Drug Development Research Supplement 1:57-66 (1982)

# The Effects of Clobazam Upon Critical Flicker Fusion Thresholds: A Review

**A.C. Parrott**

*Department of Psychology, University of Leeds, Leeds, England*

## ABSTRACT

**Parrott, A.C.:** The effects of clobazam upon critical flicker fusion thresholds: a review. Drug Dev. Res. **S1**:057-066, 1982.

The effects of the 1,5-benzodiazepine derivative clobazam upon critical flicker fusion (CFF) values in normal subjects is reviewed. All studies reviewed were double-blind and placebo controlled. Single acute doses of 10 or 20 mg did not lead to significant CFF changes, whereas repeated doses of 20 mg clobazam a day for 4 days produced a significant elevation in CFF thresholds. Possible pharmacokinetic reasons for this CFF elevation after repeated doses are discussed. Equivalent investigations of clobazam at higher dose levels (30 to 60 mg) showed a similar difference in the effects of acute versus repeated doses; single acute doses led to significant CFF decrements, while repeated administrations led to similar clobazam and placebo CFF levels. The patterns of CFF changes with this 1,5-benzodiazepine anxiolytic agent seems to be different from the CFF changes generally reported with the 1,4-benzodiazepine anxiolytic agents (generally CFF reductions), and suggests possible central nervous system alerting affects after repeated administration at the lower dose levels.

**Key words: critical flicker fusion, clobazam, benzodiazepines, arousal, anxiety**

## INTRODUCTION

Critical flicker fusion (CFF) threshold values have been investigated in psychopharmacological investigations involving a wide variety of psychotropic agents. Smith and Misiac [1976] in their review of the effects upon CFF of acute single doses of psychotropic agents, concluded that the direction of the CFF change was clearly related to the nature of the psychotropic agent. Of 12 studies involving central nervous system (CNS) stimulants (e.g., amphetamine, dextroamphetamine), 10 produced significant CFF increments, 2 produced nonsignificant changes, and none produced significant CFF decrements. In contrast, of 28 studies involving hypnotic-sedatives (e.g., secobarbital, chloral-hydrate), none produced significant CFF increments, 6 produced nonsignificant

Address reprint requests to Dr. A.C. Parrott, Department of Psychology, University of Leeds, Leeds LS2 9JT, England.

0272-4391/82/00S1-0057$03.00 

changes, while 22 produced significant CFF decrements. Smith and Misiac [1976] concluded: "As expected, stimulants increased CFF while hypnotics decreased it." CFF threshold changes have also been shown to be generally closely related to subjective self-ratings of alertness [Grundström et al., 1978; Parrott, 1982].

Smith and Misiac [1976] further reviewed the effects of anxiolytics (meprobamate, chlordiazepoxide, diazepam) upon CFF thresholds. CFF changes were frequently not significant at the lower dose levels, but at the higher dose levels, significant CFF decrements were produced. Grundström et al. [1978] reported significant CFF reductions with the 1,4-benzodiazepine derivatives diazepam and nitrazepam. Kleinknecht and Donaldson [1975] concluded that CFF decrements were generally associated with diazepam. Wittenborn [1979] similarly concluded that the CFF procedure was "invariably discriminating" in investigations involving 1,4-benzodiazepine agents; CFF decrements again being reported.

The present review is concerned with CFF changes in normal subjects under the anxiolytic 1,5-benzodiazepine derivative clobazam. CFF changes under clobazam have been investigated by the present researchers in 15 different studies (Table 1), involving 36 separate dose level/drug duration conditions (Tables 2 to 5). Of these 36 clobazam conditions, 5 produced significant CFF increments, 27 produced nonsignificant changes, and 4 produced significant CFF decrements. These different conditions differed markedly, however, in dose levels and durations of drug administration before CFF testing. Both of these factors may have been of importance in determining the significance and direction of any CFF change. In particular, the significant CFF decrements generally resulted from the acute effects of high doses (30 to 60 mg), while the significant CFF elevations were generally found after repeated doses (over 4 days) at the lower dose levels (20 and 30 mg). Therefore after an initial review of the individual studies, data from similar dose level/testing period conditions was grouped together to form data for larger overall analyses. These larger sample sizes allowed the CFF changes to be statistically analysed more powerfully.

