during a routine blood donor test at the hospital. The subject related that laboratory tests of his hepatic functions were normal at that time. Also he had experienced no clinical signs of hepatitis B. After his reaction, however, the subject partly contradicted his earlier statements by now relating that his liver functions were not completely normal and that they were being monitored by a internal medicine specialist. The Medical Supervisor contacted the physician (with permission from the subject), and a written medical report has been sent.

APPENDIX B **Adverse reaction to triazolam by subject # 17.**

A 23 year old woman (height: 1.59 m; weight 61.5 Kg) suffered from a severe headache after three days of treatment during her second treatment period. As a consequence, she complained of malfunctioning during her night work as nurse in an elderly home. She was then visited by the medical supervisor. It was at that moment decided to stop the ongoing treatment phase. After this, the subject's complaints disappeared.
During the first treatment period, no abnormalities had occurred. On her own request, the subject volunteered not to withdraw from the experiment entirely and thus to continue participation for the following two treatment phases.
However, because this particular treatment wasn't continued, we later decided not to include her (incomplete) data in the descriptive and analytical statistics.

Sleep Quality Scale-Specific

Name

Date

Time

Y= yes, N= no

	Y	N
0. I slept deeply last night		
2. I find that I slept very badly last night		
11. I lay awake more than a half hour last night before I fell asleep		
4. I woke up several times during the night last night		
13. I felt tired when I got up this morning		
12. I feel that I got to little sleep last night		
5. I got out of bed during the night last night		
14. I felt well rested when I got out of bed this morning		
7. I feel that I slept only a couple of hours last night		
9. I feel that I slept well last night		
1. Last night I did not close my eyes once		
10. I fell asleep easily last night		
6. After I woke up last night I had difficulty falling asleep again*		
3. I tossed and turned a good deal last night		
8. I didn't sleep more than five hours last night		

** If you did not wake up last night, then this question need not to be answered*

APPENDIX C Subjective sleep quality scale (translated from Dutch)

APPENDIX D Schematic map of the city-driving test route

Onderzoeknr:

Ppnr:

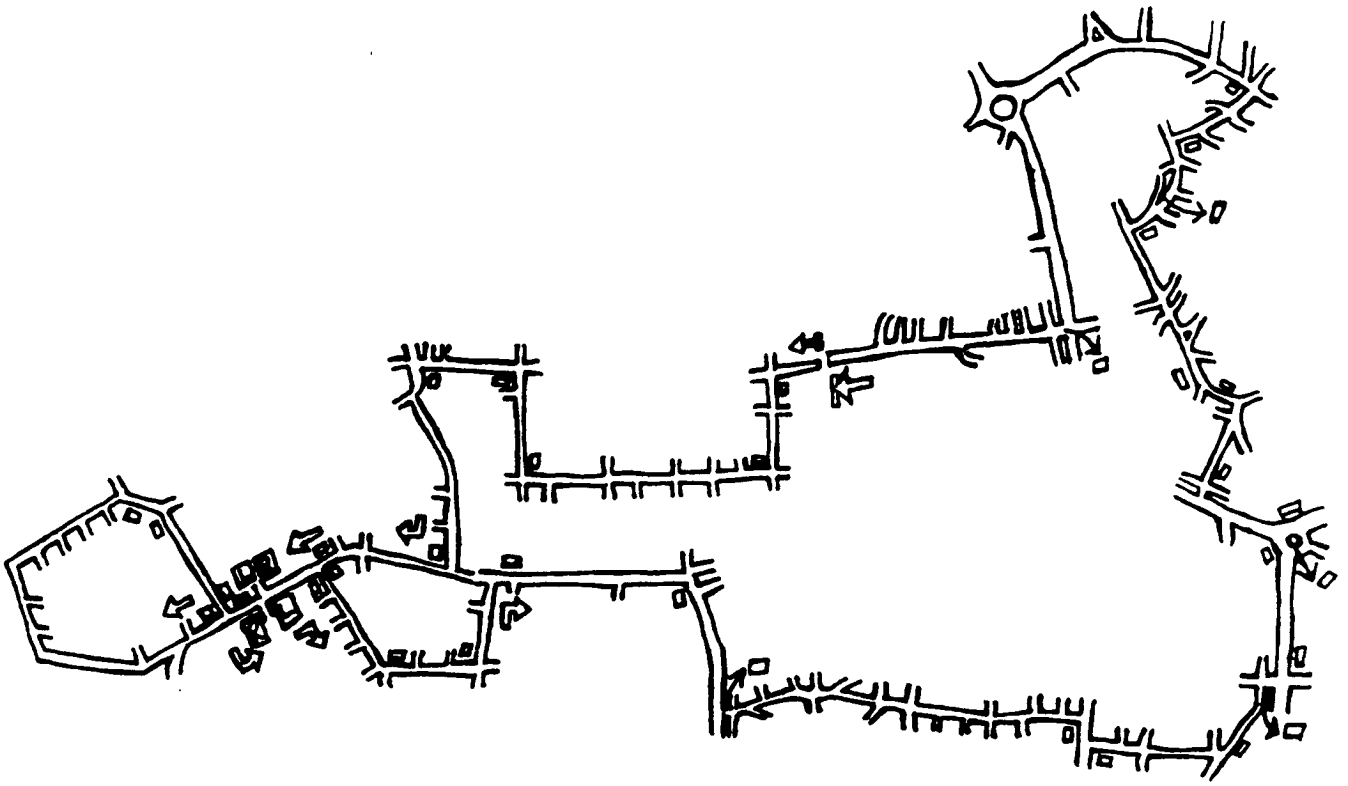
Conditie:

