REVIEW OF CLINICAL STUDIES ON CLOBAZAM

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- 1 Clobazam was compared with placebo and diazepam in 45 double-blind studies.
- 2 Clobazam dosage ranged from 5 mg daily (paediatric patients) to 120 mg daily (psychiatric in-patients). Usual daily dosage in out-patient therapy ranged from 20–30 mg clobazam.
- 3 Treatment duration varied from a few days up to 3.5 years. The usual duration of treatment was 2–4 weeks.
- 4 Clobazam was shown to be an efficacious and well tolerated anxiolytic agent in various neurotic and psychosomatic disorders.
- 5 Dosages showing distinct anxiolytic effects in out-patient therapy did not impair psychomotor performance.

Introduction

THE efficacy and safety of clobazam in comparison with placebo and/or diazepam have been investigated in 45 double-blind trials. In addition 52 open studies have been carried out. A total of 2312 patients participated in the double-blind trials and 3824 patients in the open studies.

The patients suffered from neurotic and psychosomatic disorders displaying symptoms of anxiety, tension, restlessness, irritability and insomnia.

Long-term studies lasted from 3 months up to 3.5 years. In these studies the following variables were monitored: body weight, heart rate, blood pressure, ECG and laboratory data comprising blood analyses and tests of hepatic and renal function.

Clobazam was administered in daily dosages from 5 mg in children to 120 mg in adult psychiatric in-patients.

The usual clobazam dosage in out-patient therapy was 20–30 mg daily. The duration of treatment ranged from several days up to 3.5 years; however, most of the patients were treated for 2–4 weeks. The psychiatric symptoms were assessed using standardized rating scales (Clinical Global Impression, Hamilton Anxiety Scale, Brief Psychiatric Rating Scale, Taylor Manifest Anxiety Scale, Anxiety Status Inventory, Morbid Anxiety Inventory, Symptom Check List).

The diagnoses were established according to the WHO classification.

Efficacy

Double-blind studies (clobazam compared with placebo)

Clobazam was compared with a placebo in 16 double-blind studies (Table 1).

In 14 trials clobazam proved to be distinctly more effective than placebo, the level of significance being $P < 0.05$. The results of one study demonstrating these findings are shown in Figure 1 (Devanathan & Channabasavanna, 1977).

Figure 1 Clobazam compared with placebo in 47 out-patients with anxiety neurosis (Devanathan *et al.*, 1977). Hamilton Anxiety Scale (total scores). Hatched columns, clobazam 30–40 mg daily; open columns, placebo.

Table 1 Double-blind studies (clobazam compared with placebo)

<i>Investigator</i>	<i>Patient number*</i>	<i>Clobazam dosage (mg daily)</i>	<i>Duration (weeks)</i>	<i>Efficacy (at least P<0.05)†</i>
Abrahams (USA, 77)	190 (1)	40–80 (60.6)‡	1	C > P (2)
Barberini (I, 70)	50 (1)	30	4	C > P (4)
Baudet (F, 76)	34 (3)	15	4	C > P (4)
Charalampous (USA, 77)	30 (1)	40–80 (48.6)	1	C > P (1,2)
Ciparrone (BR, 77)	30 (1)	20–90 (35.0)	5	C > P (1,2)
Devanthan (IND, 77)	47 (1)	30–40 (30.8)	4	C > P (2)
Figueiredo (BR, 77)	30 (3)	20–30	4	C > P (2)
Freitas (BR, 76)	30 (3)	20–40	4	C > P (1)
Goldberg (USA, 77)	79 (1)	20–80 (56.8)	4	C > P (1)
Laverdant (F, 76)	80 (3)	15	2	C > P (1)
Mauri (I, 70)	40 (3)	30	3	C > P (2)
Nibra (M, 74)	40 (1)	30	2	C > P (2)
Okaware (BR, 77)	30 (3)	10–30 (18.8)	5	C > P (1)
Ribeiro (BR, 77)	30 (3)	10–30	3	C > P (1,2)
Lipke (BR, 76)	30 (3)	20–40	4	C = P (3)
Kurland (USA, 77)	50 (1)	20–60	5	C < P (3)
16 Studies	820	10–90	1–5	14C>P, 1C=P, 1C<P

* 1, Neurotic out-patients; 2, neurotic in-patients; 3, non-psychiatric patients.