One further factor which may be of importance in influencing CFF changes is personality; and with particular regard to the effects of anxiolytic agents, personality anxiety levels [Janke et

**TABLE 1. Chronological List of Investigations Into Critical Flicker Fusion (CFF) Changes Under Clobazam**

| Study reference number | Publication reference | Sample size (N) | Dose regimen | | | Dose levels (mg) |
|---|---|---|---|---|---|---|
| | | | Single daytime | Single nocturnal | Other | |
| 1 | Hindmarch (1979a) | 10 | | | X | 10 (t.d.s.) |
| 2 | Hindmarch (1979a) | 19 | | X | | 20 |
| 3 | Parrott & Hindmarch (1975) | 5 | X | | | 20 |
| 4 | Hindmarch (1979b) | 10 | | | X | 10 (t.d.s.) |
| 5 | Unpublished | 8 | | X | | 20 |
| 6 | Parrott and Hindmarch (1977) | 10 | X | | | 20 |
| 7 | Parrott and Hindmarch (1978) | 8 | X | | | 10,20 |
| 8 | Hindmarch and Parrott (1978) | 9,10,8 | | X | | 20,30,40 |
| 9 | Hindmarch and Parrott (1980a) | 10 | | X | | 10,20 |
| 10 | Unpublished | 20 | X | | | 10,20 |
| 11 | Hindmarch and Parrott (1980b) | 12 | | X | | 20 |
| 12 | Unpublished | 32 | X | | | 20 |
| 13 | Unpublished | 10 | | | X | 10 (t.d.s.) |
| 14 | Hindmarch and Parrott (1979) | 10 | | X | | 30 |
| 15 | Gudgeon & Hickey (1981) Parrott & Munton (1981) | 12 | X | | | 10,20,30, 40,60 |

Note: The raw data for study 1 was missing, and results from this study were therefore not incorporated in any further analyses.

**TABLE 2. Critical Flicker Fusion (CFF) Values From Single Daytime Dose Investigations of Clobazam, in Comparison With Placebo**

| Study reference number (Table 1) | Clobazam dose (mg) | Sample size (N) | Drug condition and testing period | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | Placebo | | | Clobazam | | |
| | | | Pretest | Post 1.5 hr | Post 3 hr | Pretest | Post 1.5 hr | Post 3 hr |
| 7 | 10 | 8 | 29.8 | 29.6 | 29.2 | 28.9 | 29.2 | 29.2 |
| 10 | 10 | 20 | 30.9 | 31.5 | 30.8 | 31.6 | 31.5 | 31.6 |
| 3 | 20 | 5 | 31.7 | No data | 31.0 | 31.0 | No data | 30.5 |
| 6 | 20 | 10 | 29.2 | 28.7 | 28.6 | 29.1 | 27.9 | 28.5 |
| 7 | 20 | 8 | 29.8 | 29.6 | 29.2 | 29.0 | 28.2 | 28.2 |
| 10 | 20 | 20 | 30.9 | 31.5 | 30.8 | 31.2 | 30.8 | 31.0 |
| 12 | 20 | 32 | 31.8 | 31.3 | 30.8 | 31.6 | 31.0 | 31.2 |

Paired t-tests were calculated between placebo and clobazam at each testing period; none were significant.

**TABLE 3. Critical Flicker Fusion (CFF) Values From an Acute Daytime Dose Investigation of Clobazam (Study Reference Number 15)**

| | | Dose level clobazam (mg) | | | | | |
|---|---|---|---|---|---|---|---|
| Postdrug administration period | Background-noise conditions | Placebo | 10 | 20 | 30 | 40 | 60 |
| 1 hr 45 min | Normal testing[a] | 29.6 | 29.6 | 29.2 | 28.8* | 28.1* | 28.0* |
| 1 hr 50 min | Low noise[b] | 28.5 | 28.1 | 27.2* | 27.0* | 26.8* | 26.0* |
| 1 hr 55 min | High noise[b] | 28.3 | 28.1 | 27.4 | 27.1* | 26.5* | 26.1* |

[a]Data from AG.
[b]Data from TM.
*Confidence limits ($P = 0.05$) for placebo/dose level comparisons.
Note: One-way anovar main dose level effects were significant ($P < 0.001$) for each testing condition.