Dagnr:

Naam:

Datum:

Starttijd:



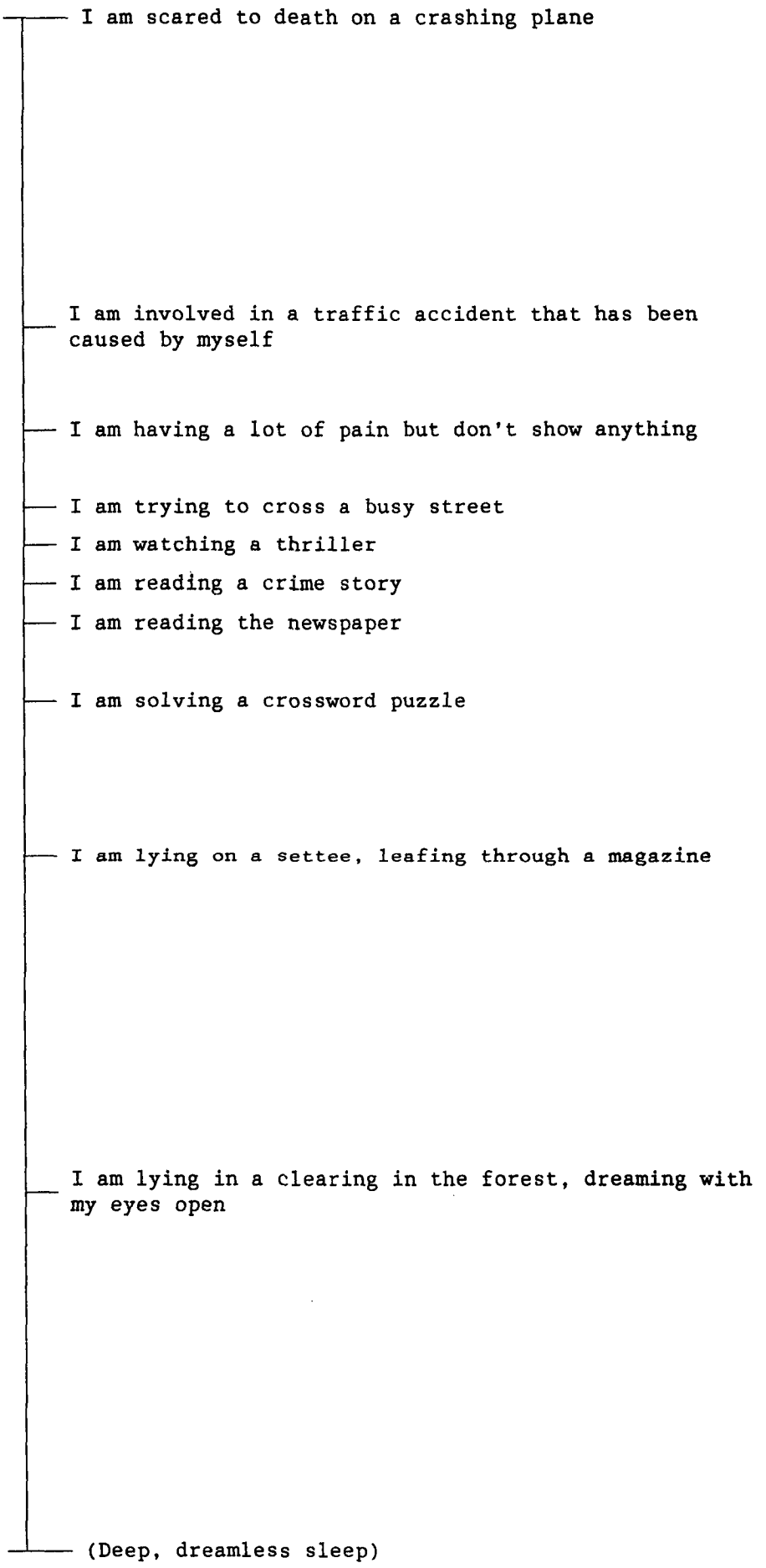
APPENDIX E TLC-program

```
procedure timetolinecrossing(var ybaan,dybaan,snelh,sturad,freq,tlc:real;j:integer);

     { ybaan  = current lateral position in m }
     { dybaan = lateral speed in m/s }
     { snelh  = speed in m/s }
     { sturad = steering angle in radians }
     { freq   = sample frequency in Hz  = 4 }
     { tlc    = time to line crossing in seconds }
     { j      = loop counter }

const za=1.1918451;     { distance between vehicle center of gravity and rear axis  }
      zv=1.4581549;     { distance between vehicle center of gravity and front axis }
      autobr=1.57;      { vehicle width }
      wegbr=3.685;      { lane width }
      a=45.58;          { G * 1 = 17.2 * 2.65 = steering system gear ratio * wheel base }
      b=9.127E-4;       { K = stability factor }
      c=0;

var diav,psiv,diaa,psia,ylivo,yliac,yrevo,yreac,psi,hautobr,dx,straal,
    r1,r2,psi2,y1,y2,psitot,r3,y3,check,psi3,psit3,rx,yaw: real;

begin
  psi3:=-999;
  psit3:=-999;
  hautobr:=autobr/2;                              { half vehicle width }

  diav:=sqrt(sqr(hautobr)+sqr(zv));               { distance between vehicle's c.g. and front corner's }
  psiv:=arctan(hautobr/zv);                       { angle of vehicle's c.g. with front corner's }
  diaa:=sqrt(sqr(hautobr)+sqr(za));               { distance between vehicle's c.g. and rear corner's }
  psia:=arctan(hautobr/za);                       { angle of vehicle's c.g. with rear corner's }

  if (sqr(snelh)-sqr(dybaan))>0 then
    dx:=sqrt(sqr(snelh)-sqr(dybaan))              { dx = forward speed }
  else
    dx:=0;

  if dx>0 then
    psi:=arctan(dybaan/dx)                        { heading angle in radians }
  else
    psi:=0;

  yaw:=(pre-psi)*freq;                            { yaw rate }
  if j>2 then
    corbas(snelh,yaw,ybaan,dybaan);               { correction lateral position }
  pre:=psi;

  if ((sturad>=-0.0001) and (sturad<=0.0001)) then
    begin
      if ((dybaan>=-0.0001) and (dybaan<0.0001)) then
        begin
          straal:=9999.9;
          tlc:=9.9;                               { setting tlc when its value would approach infinity }
          if sturad<0.0000 then
