

Alprazolam and Exposure Alone and Combined in Panic Disorder with Agoraphobia A Controlled Study in London and Toronto

ISAAC M. MARKS, RICHARD P. SWINSON, METIN BAŞOĞLU, KLAUS KUCH, HOMA NOSHIRVANI,
GERALDINE O'SULLIVAN, PAUL T. LELLIOTT, MARLENE KIRBY, GARY McNAMEE,
SEDA SENGUN and KIM WICKWIRE

A cross-national randomised trial of alprazolam for chronic panic disorder with agoraphobia was run. Compared with previous trials it had three new features: an exposure therapy contrast group, a six-month treatment-free follow-up, and a low rate of early placebo drop-outs ('non-evaluables'). The dose of alprazolam was high (5 mg/day). The 154 patients had eight weeks of: alprazolam and exposure (combined treatment); or alprazolam and relaxation (a psychological placebo); or placebo and exposure; or placebo and relaxation (double placebo). Drug taper was from weeks 8 to 16. Follow-up was to week 43. Results were similar at both sites. Treatment integrity was good. All four treatment groups, including double placebo, improved well on panic throughout. On non-panic measures, by the end of treatment, both alprazolam and exposure were effective, but exposure had twice the effect size of alprazolam. During taper and follow-up, gains after alprazolam were lost, while gains after exposure were maintained. Combining alprazolam with exposure marginally enhanced gains during treatment, but impaired improvement thereafter. The new features put previous trials in a fresh light. By the end of treatment, though gains on alprazolam were largely as in previous studies, on phobias and disability they were half those with exposure. Relapse was usual after alprazolam was stopped, whereas gains persisted to six-month follow-up after exposure ceased. Panic improved as much with placebo as with alprazolam or exposure.

The US Food and Drug Administration (FDA) approves alprazolam, a benzodiazepine drug, for patients with panic disorder, most of whom have some agoraphobia (Ballenger *et al*, 1988; Lesser *et al*, 1988). Efficacy was reported in studies lasting four to eight weeks (Ballenger *et al*, 1988; Chouinard *et al*, 1982; Dunner *et al*, 1986; Cross-National Collaborative Panic Study, Second Phase Investigators (CNCSP), 1992; Andersch *et al*, 1991) whose designs were problematic (Marks *et al*, 1989, 1992). Firstly, they had very high early placebo drop-out rates. Secondly, they lacked follow-up, despite patients suffering very chronic illness. Thirdly, they did not compare alprazolam with exposure therapy, after which agoraphobia/panic remained much improved for four to seven years in four countries (O'Sullivan & Marks, 1990). In a 12-week study, alprazolam was no better than placebo, though cognitive exposure therapy was (Klosko *et al*, 1988). The recent UK ban on the alprazolam congener triazolam emphasises the need for care in appraising benzodiazepines and for effective non-drug alternatives.

The present international study corrected earlier problems by: (a) minimising early drop-outs ('non-evaluables'); (b) continuing after eight weeks' treatment into an eight-week taper phase and beyond

into six-month follow-up without treatment, to 10 months after trial entry; and (c) comparing alprazolam and exposure alone and combined with a double control group. It was randomised, run double blind for drug and single blind for psychological treatment, and was the largest drug/exposure study so far.

Method

The study compared alprazolam and exposure, alone and combined, and a drug and a psychological placebo (relaxation (Marks, 1987)). Patients were randomised to one of four treatment conditions:

- AE, alprazolam and live exposure (combined treatment)
- AR, alprazolam and relaxation
- PE, placebo and live exposure
- PR, placebo and relaxation (double placebo).

Before entry to the trial, patients had a physical examination and laboratory tests, and gave informed written consent. Any psychotropic medication was withdrawn, and this was followed by screening and drug-free washout (mean 23 days, s.d. 17) to week 0.

Over 10 months subjects had individual out-patient treatment from weeks 0 to 8, taper of medication to zero from weeks 8 to 16, and then follow-up to week 43 without drug or psychological treatment. Patients visited hospital: during treatment, seven times (weeks 0, 1, 2, 3, 4, 6,

8) and two telephone contacts (weeks 5, 7); during taper, four times (weeks 10, 12, 14, 16) and four telephone contacts (weeks 9, 11, 13, 15); during follow-up four times (weeks 18, 23, 29, 42). To be evaluable, patients had to complete week 6.

Selection criteria

The London and Toronto sites used the same selection criteria. Patients had to: (a) have panic disorder with marked phobic avoidance (agoraphobia with panics) at a structured clinical interview, standardised for inter-rater reliability, for DSM-III (SCID-UP; Spitzer & Williams, 1983); (b) over the last four weeks, have at least one three-symptom panic a week, and at least two past unexpected three-symptom panics; (c) over the last year, have regular phobic avoidance of multiple situations – a minimum mean score of 5 (range 0–8) on the four main target phobias (see below); (d) be aged 18–65; (e) agree to oral medication and to exposure therapy; (f) be on adequate contraception; (g) give written informed consent.

Exclusion criteria were: (a) suicidal urges; (b) pregnancy or lactation; (c) past epilepsy; (d) abnormal laboratory values or serious illness; (e) past or present psychosis; (f) bipolar disorder; (g) dementia; (h) cyclothymic disorder; (i) past or current major depression or melancholia, unless it postdated panics and panics predominated over the depression; (j) substance abuse in the last six months; (k) obsessive-compulsive disorder; (l) unavailable for regular visits; (m) unable to stop prior psychotropic drugs, alpha or beta blockers or agonists; (n) in psychological treatment outside the study or failed to respond in the last two years to adequate alprazolam or exposure; (p) hypersensitive to benzodiazepines.

The treatment

After baseline evaluation at week 0, a psychiatrist gave the medication and an experienced behaviour therapist (psychiatrist, nurse or other) gave the psychological treatment. Patient contact with the therapists was from weeks 0 to 8. During subsequent taper and follow-up, contact was with the assessor (no more than 30 minutes per out-patient visit or 15 minutes per telephone interview).