**TABLE 4. Critical Flicker Fusion (CFF) Values (Morning Testing), From Nocturnal Dose Investigations of Clobazam, in Comparison With Placebo**

| | | | Testing session period | | | | |
|---|---|---|---|---|---|---|---|
| | | | | Nights on clobazam | | | |
| Study reference number (Table 1) | Clobazam dose (mg) | Sample size (N) | Pretest | 1 | 2 | 3 | 4 |
| 5 | 20 | 8 | 26.7 | | 26.4 | | 27.1 |
| 8 | 20 | 9 | 28.6 | | 29.5** | | 29.3* |
| 4 | 30 | 10 | 30.6 | 31.4 | | | 31.4** |
| 8 | 30 | 10 | 30.0 | | 29.3 | | 29.2 |
| 8 | 40 | 8 | 28.1 | | 28.4 | | 28.2 |

Paired t-tests comparisons between each pretest and postdrug administration testing session. Two-tailed significance values:
*$P < 0.05$.
**$P < 0.01$.

**TABLE 5. Critical Flicker Fusion (CFF) Values (Morning Testing) From Various Investigations of Clobazam, in Comparison With Placebo**

| Study reference number (Table 1) | Clobazam dose (mg) | Nights on medication | Sample size (N) | CFF values (Hz) | |
|---|---|---|---|---|---|
| | | | | Placebo | Clobazam |
| 9 | 10 | 1 | 10 | 31.2 | 31.3 |
| 2 | 20 | 1 | 19 | 36.1 | 34.9 |
| 9 | 20 | 1 | 9 | 31.9 | 31.0** |
| 11 | 20 | 1 | 12 | 29.6 | 30.1 |
| 11 | 20 | 4 | 12 | 29.7 | 30.5** |
| 13 | 30 | 2 | 10 | 30.7 | 31.5 |
| 14 | 30 | 3 | 10 | 30.2 | 32.0** |
| 14 | 30[a] | 3 | 10 | 30.8 | 31.0 |

Paired t-test comparisons between placebo and clobazam (two-tailed):
**$P < 0.01$.
[a]P.M. testing.

al., 1979]. With reference to the effects of clobazam, Leygonie et al. [1975], investigating sleep, and Parrott and Hindmarch [1977], investigating psychomotor performance, reported significant differences between high-anxiety and low-anxiety subjects. Therefore CFF changes were analysed for the effect of personality anxiety levels, as indicated by the Middlesex Hospital Questionnaire (MHQ) anxiety subscale scores [Crown, 1974].

## METHOD

### Experimental Procedures

The 15 reviewed studies are listed in Table 1. Two types of investigations are included, acute single dose, and repeated dose. In the acute-dose investigations, an initial pretest (generally between 8:30 A.M. and 10:30 A.M.) was followed by postdrug administration testing sessions, generally 1.5 and 3 hr after drug administration. The results from the acute dose studies are listed in Table 2. Data from the most recent acute-dose study [Gudgeon and Hickey, 1981; Parrott and Munton, 1981] is presented separately (Table 3), since it differs in methodological aspects from the other acute dose studies (e.g., CFF measurements were taken at different times after drug administration; some CFF measurements were taken under different background-noise conditions). The repeated-dose investigations comprised either nocturnal drug administrations (½ hr before bed), or daytime repeated administrations (three doses per day [t.d.s.]). CFF measurements were taken in the mornings (generally between 8:30 A.M. and 10:30 A.M.) following 1 to 4 consecutive days on drug. The results from these repeated dose studies are listed in tables 4 and 5.

### Critical Flicker Fusion Thresholds

CFF measurements were determined by the psychophysical method of limits with two ascending and two descending thresholds. Subjects were seated 1 m away from the set of four flickering diode lights in a darkened room (blinds partially drawn). The split-half reliability coefficient of this CFF testing procedure has been determined; a reliability coefficient of $r = +0.94$ was obtained for 101 CFF measures from different subjects in a range of five studies [Parrott, 1982].

### Personality

MHQ was completed by subjects in all studies (except study 2). The anxiety subscale provides an index of mixed trait/state anxiety [Crown, 1974]. Subjects with anxiety subscale scores of greater than seven were arbitrarily designated as "high anxiety" subjects; those with scores of less than six were designated as "medium-low anxiety" subjects.

### Subjects

Subjects were all normal volunteers, in the age range 18 to 50. Subjects with a medical history of renal, hepatic, cardiac, or psychiatric problems were excluded; as were those under concurrent medication (except the contraceptive pill).

### Drug Conditions

All investigations were double-blind, placebo controlled, with matching clobazam and placebo capsules.