            tlc:=tlc*-1;
          exit;
        end
      else
        begin
          if dybaan>0 then tlc:=yrevo/dybaan;     { setting tlc when steering angle is zero but not heading angle }
          if dybaan<0 then tlc:=(wegbr-ylivo)/dybaan;
          exit;
        end;
    end
  else
    straal:=(a*(1+b*sqr(snelh)))/sturad;          { circle diameter of predicted path }

  ylivo:=diav*sin(psi+psiv)+ybaan;
  yrevo:=diav*sin(psi-psiv)+ybaan; { 4 car corner positions }
  yliac:=ybaan-diaa*sin(psi-psia);
  yreac:=ybaan-diaa*sin(psi+psia);

  if ((ylivo >= wegbr) or (ylivo <= 0.00) or
      (yrevo >= wegbr) or (yrevo <= 0.00) or      { check if car is not currently between the lines }
      (yreac >= wegbr) or (yreac <= 0.00) or
      (yliac >= wegbr) or (yliac <= 0.00)) then
    begin
      tlc:=0.00;
      exit;
    end;
```

```
{ calculation tlc-values    Tlc<0 -> passage middle line
                            Tlc>0 -> passage side line }

if (straal >= 0) then
  begin
    r2:=sqrt(sqr(straal-hautobr)+sqr(zv));
    psi2:=psi-arctan(zv/(straal-hautobr));
    y1:=r2*cos(abs(psi2));
    y2:=y1-yrevo;
    rx:=y2/r2;
    psitot:=psi2+arccos(rx);
    tlc:=psitot*straal/snelh;                    { tlc to the right }

    { check on passage middle line }

    r3:=sqrt(sqr(straal+hautobr)+sqr(zv));
    y3:=y2+wegbr;
    check:=r3-y3;
    if ((check >= 0.00) and (psi >= 0.00)) then
      begin
        rx:=y3/r3;
        psi3:=arccos(rx);
        psit3:=psi2-psi3;
        tlc:=psit3*straal/snelh; { tlc to the left }
      end;
  end
else
  begin
    r1:=abs(straal);
    r2:=sqrt(sqr(r1-hautobr)+sqr(zv));
    psi2:=psi-arctan(zv/(r1-hautobr));
    y1:=r2*cos(abs(psi2));
    y2:=y1-(wegbr-ylivo);
    rx:=y2/r2;
    psitot:=arccos(rx)-psi2;
    tlc:=psitot*straal/snelh;                    { tlc to the left }

    { check on passage right side line }

    r3:=sqrt(sqr(r1+hautobr)+sqr(zv));
    y3:=y2+wegbr;
    check:=r3-y3;
    if ((check >= 0.00) and (psi < 0.00)) then
      begin
        rx:=y3/r3;
        psi3:=arccos(rx);
        psit3:=psi2+psi3;
        tlc:=psit3*straal/snelh; { tlc to the right }
      end;
  end;
 if tlc>9 then tlc:=9.0;
 if tlc<-9 then tlc:=-9.0;
end;
```