Medication

Dosing was as in the Phase 2 Cross-National study (CNCPS, 1992). Alprazolam tablet strengths were 1.0 mg from weeks 0–8, and during taper were 1.0, 0.5, 0.375 and 0.25 mg; placebo tablets were matched. Tablets began at week 0 with 1 mg a day, rising to a mean of 6 mg a day, or more (up to 10 mg a day) if needed to abolish panics, along with marked fall in avoidance. Up to three attempts were made to raise medication to 10 tablets a day. Rise in dose ceased when patients became panic-free with much reduced avoidance, or had undue side-effects, in which case dose was reduced stepwise until tolerance occurred, after which it was raised again. From weeks 8 to 16, medication was tapered no faster than one tablet a day per three days, down to 4 mg; below that taper was even slower, with the

number of tablets held steady down to 0.25 mg, and thereafter reduced by one tablet a week (the patient did not know the dose). Dose at week 8 decided taper duration (mean of 8.4 weeks, s.d. 1.1), after which treatment ceased.

Psychological treatment

At screening, the assessor and patient agreed which situations were feared and avoided regularly and most needed help (the phobic targets). After randomisation the patient was given the tablets to start after the week 0 session, and met the therapist for 45 minutes to discuss the phobic targets and the therapy rationale and plan. Exposure followed the lines of the manual *Living with Fear* (Marks, 1978). Cognitive therapy was not used.

Treatment sessions, at weeks 1, 2, 3, 4, 6 and 8, began and ended with 15 minutes of audiotaped discussions, between which were two hours of live exposure or an hour of relaxation. All patients kept a daily panic/anxiety and activity diary from weeks 0 to 18, and for weeks 22, 28, and 42.

Exposure. At week 0 exposure patients were asked to read Chapter 12 on self-exposure from *Living with Fear*. With the therapist they planned an exposure homework programme starting with the four phobic targets. At weeks 1, 2, 3, 4, 6 and 8, in the first 15 minutes the therapist discussed the patient's diaries since the last visit, rated compliance, and agreed a plan for that day's exposure. Starting from the clinic, the patient then completed two hours of exposure to one or more phobic targets, and rated anxiety every 30 minutes. As fear reduced, exposure from the clinic focused on further phobic targets and then other situations.

At weeks 1 and 2, the patient's two-hour exposure to the phobic targets was with the therapist present initially and then withdrawing to a known spot or telephone. Therapist-accompanied exposure lasted a mean of 37 minutes per session (AE, 36 minutes; PE, 38 minutes; London, 36 minutes; Toronto, 38 minutes) and a mean total of 216 minutes across sessions. Very few patients were escorted at weeks 3, 4, 6 and 8. In the final 15 minutes of the session (at the clinic) the patient and therapist agreed and set self-exposure homework tasks for one to two hours a day and not less than four times a week, each to be recorded in the activity diary. In weeks 5 and 7 patients did not visit hospital but were telephoned to monitor progress.

Relaxation. At week 0 the therapist gave relaxation patients three half-hour audiotapes of instructions (Wolpe & Lazarus, 1966) to use for relaxation homework for an hour daily while sitting or lying comfortably and listening to one of the three tapes. In sessions at weeks 1, 2, 3, 4, 6 and 8, in the first few minutes the therapist discussed the patient's diaries, agreed a plan for that day's one-hour relaxation session in the clinic, and checked progress for a few minutes before and after it. Self-relaxation homework was set between sessions for at least an hour daily with a new tape in each of the first three weeks and with any of the three tapes from week 4 onwards. Each relaxation task was to be noted in the diary. No exposure instructions were given; patients who asked about exposure were told "do whatever you wish".

Patient adherence

At each visit the number of remaining tablets was noted. Venous blood (7 ml) was taken at weeks 0, 4, 8, 18, 23 and 43, to analyse plasma benzodiazepines and psychotropic drug levels at Dr David Greenblatt's laboratory at Tufts-New England Medical Center. Patients had written instructions how to take medication and do psychological treatment, and had to keep a daily record of drug and exposure or relaxation therapy. The therapist rated compliance at weeks 1, 2, 3, 4, 6, 8, 10, 12, 14, 16 and 18.

Outcome measures

Assessor and self-ratings were made at weeks 0, 2, 4, 6, 8, 9, 10, 11, 12, 13, 14, 15, 16, 18, 23 and 43. In order to remain blind, the assessor was not told, and asked patients not to reveal, the treatment condition.

Phobia

Four phobic targets were each rated 0–8 by both subject and assessor for avoidance (total 0–32) and for fear (total 0–32). This was a scale modified from Gelder & Marks (1966).

A 15-item Phobia Questionnaire (PQ) was completed, each item rated 0–8 for avoidance and 0–8 for fear. Five items each concerned agoraphobia, blood injury, and social phobia, yielding three factor scores (each 0–40) and total phobia (0–120). Global phobia was also rated (0–8). This questionnaire was modified from Marks & Mathews (1979).

Panic

Attack and Anticipatory Anxiety Scale (developed for this study by Sheehan) rated numbers of spontaneous and situational panics (both major – 3 or more symptoms from the DSM-III criteria – and minor – fewer than 3 symptoms), and anticipatory anxiety (0–10 intensity score, and % of time per day) and % of day panic free. The scale was scored from the patient's panic diary, by consensus between rater and subject. A composite panic index was calculated as the log of frequency \times intensity \times duration of panics.

Mood

Three scales were used to rate mood: the Hamilton Rating Scale of Anxiety (14 items, total score 0–56) (Hamilton, 1959), the Hamilton Rating Scale for Depression (17 items, total score 0–52) (Hamilton, 1960) (both rated by the assessor) and the self-rated Beck Depression Inventory (21 items, total score 0–63) (Beck *et al*, 1961).

Disability

Disability was self-rated for the areas of work, social and leisure, family, and home, yielding three subscales, each scored 0–10. Work, social, and family adjustment was rated on one 0–8-point scale by the assessor (Marks, 1985, 1986).