### Data Analysis

Since subjects were their own controls, clobazam/placebo statistical comparisons generally comprised paired t-tests. In the dose-ranging study however, (study 15, Table 1), a one-way anovar repeated measures drug effect analysis was followed by confidence limits comparisons between each condition.

Several of the reviewed studies comprised equivalent "dose level" and "period after drug administration" conditions. Data from these studies were therefore combined. Five groups of data

were thus generated, namely: (dose, followed by period on drug) 20 mg/1.5 hr (N = 70); 20 mg/3 hr (N = 75); 20 mg/1 night (N = 40); 20 mg/4 nights (N = 29); 30 mg/4 nights (N = 20). These five groups of data were analysed separately, by two-way anovar for main effect of drug (clobazam/placebo), personality (high/low MHQ anxiety subscale scores), and drug/personality interactions. (Note: the 20 mg/1 night data was incomplete for personality data, and was therefore analysed only for drug effects.)

## RESULTS

The results of the individual studies are summarised in Tables 2 through 5. Thirty-six statistical comparisons between clobazam and placebo are further discussed. (Note: the afternoon testing data [study 14, Table 5], and background-noise testing data [study 15, Table 3], are not further discussed, since equivalent normal testing condition values from these studies are presented for discussion.) Of the 36 comparisons, 4 demonstrated significant CFF decrements. Three of these decrements were found for the high dose levels (30, 40, and 60 mg) in an acute-dose study (Table 3); the other decrement was after a single nocturnal dose of 20 mg (Table 5). Five of the 36 comparisons demonstrated significant CFF elevations. These were found after repeated doses of 20 mg (Tables 4 and 5) and repeated doses of 30 mg (Tables 4 and 5). The other 27 comparisons between clobazam and placebo were all nonsignificant.

The results of the combined data analyses are presented in Table 6. There was no significant difference between 20 mg clobazam and placebo either 1.5 or 3 hr after drug administration. After one night, CFF values on 20 mg clobazam were lower than those on placebo, this comparative CFF reduction approached significance (two-tailed, $P < 0.10$). After 4 consecutive nights on 20 mg clobazam, CFF values were significantly elevated compared to placebo ($P < 0.05$). The mean group values from these analyses of 20 mg clobazam are presented graphically (Fig. 1). After 4 consecutive nights on 30 mg clobazam, CFF values did not differ significantly between placebo and clobazam. None of the "anxiety level" effects were significant, nor were any of the drug/anxiety interactions. The anxiety effects are not further discussed in this review.

## DISCUSSION

The effects of clobazam upon CFF thresholds are related to two important factors, dose level and duration of drug administration. At the 20 mg dose level, clobazam did not lead to significant CFF changes, either 1.5 or 3 hr after drug administration (tables 2 and 5). However, after repeated administrations at this dose level (20 mg/day, for 4 days), CFF values were significantly elevated ($P < 0.05$, Table 6). These conclusions are based upon analyses of fairly large subject sample sizes (from N = 29, to N = 75). Higher dose levels of clobazam (30 and 40 mg) have been investigated in less detail, but a similar difference in the effect of acute doses, compared to repeated doses, is apparent. Acute single doses of 30 and 40 mg clobazam led to significant CFF decrements (Table 3), whereas repeated doses at the same dose levels produced nonsignificant CFF changes compared to placebo. The overall mean CFF values for placebo and clobazam after 4 days were very close (clobazam 30 mg, 30.3 Hz; placebo, 30.3 Hz; clobazam 40 mg, 28.2 Hz; placebo, 28.1 Hz). These conclusions regarding the 30 and 40 mg dose levels are, however, based upon comparatively smaller sample sizes (from N = 10 to N = 20), and should therefore be interpreted more cautiously. However, it may be suggested that at these higher dose levels (30 and 40 mg) an acute dose causes significant CFF reduction; changes after 4 days of repeated administration are similar to those seen with placebo.

The effects of 10 mg clobazam/day have not been fully investigated. Acute single doses of 10 mg clobazam did not impair CFF levels either 1.5 or 3 hr after administration (Table 2), or after a single nocturnal administration (Table 3). The effects of repeated administration of 10 mg/day have not been investigated.