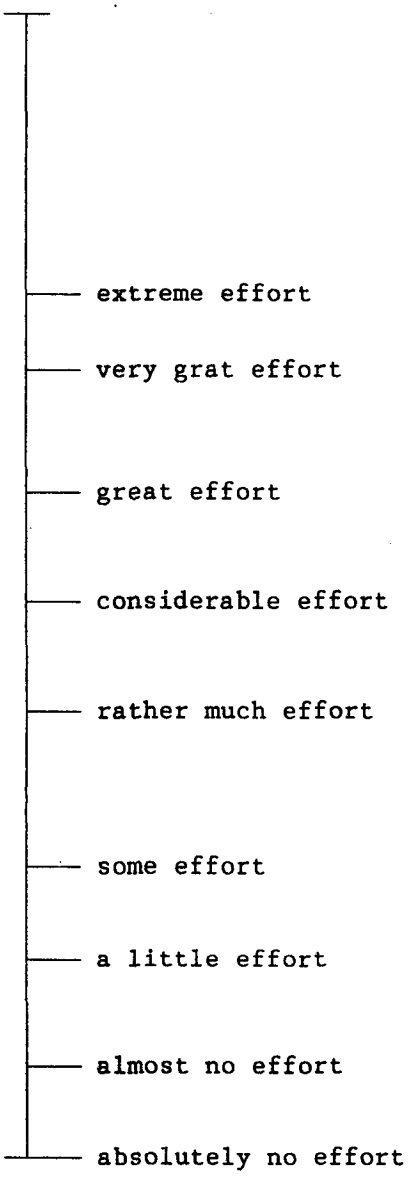
APPENDIX F **Subjective mental activation scale**

Would you please, by means of placing an "x" at the appropriate point on the scale below, indicate the situation that best matches your state of activation during the task you've just finished.