Global improvement

The assessor rated Clinician's Global Improvement (CGI) on a seven-point scale (1 = very much improved, 7 = very

much worse); the effect of the panic disorder on the patient's life was also rated by the assessor, on a five-point scale (1 = worse, 5 = marked). The Symptom Checklist (SCL-90; Derogatis *et al*, 1973) was self-rated by the patient (total score of 0–182). Patients also rated Global Improvement (PGI).

Method of analysis

Outcome is mainly reported at weeks 4, 8 (end of treatment), two weeks after the drug taper (week 18), and follow-up at weeks 23 and 43. Between-treatment analyses remain valid through taper and follow-up, as they include only patients who had kept to protocol by a given time. Each of the four treatment groups contained similar numbers of protocol leavers (χ^2 , NS). Results are given of individual measures to facilitate comparison with changes on them in previous studies. To avoid over-inference from chance findings with multiple tests, emphasis is on outcomes that were consistent across analyses and measures, and on the following primary efficacy measures, chosen at the start of the study:

- (a) four phobic targets (avoidance and fear)
- (b) PQ agoraphobia (avoidance and fear)
- (c) total number of major panics
- (d) change in number of major panics since baseline
- (e) % panic-free patients
- (f) Hamilton anxiety
- (g) disability
- (h) CGI

To use all data in a cohort attenuating over time, analyses of covariance (ANCOVAs) were done separately for weeks 4, 8, 18 (2 weeks post-taper), 23 and 43 (Table 1). ANCOVA partialled out all differences at baseline and examined the main effects of drug (AE + AR v. PE + PR), psychological treatment (AE + PE v. AR + PR) and site (London v. Toronto), and their two-way and three-way interactions.

Results

Patients were referred by professionals; in London self-referrals were also accepted (51 of 82 trial entrants). About 10% of enquirers met the criteria and entered the trial. No study entrant had had previous adequate alprazolam or exposure (no alprazolam non-responders were referred, and only two were excluded owing to non-response to previous exposure). Over three years, 154 patients entered (of whom 134 were evaluable at week 6) – 82 (69 evaluable) in London and 72 (65 evaluable) in Toronto. There were 20 non-evaluable drop-outs from weeks 0 to 6 (13 in London, 7 in Toronto) – a total drop-out rate of 13%. Across both sites the drop-out rate did not differ significantly among the four conditions (15% AE, 5% AR, 18% PE, 13% PR); nor did attenuation after week 6 (Table 1).

Treatment integrity

Medication. On tablet counts, by weeks 4 and 8, patients respectively took a mean of 4.4 (s.d. 1.7) and 5.8 (s.d. 1.4) mg a day of alprazolam, and 5.1 (s.d. 2.2) and 7.4 (s.d. 2.2) tablets

Table 1
Means, standard errors and numbers of patients (London and Toronto samples combined)

		Week					
		0 (n = 154)	4 (n = 134)	8 (n = 129)	18 ¹ (n = 98)	23 (n = 89)	43 (n = 76)
Numbers of patients	AE	40	34	34	28	26	17
	PE	38	32	30	24	21	23
	AR	37	34	34	25	24	18
	PR	39	34	31	21	18	17
<i>Mean (s.e.) ratings on:</i>							
Four phobic targets ² avoidance (A) (0-32)	AE	30 (0.4)	11 (1.5)	7.3 (1.2)	9.5 (1.7)	11 (2.2)	8.8 (2.6)
	PE	29 (0.6)	15 (1.4)	8.2 (1.4)	5.0 (1.7)	5.7 (1.7)	5.5 (1.8)
	AR	30 (0.4)	20 (1.7)	17 (1.6)	18 (2.0)	20 (2.9)	19 (2.5)
	PR	29 (0.5)	23 (1.5)	22 (1.7)	17 (2.4)	18 (2.3)	17 (2.5)
PQ agoraphobia ² avoidance (S) (0-32)	AE	29 (1.3)	14 (1.6)	11 (1.6)	13 (2.1)	14 (2.4)	11 (2.4)
	PE	25 (1.7)	15 (1.9)	11 (1.8)	8 (2.0)	9 (2.4)	6.8 (1.9)
	AR	24 (1.6)	18 (2.7)	16 (2.0)	16 (2.5)	17 (2.3)	19 (3.0)
	PR	26 (1.8)	20 (2.0)	21 (2.2)	17 (2.9)	16 (2.7)	16 (3.1)
Total number of: major panics per week ²	AE	4.9 (0.7)	2.4 (0.7)	1.1 (0.5)	1.4 (0.6)	2.4 (0.8)	0.7 (0.4)
	PE	6.8 (1.1)	6.4 (2.4)	2.5 (0.7)	2.6 (1.4)	1.6 (0.9)	0.2 (0.1)
	AR	5.4 (0.8)	2.1 (0.6)	1.7 (0.6)	2.2 (0.8)	2.3 (0.9)	2.2 (1.1)
	PR	3.9 (0.7)	2.0 (0.5)	1.0 (0.3)	0.9 (0.4)	0.6 (0.3)	1.2 (0.6)
spontaneous major panics per week	AE	1.5 (0.4)	0.2 (0.1)	0.1 (0.1)	0.3 (0.1)	0.8 (0.4)	0.3 (0.2)
	PE	2.3 (0.9)	2.0 (1.3)	1.2 (0.5)	0.3 (0.2)	0.1 (0.1)	0.1 (0.1)
	AR	2.2 (0.7)	1.0 (0.5)	1.3 (0.6)	1.1 (0.5)	1.3 (0.7)	0.7 (0.4)
	PR	3.0 (1.9)	0.5 (0.2)	0.4 (0.2)	0.1 (0.1)	0.1 (0.1)	0.1 (0.1)
Hamilton depression (0-56)	AE	14 (1.0)	9.2 (1.0)	7.8 (0.9)	10 (1.4)	9.7 (1.3)	6.2 (1.0)
	PE	15 (1.0)	10 (1.1)	9.9 (1.1)	7.6 (1.2)	8.9 (1.5)	7.5 (1.5)
	AR	13 (0.9)	7.9 (0.8)	8.5 (0.8)	11 (1.2)	11 (1.3)	9.1 (1.5)
	PR	10 (0.8)	9.1 (0.7)	9.0 (1.0)	8.2 (1.4)	7.6 (1.2)	7.1 (1.3)
Disability (work/social) ² (A) (0-8)	AE	7.1 (0.1)	-	2.9 (0.3)	3.9 (0.4)	-	3.3 (0.6)
	PE	6.9 (0.1)	-	3.9 (0.4)	3.0 (0.4)	-	2.4 (0.5)
	AR	7.0 (0.1)	-	4.7 (0.3)	5.3 (0.4)	-	5.4 (0.5)
	PR	6.8 (0.2)	-	6.0 (0.3)	5.1 (0.5)	-	4.9 (0.5)
Clinician's global impres- sion (CGI) ² (A) (1-7)	AE	-	2.6 (0.2)	2.0 (0.1)	2.3 (0.2)	2.3 (0.2)	1.8 (0.2)
	PE	-	2.8 (0.2)	2.2 (0.2)	1.8 (0.2)	2.0 (0.2)	1.6 (0.2)
	AR	-	2.9 (0.2)	2.6 (0.2)	3.1 (0.2)	3.4 (0.2)	2.9 (0.3)
	PR	-	3.4 (0.2)	3.4 (0.2)	2.9 (0.2)	2.9 (0.2)	2.9 (0.3)