Various factors may be proposed to account for the differential effect of clobazam in single-dose and repeated-dose schedules. First, although single doses of clobazam have peak serum (clobazam) levels 1 to 4 hr after administration, repeated doses lead to steady-state serum clobazam

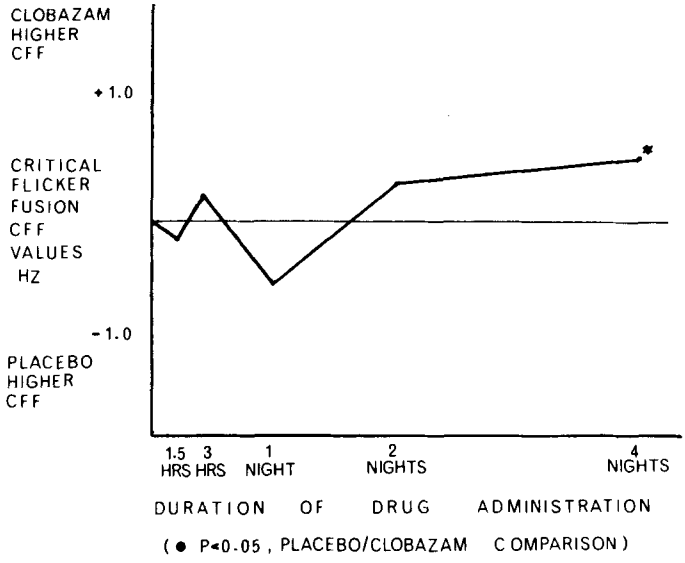


Fig. 1.

**TABLE 6. Critical Flicker Fusion (CFF) Values Anaysed by Two Way Anovar for Drug Effects (Placebo v Clobazam), and Personality Effects (MHQ Anxiety Scores, Low v High)**

| Testing condition and clobazam dose (mg) | Study reference no. (Table 1) | Sample size (N) | Significance levels | |
|---|---|---|---|---|
| | | | Drug effect[a] | Personality effect[a] |
| 20 single morning dose 1½hr post-administration | 6,7,10,12 | 70 | N.S. | N.S. |
| 20 single morning dose 3hr post-administration | 3,6,7,10,12 | 75 | N.S. | N.S. |
| 20 Nocturnal dose 1 Night | 2,9,11 | 40 | N.S.($p<.10$) | N.S. |
| 20 Nocturnal dose 4 consecutive nights | 5,8,11 | 29 | Clobazam Significant Elevation ($p<.05$) | N.S. |
| 30 Nocturnal dose 4 consecutive nights | 4,8 | 20 | N.S. | N.S. |

[a]None of the ANOVAR drug/personality interaction effects were significant.

levels only after about 7 days [Rupp et al., 1979]. The repeated dose CFF effect may reflect this gradual increase in serum clobazam levels over a period of days. A second possible factor is the biotransformation products of clobazam, especially N-desmethylclobazam [Rupp et al., 1979]. After a single clobazam dose, N-desmethylclobazam serum concentrations are lower than the serum concentrations of the parent compound. However, after repeated administrations, the serum con-

centrations of N-desmethylclobazam rapidly build up to levels higher than those of clobazam. After 4 to 5 days N-desmethylclobazam serum concentrations become higher than clobazam serum concentrations, and after 28 days N-desmethylclobazam serum concentrations reach levels about eight times those of serum clobazam [Rupp et al., 1979]. The changes in CFF levels with repeated administrations may therefore be related to the rapidly increasing levels of N-desmethylclobazam.

The acute single dose effects of clobazam have only been extensively investigated for 20 mg clobazam, which shows no CFF impairment in relation to placebo (Table 2). Similarly 10 mg clobazam has no acute-dose effects upon CFF. Higher dose levels (30, 40, and 60 mg) have only been investigated in one study, where significant CFF decrements were found (Table 3). These acute single dose effects of clobazam, a 1,5-benzodiazepine derivative, may be compared to the CFF effects produced by 1,4-benzodiazepine derivatives. Wittenborn [1979] found CFF decrements to be widely reported with the 1,4-benzodiazepines. Smith and Misiac [1976] concluded that CFF decrements were commonly found with the 1,4-benzodiazepines, particularly at the higher dose levels. Kleinknecht and Donaldson [1975] concluded that CFF decrements were generally associated with diazepam, even at comparatively low dose levels. On the basis of these reviews it might be predicted that the acute dose effects of 1,4-benzodiazepines (e.g., diazepam, chlordiazepoxide) upon CFF might be significantly greater than those of clobazam. However, Gudgeon and Hickey (1981) reported no significant differences between diazepam and clobazam in a dose-ranging study (where dosage comparisons were made on the basis of a ratio of 2 clobazam:1 diazepam, e.g., 20 mg clobazam to 10 mg diazepam).