† Superiority of one drug to the other. 1, Clinical Global Impression; 2, Hamilton Anxiety Scale; 3, Symptom Check-list; 4, other.

‡ Means are indicated in brackets.

Table 2 Double-blind studies (clobazam compared with diazepam)

<i>Investigator</i>	<i>Patient number*</i>	<i>Dosage (mg daily)</i>		<i>Duration (weeks)</i>	<i>Efficacy (P < 0.05 at least)†</i>
		<i>Clobazam</i>	<i>Diazepam</i>		
Arioni Faccini (I, 71)	60 (1)	20–80	10–40	1	C=D
Ban (CDN, 77)	40 (1,2)	30–60	15–30	4	C=D
Bianchi (I, 70)	32 (3)	10–30	5–15	2	C=D
Castelluccio (RA, 76)	29 (1)	30	15	4	C=D
Chappa (RA, 76)	33 (1)	30	15	4	C=D
Chaudron (B, 77)	28 (3)	20	10	4	C=D
Deongaji (IND, 77)	40 (1)	30–40	15–20	4	C=D
Fann (USA, 77)	162 (1)	30–80 (50.2)‡	15–40 (25.5)	2	C=D
Furletti Lages (BR, 76)	35 (3)	30	15	4	C=D
Grimbaum (BR, 75)	40 (3)	30	15	4	C=D
Guz (BR, 75)	35 (1)	10–80 (36.5)	10–60 (17.5)	4	C=D
Heller (B, 77)	34 (3)	20	10	4	C=D
Laudano (RA, 77)	34 (3)	30	15	6	C=D
Mendels (USA, 77)	61 (1)	20–80	10–40	5	C=D
Sjøsby (N, 77)	60 (1)	30	15	12	C=D
Sena Rocha (BR, 76)	36 (3)	30	15	4	C=D
Soldato (I, 71)	30 (1)	40	20	3	C=D
De Souza (BR, 76)	47 (3)	30	15	4	C=D
Tessore (I, 75)	30 (3)	30	15	2	C=D
Weber (USA, 77)	50 (1)	20–60	10–30	5	C=D
Botter (NL, 75)	47 (1)	20 (Ev. D.)	15 (5 three times daily)	4	C>D (2)
Ananth (CDN, 78)	32 (1)	30–80	15–40	3	D>C (2) D=C (1,3)
22 Studies	995	1 –80	5–60	1–12	

* 1, Neurotic out-patients; 2, neurotic in-patients; 3, non-psychiatric patients.

† 1, Clinical Global Impression; 2, Hamilton Anxiety Scale; 3, Anxiety Status Inventory.

‡ Means are indicated in brackets.

20 studies: C=D

1 study : C>D

1 study : C<D

In another study no significant difference between clobazam and placebo was found, and in a further study better therapeutic effects were observed with the placebo. Deviant findings like the latter two have occurred in the treatment of anxious-neurotic patients. They may be due to individual investigational settings (Debus & Janke, 1977) together with non-specific factors such as the severity of the anxiety (Downing & Rickels, 1978), the experience of the observer (Heimann, 1975) or the attitude of doctor and patient to the pharmacotherapy and psychotherapy (Rickels & Cattell, 1969; Uhlenhuth *et al.*, 1966).

Double-blind studies (clobazam compared with diazepam)

A dose ratio of clobazam to diazepam 2:1 was chosen for the clinical trials based on the results of pharmacological and clinical pharmacological studies. Table 2 summarizes the details of the 22 studies comparing clobazam and diazepam.

Comparisons of global efficacy (Clinical Global Impression, total scores of anxiety scales) revealed no significant difference between the two compounds in 20 studies. In the other two studies either clobazam or diazepam was significantly more effective than the comparator.