A = assessor-rating, S = self-rating.

1. Two weeks post-taper.

2. Primary efficacy variable.

of placebo. Mean plasma alprazolam level was 45 ng% at weeks 4-8 among alprazolam cases and virtually 0 for placebo cases. According to the results of plasma assay of alprazolam and diazepam, patients adhered well to the regime; cheating was rare and did not affect outcome.

Psychological treatment. Dr Matig Mavissakalian's team in Ohio blindly rated randomly chosen audiotaped psychological treatment sessions. Ratings discriminated well between exposure and relaxation, which was given appropriately at both sites.

Sample features at week 0

London and Toronto cases are pooled as they were so similar. For the 144 intent-to-treat (ITT) cases, who had at least a week of treatment, mean age was 35, mean

problem duration 8 years for panic and for agoraphobia, and 81% were women. All had panic disorder and agoraphobia, 86% with marked agoraphobic avoidance (mean phobic target avoidance = 7.3 assessor rating and 7.1 self-rating (0-8-point scale), PQ agoraphobic avoidance 26 and fear 27 (0-40-point scales)). Mean number of major panics per week was 7.4 (s.d. 11; 5.2 situational, 2.2 spontaneous). Ten per cent had current and 30% past major depression, but initial dysphoria was mild - mean scores on the Hamilton and Beck depression scales were 13 and 18 respectively. Ten per cent also had social phobia and 25% specific phobia.

These baseline features were compared (ANOVAs) for completers v. non-completers (London and Toronto cases). Compared with the 20 drop-outs from weeks 0-6, the 134 cases evaluable at week 6 were similar on 14 of 18 measures

Table 2
Main significant effects (ANCOVAs) (London and Toronto samples combined)

	Weeks 0-4 (n = 134)		Weeks 0-8 (n = 129)		Weeks 0-18 ¹ (n = 98)		Weeks 0-23 (n = 89)		Weeks 0-43 (n = 76)	
	A	E	A	E	A	E	A	E	A	E
<i>Phobias</i>										
Four targets: fear (A) ²	0.005	0.000	0.002	0.000		0.000		0.000		0.000
Four targets: avoidance (A) ²	0.001	0.000	0.006	0.000		0.000		0.000		0.000
PQ agoraphobia: fear ²		0.03		0.000		0.001		0.000		0.000
PQ agoraphobia: avoidance ²		0.000		0.000		0.000		0.000		0.000
<i>Panics</i>										
Total no. ²								0.02 ³		
situational	0.02									
spontaneous					0.02 ³		0.03 ³			
Anticipatory anxiety: duration	0.003									0.02
<i>Mood</i>										
Hamilton anxiety ²	0.02					0.05				0.006
Hamilton depression										0.04
<i>Work/social</i>										
Disability (A) ²	-.4	-.4	0.000	0.000		0.000	-.4	-.4		0.000
<i>Global improvement</i>										
CGI (A) ²		0.04	0.003	0.000		0.000		0.000		0.000
PGI (S)	0.001		0.001			0.001		0.000		0.004

A = Alprazolam v. placebo.

E = Exposure v. relaxation.

(A) = assessor rating, (S) = self-rating.

1. Two weeks post-taper.

2. Primary efficacy variable.

3. Alprazolam worse than placebo.

4. Not measured.

Blank cells not significant.

(including panic) and more ill on the remaining measures. There was no bias in baseline features between continuers and discontinuers after week 6 (at week 8, 2 weeks post-taper at week 18, or weeks 23 or 43). The 82 entrants and 64 refusers who did not enter the trial in London had similar sex, age and illness duration (no Toronto data).

Testing with ANOVAs across both sites, the week 0 scores across the four treatment conditions (AE, PE, AR, PR) did not differ significantly on 15 of 18 measures, including panic; the PR group scored less than the other groups on SCL-90, and Hamilton anxiety and depression scales.