The repeated dose effects of 1,4-benzodiazepines upon CFF have not been widely reported. Kleinknecht and Donaldson [1975] list only single-dose investigations of diazepam. Seppala et al. [1980] however, report significant CFF reductions with 10 mg diazepam/day, both on day 1 and day 2 of a 2-day duration study. Hindmarch [1979] reported a significant CFF decrement after 4 days of chlordiazepoxide (10 mg t.d.s.), but not after diazepam (5 mg t.d.s.). Clobazam (10 mg t.d.s.) in this study had produced a significant CFF increment.

The effects of clobazam upon CFF are paralleled in some ways by the changes in psychomotor performance tasks. Hindmarch [1979], Rigal and Savelli [1975], Salkind et al. [1979], and Wittenborn [1979] each concluded that clobazam was similar to placebo and generally different from the 1,4-benzodiazepines; on some performance tests [balance beam, Wittenborn, 1979; choice reaction time, Hindmarch, 1979a] clobazam was significantly better than placebo. Wittenborn [1979] ended his review of 1,4-benzodiazepines and psychomotor performance by stating: "The association between the impairment resulting from the benzodiazepines and the reduction of critical flicker fusion frequency is provocative and should be examined intensively." Similarly, the association of CFF and psychomotor test performance changes with clobazam needs further elaboration.

Although CFF levels are widely used as an index of CNS arousal levels, particularly in psychopharmacological investigations [Smith and Misiac, 1976], the exact meaning of CFF threshold changes is difficult to specify. Arousal is not a simple concept, either anatomically or neurochemically. A fairly simple arousal model may be applicable to these psychoactive compounds with fairly consistent effects upon different types of arousal measure (psychological and physiological), (e.g., amphetamines or barbiturates), but a simple arousal model may be more difficult to apply to other psychoactive agents such as neuroleptics, antidepressants, and anxiolytics. Neuroleptics, for instance, with their "tranquillization without sedation" cannot readily be described with reference to a simple unitary model of arousal; furthermore, they have a variety of effects both upon CFF [Smith and Misiac, 1976], and upon the relationships between CFF changes and changes in self-reported alertness [Grundström et al., 1977; Parrott, 1982]. Anxiolytic agents such as the benzodiazepine derivatives may also exhibit complex effects upon arousal systems, affecting arousal levels either directly, or indirectly (e.g., through anxiety reduction); they may, therefore, have a range of effects upon different aspects of arousal/alertness, and upon CFF levels. The interrelationships between anxiety and arousal changes produced by anxiolytic aspects is an important but difficult problem [Janke et al., 1979]. Lader [1979] has suggested that the development of anxiolytic agents which are without arousal-reducing properties is desirable, although this ideal

description is a simplified model of a complex problem. However, with regard to clobazam, its effects upon CFF (as an arousal index) certainly seems to be different from the effects of the 1,4-benzodiazepines, particularly in the significant repeated-dose CFF elevation. A wider range of arousal/alertness measures should, however, be involved, along with longer durations of drug administration, and a wider range of dose levels, in future investigations of the arousal/alertness changes produced by clobazam.

## REFERENCES


Crown, S.: The Middlesex Hospital Questionnaire (MHQ) in clinical research. Pharmacopsychiatry **7:** 111–124, 1974.

Grundström, R., Holmberg, G., Ledermann, H. and Livstedt, B.: Sedative properties of doxepin in comparison with diazepam. Psychopharmacology (Berlin) **54:** 165–169, 1977.

Grundström, R., Holmberg, G. and Hansen, T.: Degree of sedation obtained with various doses of diazepam and nitrazepam. Acta. Pharmacol. Toxicol. (Copenh) **43:** 13–18, 1978.

Gudgeon, A.C. and Hickey, B.: Comparative effects of clobazam and diazepam upon psychomotor performance and critical flicker fusion thresholds. Roy. Soc. Med. Int. Cong. Sym. Ser. **43:** 1–5, 1981.

Hindmarch, I.: Some aspects of the effects of clobazam on human psychomotor performance. Br. J. Clin. Pharmacol. **7:** Suppl. 1 77S–82S, 1979a.