In addition, seven three-way comparisons (clobazam/diazepam/placebo) were carried out. In five of these studies it was demonstrated that clobazam had equal global therapeutic efficacy as compared with diazepam, whereas in the other two studies clobazam was found to be superior (Table 3).

The majority of the reported 29 studies (two-way and three-way studies) did not show differences between clobazam and diazepam in their global efficacy.

However, a discernible difference was readily seen in symptom amelioration: anxiety, tension and

gastrointestinal symptoms were more clearly alleviated with clobazam in comparison with diazepam in several studies, whereas a similar superiority with diazepam was not observed in any study. In the individual studies indicated in Table 4, the following symptoms were improved with clobazam: fears, sensory and autonomic anxiety symptoms (for example, blurred vision, feelings of weakness or dry mouth, flushing); and with diazepam: obsessive-compulsive and muscular symptoms (for example, increased muscular tone or stiffness). Due to the heterogeneity of the reported studies detailed statistical evidence is given in Table 4.

Safety

Doses used in out-patient treatment produced only mild side-effects which disappeared either spontaneously or with dose reduction. Special long-term studies did not show any clinically relevant changes in vital signs or laboratory data.

Clobazam was well tolerated even by patients at increased risk, such as children, geriatric patients and patients with a history of myocardial infarction.

No signs of habit-forming potential or withdrawal symptoms were reported in any of the trials, including the long-term studies.

Double-blind studies (clobazam compared with placebo)

Side-effects were reported in ten studies (Figure 2). In eight of those the incidence was higher with clobazam; one study showed an equal incidence and the other a larger number of side-effects with placebo.

Drowsiness was the most common side-effect; it was seen about two to three times more often with clobazam than with placebo.

Other side-effects observed in at least three studies were dizziness, fatigue, nausea and dry mouth. Apart

Table 3 Placebo-controlled double-blind studies (clobazam compared with diazepam)

Investigator	Patient number*	Dosage (mg daily)		Duration (weeks)	Efficacy ($P < 0.05$ at least)
		Clobazam	Diazepam		
Coste-Simonin (F, 75)	135 (3)	10/15/20	5/7.5/10	4	C ₂₀ (1)†
Cottin (F, 75)	119 (2)	15/30	15	2	C ₃₀ = D ₁₅ > P (2)†
Martin (F, 75)	40 (3)	15/30	15	2	C ₃₀ > D ₁₅ > P (2)
Oulès (F, 75)	40 (2)	15/30	15	2	C ₁₅ + C ₃₀ = D ₁₅ > P (1,2)
Pinelli (I, 75)	27 (2)	30	15	3	C ₃₀ = D ₁₅ = P (2)
Ruiz (E, 76)	112 (1)	30	15	24	C ₃₀ = D ₁₅ > P (2)
Salkind (GB, 77)	41 (3)	10-60 (35.7)	5-30 (18.6)	2	C = D > P (2)
7 studies	497	10-60	5-30	2-24	5 studies: C = D 2 studies: C > D

* 1 Neurotic out-patients; 2, psychiatric in-patients; 3, non-psychiatric patients.

† Significant improvement under one drug. 1, Clinical Global Impression; 2, Hamilton Anxiety Scale.

‡ > Significant superiority of one drug to the other.

Figure 2 Patients with side-effects in 10 double-blind studies, clobazam (hatched) compared with placebo (open).

from dry mouth, which was reported more frequently with clobazam, all side-effects occurred with equal frequency under both treatments.

On the whole, clobazam's rate of side-effects ranged from 10–63% and that of placebo from 0–43%. No linear relationship between the dose level and occurrence of side-effects could be found.

Double-blind studies (clobazam compared with diazepam)

In 16 studies the occurrence of side-effects was reported. In eight out of these more side-effects were

observed with diazepam; in two studies there was an equal incidence of side-effects, and in six studies more side-effects occurred with clobazam (Figure 3).