Table 3
Effect size¹ on primary efficacy variables (Toronto and London samples combined)

	Week 4 (n = 134)			Week 8 (n = 129)			Week 18 ² (n = 98)			Week 23 (n = 89)			Week 43 (n = 76)		
	AE	PE	AR	AE	PE	AR	AE	PE	AR	AE	PE	AR	AE	PE	AR
Four targets: fear (A)	1.5	0.9	0.5	1.8	1.3	0.8	0.9	1.2	0.1	1.0	1.3	-0.1	1.1	1.2	-0.1
Four targets: avoidance (A)	1.8	1.1	0.6	1.9	1.7	0.8	1.0	1.4	0.1	1.0	1.6	-0.2	1.0	1.3	-0.1
PQ agoraphobia: fear (S)	0.8	0.7	0.4	1.2	1.2	0.5	0.8	1.2	0.3	1.4	2.0	0.4	1.6	1.8	0.2
PQ agoraphobia: avoidance (S)	1.2	0.8	0.4	1.4	1.2	0.5	1.0	1.2	0.3	1.4	1.6	0.4	1.6	1.7	0.0
Total panics (major) ³	0	-0.5	0.01	0.2	-0.1	0.1	0	-0.1	0.1	-0.1	0	-0.2	0.6	0.6	0.4
Hamilton anxiety (A)	1.0	0.7	1.0	1.0	0.6	0.5	0.7	0.9	0.3	0.8	1.1	0.2	1.1	1.2	0.8
Clinician's global improvement (CGI) (A)	0.8	0.6	0.5	1.2	1.1	0.7	0.5	1.0	-0.2	0.5	0.8	-0.5	1.0	1.2	0.0

(A) = assessor rating, (S) = self-rating.

1. (Change since week 0 in AE, PE or AR - change since week 0 in PR)/(s.d. of PR at week 0).

2. Two weeks post-taper.

3. Square root, and excludes 12 patients with grossly outlying figures at week 0.

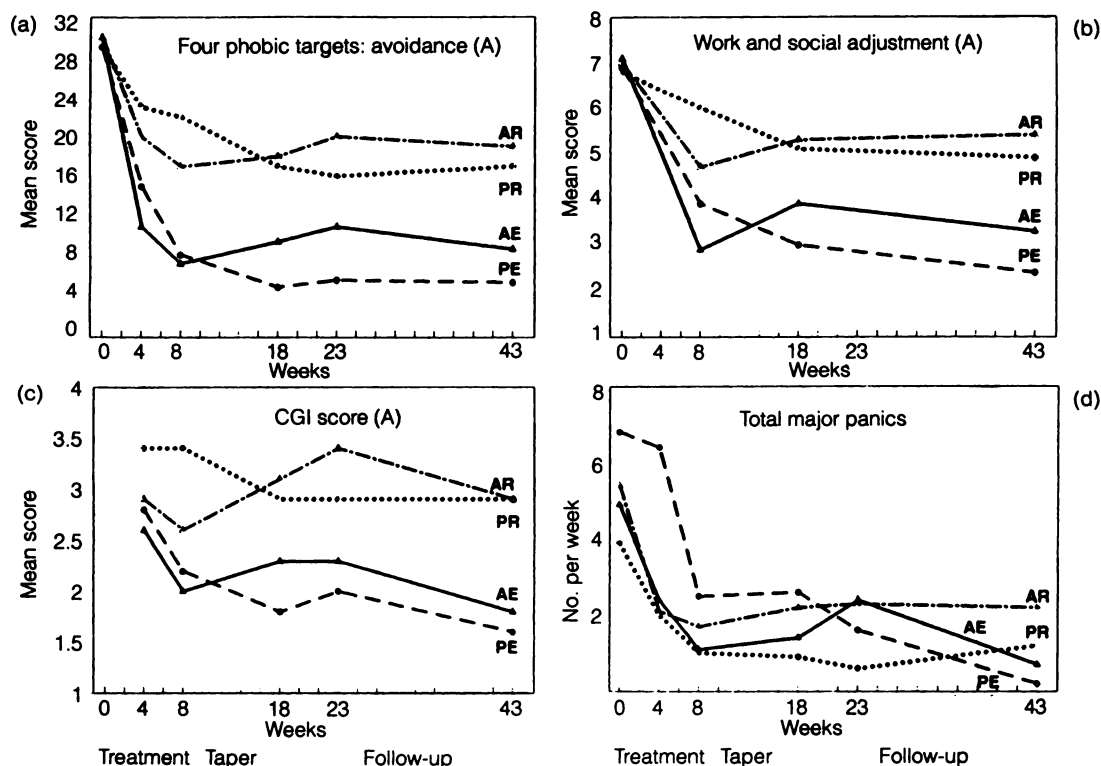


Fig. 1 Means (London and Toronto samples combined) through treatment, taper and follow-up: (a) four main phobic targets: avoidance (assessor); (b) work and social disability (assessor); (c) CGI (assessor); (d) total number of major panics per week. Week 0, $n=144$; week 4, $n=134$; week 8, $n=129$; week 18, $n=98$; week 23, $n=89$; week 43, $n=76$. (A) = assessor-rated.

Outcome at end of treatment, taper and follow-up

The main effects did not differ across London and Toronto, so the two sites' results were pooled. Results were also consistent across different analyses (ANCOVA, MANOVA, post-hoc, effect size, survivor analyses, inspection of means), most measures, raters (self and assessor), and ITT and evaluable patients.

Tables 1-3 and Figs 1-3 show outcome on key measures. For brevity, most measures' means on most occasions must be omitted, but can be obtained from IMM. For each shown, results were similar on other measures of that area of clinical function and that treatment phase.

Patients taking alprazolam began to improve by week 2, but largely plateaued by week 4; there was no further improvement from weeks 6 to 8, and symptoms worsened thereafter. Gains from exposure began by week 2, grew to week 8 (by then being about twice as great in AE as in AR), and continued through taper to follow-up. This differential pattern of improvement across alprazolam and exposure is clear in Table 2; at week 18 and subsequently, most of the A (alprazolam) columns are blank, whereas most of the E (exposure) columns are not.

Non-panic measures

During treatment (weeks 4 and 8). Both alprazolam and exposure improved phobias especially, but also global outcome and, by week 8, social adjustment (Tables 1-3, Figs 1-3). Compared with that of alprazolam, the effect of exposure was usually more significant (on ANCOVAs) and seen on more measures. Alprazolam improved mood at week 4 but not thereafter.