Hindmarch, I.: A preliminary study of the effects of repeated doses of clobazam on aspects of performance, arousal and behaviour in a group of anxiety rated volunteers. Eur. J. Clin. Pharmacol. **16:** 17–21, 1979b.

Hindmarch, I. and Parrott, A.C.: A repeated dose comparison of clobazam (20, 30 and 40mg) upon aspects of sleep and early morning behaviour. Arzneim. Forsch. **28:** 2169–2172, 1978.

Hindmarch, I. and Parrott, A.C.: The effects of repeated nocturnal doses of clobazam, dipotassium chlorazepate, and placebo, on subjective measures of arousal, psychomotor performances and anxiety. Br. J. Clin. Pharmacol. **8:** 325–329, 1979.

Hindmarch, I. and Parrott, A.C.: The effects of combined sedative and anxiolytic preparations on subjective aspects of sleep and objective measures of arousal and performance: I Acute. Arzneim. Forsch. **30:** 1025–1028, 1980a.

Hindmarch, I. and Parrott, A.C.: The effects of combined sedative and anxiolytic preparations on subjective aspects of sleep and objective measures of arousal and performance: II Repeated. Arzneim. Forsch. **30:** 1167–1170, 1980b.

Janke, W., Debus, G. and Longo, N.: Differential psychopharmacology of tranquillizing and sedating drugs. Mod. Probl. Pharmacopsychiatry **14:** 13–98, 1979.

Kleinknecht, R.A. and Donaldson, D.: A review of the effects of diazepam on cognitive and psychomotor performance. J. Nerv. Ment. Dis. **161:** 399–411, 1975.

Leygonie, F., Rethore, A., Tuceyatak, F. and Yuceyatak, A.: A new anxiolytic drug clobazam: Effects upon sleep and performance levels on waking (trans). Gazette Médicale de France **82:** 1303–1310, 1975.

Parrott, A.C.: Critical Flicker Fusion Thresholds and their relationship to other measures of alertness. Pharmacopsychiatry (in press).

Parrott, A.C. and Hindmarch, I.: Clobazam, a 1,5 benzodiazepine derivative: Effects upon anxiety, arousal and performance. IRCS. Med. Sci. **3:** 177, 1975.

Parrott, A.C. and Hindmarch, I.: Comparative effects of acute doses of three benzodiazepine derivatives—clobazam, nitrazepam, and flurazepam, upon psychomotor performance under different reinforcement conditions. IRCS. Med. Sci. **5:** 166, 1977.

Parrott, A.C. and Hindmarch, I.: Clobazam, a 1,5 benzodiazepine derivative: Effects upon human psychomotor performance under different levels of task reinforcement. Arch. Int. Pharmacodyn. Ther. **232:** 262–267, 1978.

Parrott, A.C. and Munton, A.: Comparative effects of clobazam and diazepam upon psychological performance under different levels of background noise. Roy. Soc. Med. Int. Cong. Sym. Ser. **43:** 51–57, p. 1981.

Rigal, J. and Savelli, A.: Clobazam, vigilance functions and motor-car driving (trans). Gazette Médicale de France **82:** 3908–3914, 1975.

Rupp, W., Badian, M., Christ, O., Hajdu, P., Kuluarni, R.D., Taeuber, K., Uihlein, M., Bender, R. and Vanderbeke, O.: Pharmacokinetics of single and multiple doses of clobazam in humans. Br. J. Clin. Pharmacol. **7:** Supp. 1 51S–58S, 1979.

Salkind, M.R., Hanks, G.W. and Silverstone, J.T.: Evaluation of the effects of clobazam, a 1,5 benzodiazepine,

on mood and psychomotor performance in clinically anxious patients in general practice. Br. J. Clin. Pharmacol. **7:** Suppl. 1 113S–118S, 1979.

Seppälä, T., Palva, E., Mattila, M.J., Kortilla, K. and Shrotriya, R.C.: Tofisopam, a novel 3-4 benzodiazepine: Multiple dose effects on psychomotor skills and memory. Comparison with diazepam and interactions with alcohol. Psychopharmacology (Berlin) **69:** 209–218, 1980.

Smith, J.M. and Misiac, H.: Critical Flicker Fusion (CFF) and psychoactive drugs in normal subjects—a review. Psychopharmacology (Berlin) **47:** 175–182, 1976.

Wittenborn, J.R.: Effects of benzodiazepines on psychomotor performance. Br. J. Clin. Pharmacol. **7:** Suppl. 1, 61S–68S, 1979.