Side-effect rates ranged from 5–75% with clobazam and from 6–90% with diazepam. In those cases in which there was a higher incidence of side-effects with diazepam, a greater difference could be seen between the drug groups, in contrast to those instances where there was a higher incidence with clobazam.

Although drowsiness was the most frequent side-effect with both drugs, its distribution varied (Figure 4). Whereas two studies showed an equal incidence of drowsiness, five studies reported more drowsiness with

Figure 3 Patients with side-effects in 16 double-blind studies, clobazam (hatched) compared with diazepam (cross-hatched).

clobazam and in eight studies diazepam had the higher incidence of drowsiness. Again, in those cases in which there was a higher incidence with diazepam, a greater difference could be seen between both drug groups, in contrast to the studies showing a higher frequency with clobazam.

In summary, drowsiness, the most common side-effect, was noted more often with clobazam than with placebo, but less frequently than with diazepam. All other side-effects such as dizziness, headaches, dry mouth, blurred vision, constipation, depression and excitement showed no consistent pattern.

Weight gain was reported in three studies, all of

which showed a higher incidence of weight gain with diazepam.

Indications

Anxious-neurotic disturbances

The majority of the clinical trials of clobazam were carried out in anxious-neurotic out-patients. Of these, eight double-blind studies were placebo comparisons.

Clobazam's therapeutic efficacy could be clearly distinguished from placebo. Both clobazam and

Figure 4 Incidence of drowsiness in double-blind studies, clobazam (hatched) compared with diazepam (cross-hatched).

diazepam displayed similar global therapeutic effects in 16 double-blind studies, whereas several studies revealed different symptomatological actions. The results of one representative study are shown in Figure 5 and Table 5.

Open studies also confirmed clobazam's good efficacy and tolerance in anxious-neurotic patients (Boutillier, 1975; Vauterin *et al.*, 1975; Castillo Alvarado, 1976; Périvier, 1976; Vauterin, 1976; Caruso Madalena & Franchin, 1977; Miedzyrecki, 1977; Radmayr & Koeppen, 1977; Sandler *et al.*, 1977).

Psychosomatic disorders

Gastrointestinal psychosomatic disorders. Anxiety- and tension-related gastrointestinal symptoms such as stomach pains, dyspepsia, heartburn, diarrhoea or constipation were treated with clobazam in open studies (Galley, 1976; Laverdant, 1976; Pergola, 1976; Sena Rocha & Chaimowicz 1976; Figueiredo Pentead, 1977; Laudano *et al.*, 1977).

Clobazam's superiority in relieving gastrointestinal symptoms was observed in three studies by Hamilton anxiety ratings (for example, Arioni Faccini *et al.*,

Table 4 Symptomatological efficacy of clobazam and diazepam

No difference in three studies (Ban, 1977; Chappa, 1976; Mendels, 1977)

13 studies showed significant differences:

Anxiety	*C>D	Castelluccio, 1976 Martin, 1975
	*C	Cottin, 1975 Sjøsby, 1977
Fears	*C	Salkind, 1977
Tension	*C>D	Fann, 1977 Guz, 1975
Depression	*C>D	Guz, 1975
	*C	Bianchi, 1970
	*D>C	Weber, 1977
Intellectual	*C>D	Guz, 1975
	*C	A. Faccini, 1971
	*D	Bianchi, 1970 del Soldato, 1971
Insomnia	*C>D	Guz, 1975
	*C	Salkind, 1977
	(*)D>C	Fann, 1977 ($p=.06$)
Obsessive compulsive	*D>C	Weber, 1977
Sensory	*C	del Soldato, 1971
Gastrointestinal	*C>D	Heller, 1977
	*C	A. Faccini, 1971 del Soldato, 1971
Cardiovascular	*C	Chaudron, 1977 del Soldato, 1971
	*D	Salkind, 1977
Respiratory	*C>D	Castelluccio, 1976 del Soldato, 1971
	*C	Cottin, 1975
	*D	Salkind, 1977
Autonomic	*C	Bianchi, 1970
Muscular	*D	Sjøsby, 1977

*Significant improvement ($P<0.05$) – comparison to baseline or placebo at least in one trial assessment.