During taper and follow-up. During taper to 2-weeks post-taper (weeks 8-18) any significant alprazolam effect disappeared (Table 2). By week 23 the exposure effect had become significant on most measures of mood and social adjustment as well as phobias and global impression, and by week 43 was significant on all of them.

Panic

The 10 panic measures had a far greater variance than most of the other measures. During treatment, unlike other measures, total major panics fell to week 8 in all four groups, with no significant differences between them (Tables 1-3, Fig. 1(d)).

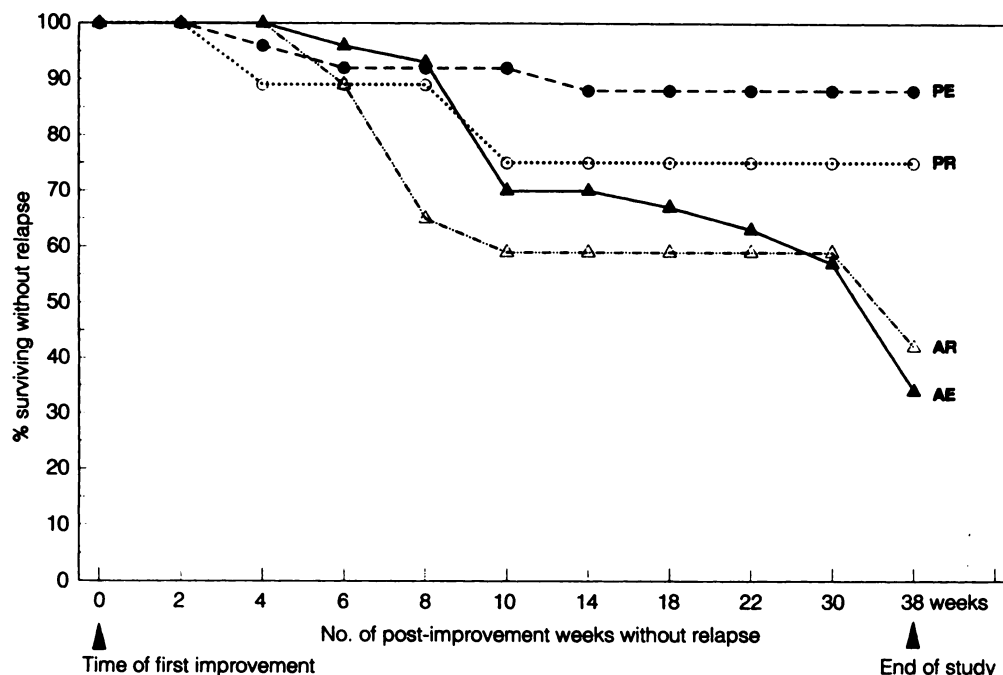


Fig. 2 Survivor analysis: cumulative proportion of patients who became much or very much improved on the assessor-rated CGI (AE, $n=27$; PE, $n=25$; AR, $n=18$; PR, $n=9$) and then remained so to the end of follow-up.

During taper and follow-up, total panics rose slightly in AE but were similarly improved across the four groups at week 43. On spontaneous panics, alprazolam became significantly worse than placebo cases. At week 23, ex-alprazolam patients were worse than ex-placebo cases on two phobia and three panic measures. Total panics fell markedly in the double-placebo group (PR) from early in treatment through to the end of follow-up.

The per cent of patients free of major panics did not differ significantly among the four groups, at week 8 being 62% AE, 43% PE, 47% AR, 47% PR; at week 23 the figures were 58% AE, 76% PE, 54% AR, 72% PR; and at week 43 they were 77% AE, 77% PE, 50% AR, 59% PR. The picture was similar on the other eight panic measures – change in total panics from baseline, total number of panics, numbers of (major and minor) situational and spontaneous panics, intensity and duration of anticipatory anxiety, and composite panic index (log of frequency \times intensity \times duration).

Other analyses

Interactions (site \times drug \times psychological treatment) were few, weak (none reached $P < 0.01$), and involved primary efficacy measures on only seven out of 95 tests; they are therefore not detailed. The absence of any significant drug \times psychological treatment interaction is noteworthy. Alprazolam with exposure was not significantly better than placebo with exposure.

Other analyses checked that outcome was consistent across different methods of analysis. Post-hoc t -test comparisons of the four treatments (controlled for experiment-wise error due to multiple comparisons) found, like the ANCOVAs, that AE and PE were significantly better than AR and PR throughout treatment and follow-up. AE was significantly better than PE on only 1 out of 34 comparisons up to week 8, and subsequently on none.

Repeated measures ANOVA (MANOVA) tested differential relapse trends after treatment ended at week 8 with a four-level treatment factor (AE, PE, AR, PR), a two-level time factor (weeks 0–8, 8–23), and treatment by time interaction. During weeks 8–23, compared with placebo patients, alprazolam patients lost some of their gains (whether with exposure or relaxation), while PE patients kept or slightly increased theirs. AE patients became slightly and significantly worse than PE patients during weeks 8–23 (Fig. 1) on four primary efficacy variables and on six other variables.

Global improvement

Proportion improved on the CGI, the survival method (SPSS-X; Lavory *et al.*, 1984) was used to determine how long patients who improved markedly to criterion ('very much improved' or 'much improved' on two successive ratings from weeks 2 to 43) remained so before having major relapse (return to a rating of 'minimally improved or worse' at two successive ratings or at week 43).