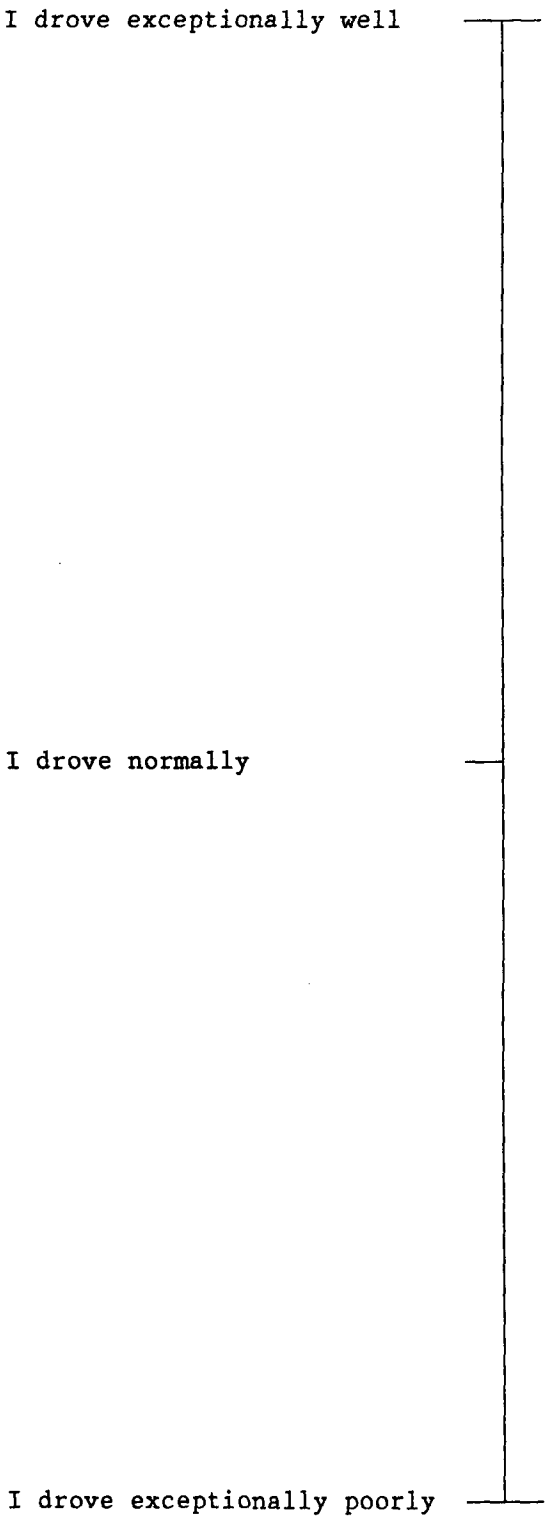

I am scared to death on a crashing plane
I am involved in a traffic accident that has been caused by myself
I am having a lot of pain but don't show anything
I am trying to cross a busy street
I am watching a thriller
I am reading a crime story
I am reading the newspaper
I am solving a crossword puzzle
I am lying on a settee, leafing through a magazine
I am lying in a clearing in the forest, dreaming with my eyes open
(Deep, dreamless sleep)

APPENDIX G **Perceived effort scale**

Would you please, by means of placing an "x" at the appropriate point on the scale below, indicate how much effort it cost you to perform the task you've just finished.



APPENDIX H **Perceived driving quality scale** (Translated from Dutch)



Please indicate the quality of your driving in the test you just finished by marking the scale with an "x" at the appropriate place.

APPENDIX I **Subjective side effects scale** *(translated from Dutch)*

Please indicate your feeling about each of the symptoms by circling one of the three answers.

* Sleepiness : severe / little / none

* Lack of concentration : severe / little / none

* Forgetfulness : severe / little / none

* Dizziness : severe / little / none

* Nausea : severe / little / none

* Feelings of unreality : severe / little / none

* Itch : severe / little / none

* Other complaints (please write below) :