>Significant superiority ($P<0.05$) to the other drug at least in one trial assessment.

Table 5 Week of onset of action* in items of Hamilton Anxiety Scale (Sjøsby, 1977)

	Clobazam	Diazepam
Anxious mood	2	—
Insomnia	2	4
Depressive mood	10	10
Tension	6	4
General muscular symptoms	—	4

*Defined as significantly more improved than unchanged or worse scores.

Figure 5 Hamilton Anxiety Scale in the course of treatment with clobazam 10 mg three times daily and diazepam 5 mg three times daily. ●, clobazam; ○, diazepam (Sjøsby, 1977). **Figure 6** Gastrointestinal symptoms in 30 psychiatric patients in a 1 week treatment (Arioni Faccini *et al.*, 1971). Hatched, Clobazam 20–80 mg daily (* $P<0.01$); cross-hatched, diazepam 10–40 mg daily; open, placebo.

1971, Figure 6). The other clinical trials in psychosomatic patients with gastrointestinal disorders showed equal improvement of psychic and somatic anxiety symptoms with clobazam and diazepam (for example, Sena Rocha & Chaimowicz, 1976, Figure 7).

Cardiovascular psychosomatic disorders. In patients with cardiovascular psychosomatic symptoms such as tachycardia, palpitations or praecordial pain, clobazam showed similar efficacy to diazepam (Coste-Simonin & Krantz, 1975; Grimbaum, 1975; Furletti Lages, 1976, Figure 8; Grand *et al.*, 1976; Moragrega Adame, 1976; Morena Villa, 1976).

Various psychosomatic disorders. In addition to the testing of clobazam in psychosomatic gastrointestinal

Figure 7 Double-blind study (clobazam compared with diazepam) in 36 patients with gastrointestinal psychosomatic symptoms (Sena Rocha, 1976). *a*, Gastrointestinal symptoms (general); *b*, dyspepsia; *c*, heartburn. Hatched, Clobazam 10 mg; cross-hatched, diazepam 5 mg; ●, clobazam 10 mg; ○, diazepam 5 mg (all doses three times daily).

Figure 8 Double-blind study (clobazam compared with diazepam) in 35 patients with cardiovascular psychosomatic symptoms (Furletti Lages, 1976). *a*, Cardiovascular symptoms (general), *b*, tachycardia; *c*, extrasystoles. Symbols as for Figure 7.

and cardiovascular disorders, trials in patients with anxiety and tension were carried out in general practice, gynaecology and dermatology (Lauret & Leroy, 1975; Plauchu & Navarro, 1975; Baudet *et al.*, 1976; Beuve-Méry & Martinet, 1976; De Souza, 1976; Becker, 1977; Ribeiro, 1977; Roger *et al.*, 1975).

Relief from psychic and somatic anxiety symptoms with clobazam was established in double-blind studies against placebo and diazepam as well as in open studies.

One multi-centre open study included 53 general practitioners, internists and gynaecologists who administered clobazam to 1073 out-patients. Improvement of symptoms in this large open study in patients with various anxiety symptoms reinforced the results found in controlled trials. Side-effects, occurring in 18% of the patients, were mild and consisted mainly of drowsiness (11%) and dizziness (2%). Although many patients received various concomitant medications, no incompatibilities with clobazam were reported.

Paediatrics. Additional pharmacotherapy with psychotropic agents can be useful in children with behaviour disorders and symptoms such as anxiety, restlessness or aggressiveness.

Clobazam was tested in an open multi-centre study in 211 children aged from 2.5 to 15 yr (Boulesteix *et al.*, 1977). Indications were general anxiety, school phobia, sleep disturbances, functional gastrointestinal symptoms and anxiety related to severe somatic illnesses such as cardiac, renal or haematological disorders.

Clobazam was administered in daily dosages from 5–15 mg. The majority of the children received clobazam 5 mg twice daily as morning and evening doses. The average duration of treatment was 4 weeks.