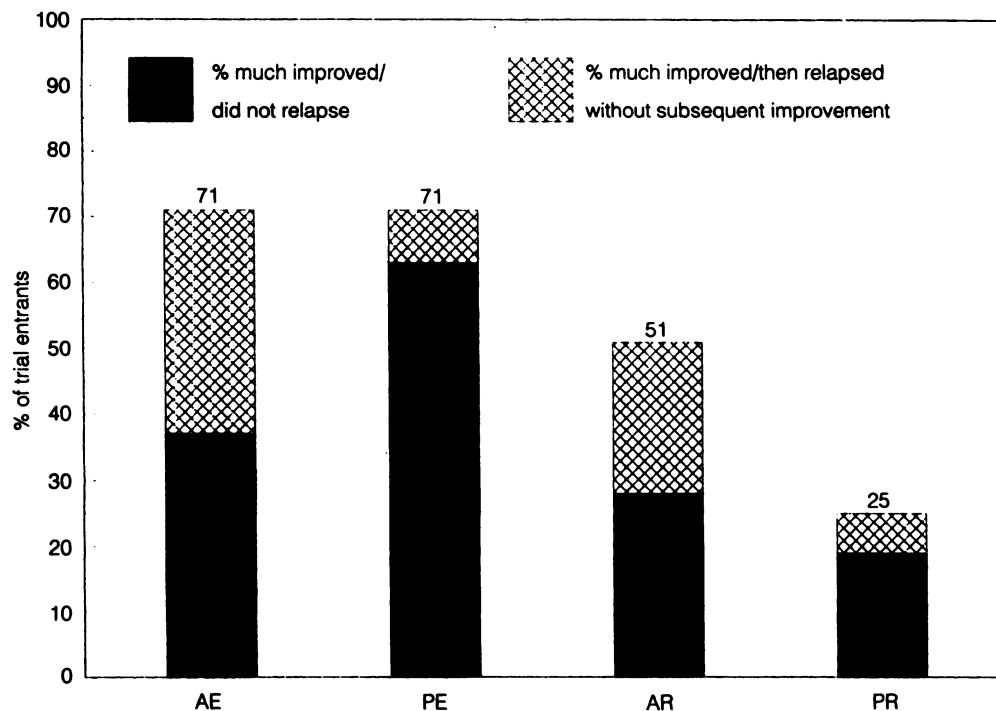


Fig. 3 Outcome of CGI at end of follow-up: % of trial entrants who became much/very much improved on the assessor-rated CGI at any time and who remained so without major relapse to the end of the study at week 43.

Figure 2 shows how many patients improved to criterion (see legend) and the cumulative proportion (probability, not %) of those improvers' durations of survival as improved to the end without major relapse (probabilities AE 0.34, PE 0.88, AR 0.42, PR 0.75). Major relapse was rare in PE but common with alprazolam (AE, AR) ($P < 0.04$ for AE v. PE and AR v. PE, Lee-Desu statistic for pairwise comparisons), mainly at 4–16 weeks after initial gains. Adding exposure to alprazolam (AE v. AR) gave minimal short-term and no long-term protection against relapse.

Figure 3 shows (hatched bars) the % of trial entrants who became 'much/very much improved' on the CGI: AE, 71%, PE, 71%, AR, 51%, PR, 25%. In a different analysis to that in Fig. 2, Fig. 3 also shows (solid bars) the % of all trial entrants (not just of improvers) who improved to criterion and then stayed well: AE, 36%, PE, 62%, AR, 29%, PR, 18% ($\chi^2 = 32$, $P < 0.0000$ across the four treatment groups). Only in PE did most trial entrants both improve and stay so to the end.

Effect size

Effect size, unlike significance tests, allows judgement of how useful gains are, changes larger than 1 being generally regarded as large. Effect size was calculated both on change scores (mean of AE, or PE, or AR – mean of PR)/

standard deviation of PR at week 0) and on raw scores, which gave a similar result. Table 3 shows effect size on change scores of some of the primary efficacy measures. For panic, the effect size was minimal because of the strong double-placebo effect. For most other measures, by week 4 effect size was greatest in AE, next biggest in PE, and smallest in AR. By week 8 effect size in each group had grown, especially in PE, in which it was now about twice that in AR for phobias. From two weeks post-taper (week 18) onwards, the effect size in PE was slightly greater than in AE and far greater than in AR, while AR's effect had mainly vanished.

Self-referral versus other referral

Outcome in London was similar in self- v. professionally-referred patients. All Toronto cases had come via doctors.

Discussion

After alprazolam withdrawal, the alprazolam effect disappeared on every measure. In contrast, after exposure therapy ceased the exposure effect persisted on almost every measure except panic until the end of the trial, at week 43. Relapse is a problem whatever the time that alprazolam (or any other

benzodiazepine) is stopped. It occurred in the present and the Upjohn Phase 1 (Ballenger *et al*, 1988) and 2 (Andersch *et al*, 1991) studies, in other trials (Dunner *et al*, 1986; Tesar *et al*, 1987; Munjack *et al*, 1989) and after withdrawal of adinazolam, an alprazolam derivative (Echeburúa *et al*, 1993).

Should alprazolam have been continued longer than eight weeks (Pecknold *et al*, 1988; Andersch *et al*, 1991)? It seems unlikely that six months, say, would have achieved more worthwhile gains than eight weeks did, given that gains did not accrue in any study over weeks 6–8, even with high doses of alprazolam. Nor was relapse prevented either by slow taper over 8 weeks (time from first to last tablet being 16 weeks), or by having added exposure (present AR and AE groups both lost gains at taper). The high-dose alprazolam effect might continue as long as drug is given but seems redundant. It has only a non-significant additive effect which disappears on discontinuation and interferes with maintenance of gains at week 18 (see also Başoğlu *et al*, 1993a). Most patients accept exposure, which yields twice more therapeutic gains by eight weeks, and which is usually maintained thereafter, despite no further clinical contact. Perhaps low-dose alprazolam has a role in some cases early in exposure, or in those who refuse exposure, but this needs testing.

No study patient was a non-responder to previous adequate treatment by alprazolam or exposure. The study attained a high dose of alprazolam. Outcome was similar across the two sites, methods of analysis, and raters.

All the panic (but not other) measures improved so much with double placebo (PR) that PR did not differ significantly at any time from the other three groups, in which panic improved too. Perhaps panic reduced with frequent travel to a clinic for supervision in a careful study. Panic measures had the same huge variance that was present in previous alprazolam studies (Ballenger *et al*, 1988; CNCPS, SPI, 1992) and are problematic as outcome indicators (Başoğlu *et al*, 1993a).