Global reduction of anxiety was reported in 87% of the children. Particularly good improvements were observed in school phobia, sleep disturbances and gastrointestinal symptoms.

Transient drowsiness was reported in 18% of the patients. No incompatibilities with concomitant medications were observed.

Good therapeutic effects as well were seen in the other open paediatric studies in in-patients and out-patients (Grenier & Rolland, 1975; Mises, 1975; Guran, 1976; Pierson, 1976; de Villard, 1976; Guran & Blanc, 1977; Lajouanine, 1977; Rochiccioli, 1977).

The usual daily dosage in these studies was 0.5 mg/kg. Tolerability was described as good in general. No evidence of sedation was noted in four studies, whereas five studies noted transient drowsiness.

Laboratory data (haematology, hepatic and renal function) were monitored in five studies, two of the studies lasting up to 6 months. No clinically relevant findings were reported.

Anxiety states in psychotic disorders. Minor tranquillizers may serve as ancillary medication in anxiety

states of psychotic patients.

In one study involving 119 in-patients, mostly schizophrenics whose basic antipsychotic treatment was haloperidol, 15 or 30 mg clobazam or 15 mg diazepam or placebo were added to their treatment (Cottin *et al.*, 1975).

Total scores on the Hamilton Anxiety Scale and Brief Psychiatric Rating Scale (BPRS) showed distinct global therapeutic efficacy with active drug treatment. The best results were achieved with clobazam 30 mg daily and diazepam 15 mg daily.

Clobazam 15 mg daily did not significantly differ from placebo with respect to global score reduction, but the items 'anxiety' and 'behaviour at interview' were significantly more improved with clobazam 15 mg daily.

Clobazam 30 mg daily differed significantly from placebo in improvement in the BPRS item 'anxiety'.

The effect of diazepam 15 mg daily, on the other hand, remained below the level of significance (Figure 9).

Figure 9 Changes in items of the BPRS after 2 weeks of concomitant therapy with placebo (a), clobazam 15 mg (b) and 30 mg (c) and diazepam 15 mg (d) in antipsychotic treatment (Cottin *et al.*, 1975). * $P < 0.05$ (C_{30}/D_{15} against P). –, Deterioration (increase of score); +, amelioration (reduction of score).

Motor retardation deteriorated under diazepam in contrast to clobazam.

Anxiety states in alcohol withdrawal. Anxiety states and their psychosomatic manifestations occur in the subacute phase of alcohol withdrawal therapy and impede therapeutic efforts.

Anxiolytic agents play a particularly important role in the treatment of these low-frustration-tolerant patients.

Clobazam in daily dosages of from 10–80 mg has

been shown to be efficacious in reducing anxious mood and depressive states in such patients (Table 6).

The good tolerability of clobazam was confirmed repeatedly; no serious side-effects were observed. Physical examinations including ECG and laboratory data showed no clinically relevant changes.

Sleep disturbances. Pharmacodynamic studies and clinical trials have consistently shown that clobazam had no pronounced sedative property in usual out-patient dosages even when the daily requirements were administered in a single dose. On the other hand, sleep disturbances improved during clobazam treatment in many anxious-neurotic patients. Thus, the hypnotic property of clobazam was investigated in a study in 186 hospitalized non-psychiatric patients (Kesson *et al.*, 1978). The ages ranged from 25–80 years. Clobazam was administered as an acute dose of 20 mg in comparison with 5 mg nitrazepam and placebo. Patients' drug preference, a simple but valid rating method (Thomson, 1958; Jick *et al.*, 1966) revealed that nitrazepam was a much more potent hypnotic in comparison with clobazam, whereas the latter's sleep-facilitating effect was somewhat stronger than that of placebo.

Kesson *et al.* (1978) therefore concluded that

clobazam in a dose of 20 mg was not suitable for use as an hypnotic. Thus, clobazam should be restricted to the treatment of sleep disturbances in patients with anxiety and tension. The improved sleep conditions in these patients may be explained by the anxiolytic and tension-relieving action of clobazam therapy facilitating sleep onset and quality.

Psychomotor performance

Animal and human pharmacology studies have shown that at a dose ratio of 2:1 clobazam produces distinctly less detrimental effects on psychomotor performance than diazepam.

Clinical trials confirmed that clobazam in out-patient dosages did not impair psychomotor performance (for example, Digit Symbol Substitution Test, Hand Steadiness Test), whereas the anxiolytic effect was at least equivalent (Doongaji *et al.*, 1978; Salkind *et al.*, 1979). These findings are of special importance, because clobazam's main indication is the treatment of disorders in out-patient settings. Thus, out-patients treated with therapeutic dosages of clobazam are not impaired in their daily activities.

Table 6 Clobazam treatment of anxiety symptoms in alcohol withdrawal

Investigator	Dosage (mg daily)		Efficacy	Tolerability
	Clobazam	Diazepam		
Martin (France, 1975)	15 (<i>n</i> = 10)	15 (<i>n</i> = 10)	$C_{15} = D$ (anxiety rating)	No clinically significant change of laboratory data (haematological, hepatic, renal)
	30 (<i>n</i> = 10)	—	$C_{30} > D$: Anxiety (physician rating) ($P < 0.001$) Anxiety (patient rating) ($P < 0.01$) Psychosomatic complaints (physician rating) ($P < 0.005$) Psychosomatic complaints (patient rating) ($P < 0.002$)	
Roux (France, 1977)	20–40 (<i>n</i> = 22)	—	29 (91%) very good/good (after 1 month)	
Uckermann (Norway, 1977)	20–80 (mainly 20–30) (<i>n</i> = 69)	—	56 (81%) very good/good (after 7–12 d)	
Knott (USA, 1977)	10–60 (<i>n</i> = 9)	—	Amelioration of anxious-depressive symptomatology	

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Discussion

PROFESSOR D. LAWSON (Glasgow) remarked that he was a little sceptical of the value of adding together a large number of heterogeneous studies and quoting aggregated results in order to come to general conclusions. In particular, with regard to the side-effects of drugs, it is well known that the data from early clinical trials are often unhelpful, as different investigators do not look for adverse effects in the same way. In general, investigators concentrate mainly on predictable effects—such as drowsiness with benzodiazepines—and ignore other events which may well be toxic effects of the drugs.

The experience with practolol had demonstrated the inadequacy of clinical trial data in identifying serious, albeit rare, side-effects. Professor Lawson asked whether there were data from the clinical trials on clobazam, on life events which may not have been recognized as toxic effects of the drug but which could prove on retrospective analysis to be side-effects of clobazam.

DR KOEPPEN replied that data on life events in the long-term trials were not available.

DR G. HANKS (London) commented that there is a limit to the amount of information which can be obtained in the clinical trial situation. A number of methods of looking at side-effects are used but none is ideal. There is a move now towards recording any life events occurring during the course of a clinical trial, as suggested by Professor Lawson, but rare side-effects

such as those associated with practolol will only be picked up by large-scale surveillance schemes following the general introduction of a drug on to the market.

DR A. NICHOLSON (Farnborough) questioned Dr Koeppen's conclusion (based to a large extent on the results of the study by Kesson *et al.*, 1978) that clobazam is not indicated as an hypnotic. From the data available about clobazam one would expect it to have a mild hypnotic effect rather like that of diazepam.

PROFESSOR LAWSON (a joint author of the paper referred to) replied that the study involved a complex design incorporating a patient-preference technique in which single doses of clobazam, nitrazepam and placebo were compared in general medical inpatients. The results indicated that clobazam fell somewhere between placebo and nitrazepam in terms of hypnotic activity and since more potent benzodiazepine hypnotics were available this would not be a realistic indication for clobazam.

DR NICHOLSON could not agree with this conclusion. The powerful long-acting benzodiazepine hypnotics have significant residual effects on performance, so that the use of drugs like diazepam and clobazam as hypnotics could be advantageous in this respect. He felt that this was an area which should be explored with clobazam.