The drop in panic in the PR group is unlikely to be due to the relaxation. In previous studies of panic disorder, the placebo groups had *no* relaxation (Ballenger *et al*, 1988; CNCPS, SPI, 1992) yet improved in panic too. The placebo response was seen only in panic, not in agoraphobia and disability, which did not improve with relaxation in controlled studies (Marks, 1987). Relaxation is, therefore, a good psychological placebo in agoraphobia/panic, despite some beliefs in its value. Had relaxation been effective, then the superior outcome on phobia and disability that exposure achieved compared with alprazolam (PE v. AR) would have been even more remarkable.

On non-panic measures, high-dose alprazolam without exposure (AR) had a small effect in the first four weeks that plateaued from weeks 4 to 8 and then was lost from taper on. Compared with exposure without drug (PE), combined alprazolam with exposure (AE) did not produce significant additional gains during treatment. The effect of exposure without drug (PE) began early, was large by the end of treatment, and grew further through taper and follow-up to week 43 (8 months after treatment), having extended to disability and mood by then. On phobias and CGI, the effect size of exposure (PE) was about twice that of alprazolam (AR) by week 8 and even greater thereafter, when most drug effect had vanished.

The present study's alprazolam outcome was like that of the Phase 1 (Ballenger *et al*, 1988; Lesser *et al*, 1988) and 2 (CNCPS, SPI, 1992; Andersch *et al*, 1991) multicentre alprazolam studies. It had similar selection criteria, measures, and dose targeted (6 mg a day) and attained (5 mg a day by week 8), and had patients of similar age (mean 35), chronicity (8 years) and female predominance (81%). Our sample had more severe panic, avoidance and disability. Severe anxiety disorders are harder to treat than less severe counterparts (Mavissakalian & Michelson, 1986; Başoğlu *et al*, 1988; Marks *et al*, 1989; O'Sullivan *et al*, 1993). There is no reason to believe that the differential treatment efficacy shown in the present study would change in other settings with less severely affected patients.

Our study managed to remedy problems in the Phase 1 and 2 trials. It compared alprazolam with exposure, was longer (10 v. 1–3 months), and had fewer placebo drop-outs at week 6 (16% v. 43–48%). The design set past results in perspective. All three studies found an early drug effect, but it was small, transient, and seen mainly on non-panic measures. In the present and Phase 1 and 2 studies, the mean percentages of placebo patients who were free of major panics at week 8 were respectively 47%, 50%, and 65%. In the Phase 2 study alprazolam had no effect on panics in patients who had panic but no avoidance; the authors concluded that the effect of alprazolam in panic disorder was via avoidance, not panic (Maier *et al*, 1991).

Of the present study's PE trial entrants, 62% were much/very much improved at their last CGI rating (mostly weeks 23 or 43) with minimal residual symptoms no longer interfering with daily life. That gains endured is important in a chronic disorder where mean duration was 5–9 years in most studies. In the Phase 1 study at week 8, 50% of alprazolam cases were still moderately or more fearful of the main phobia, 45% still avoided their main phobia often or more, and they had a mean of 1.7 panics per week.

In Phase 1 and 2 completers, by week 8 drug effect was absent on panic and other measures (Ballenger *et al*, 1988; CNCPS, SPI, 1992; Andersch *et al*, 1991), being significant mainly on 'end-point imputation'. This used notional week 8 scores imputed from week-4 scores; it assumed that the many placebo drop-outs at week 4 would have improved no further by week 8 had they stayed in. That assumption was moot (Marks *et al*, 1989) as in the Phase 1 and 2 studies (a) almost half the placebo cases dropped out by weeks 3–4, (b) placebo gains were rising just before drop-out, and (c) the present double-placebo group (PR) improved further on panic from weeks 4–8.

The present short-term outcome of alprazolam also fits that in four other panic trials. In one, ¼–3 mg alprazolam a day had an effect at weeks 1 and 2 but not at weeks 4 and 8 (Chouinard *et al*, 1982). In another (Dunner *et al*, 1986), at 6 weeks 4 mg a day alprazolam reduced anxiety but not panic, and that was on end-point analyses – completer analyses were not given (see below), and placebo drop-out rate was 43%. In a third study (Tesar *et al*, 1987), at 6 weeks 5 mg alprazolam a day had an effect on panic and anxiety only on completer, not end-point analyses (placebo drop-out rate was 60%). In a fourth study (Pecknold *et al*, 1988), at 5 weeks 3.6 mg alprazolam a day was no better than placebo at reducing panic, but was superior on phobic fear and avoidance.

Present results agree too with those in two trials with an exposure contrast group (6 mg alprazolam a day (Klosko *et al*, 1988), 1.5 mg a day (Fyer *et al*, 1987)). In both trials alprazolam had no significant effect at the end of treatment whereas exposure did. At six-month follow-up (Echeburúa *et al*, 1993) alprazolam had slightly reduced gains from exposure.

Like alprazolam, other benzodiazepines too have limited transient effects in panic/agoraphobia (Mellman & Uhde, 1986). Among antidepressants, imipramine by week 4 reduced panic/agoraphobia to a similar limited extent as did alprazolam, and relapse occurred after stopping both drugs, neither drug being better than placebo at six-month follow-up (Andersch *et al*, 1991). Antidepressants can enhance exposure as long as they are given (Brown & Hague, 1986) and, unlike alprazolam, do not reduce post-treatment gains from exposure (Sheehan *et al*, 1990). They are especially useful when dysphoria is present.

High-dose alprazolam significantly impaired therapeutic gains from exposure once all treatment was stopped, not while the drug was being taken. This could reflect state-dependent learning – what animals learn while on benzodiazepines or barbiturates is

retained less well in the drug-free state (Gray, 1987; Bouton *et al*, 1990). Higher-dose anxiolytics can interfere with GABA-ergic and other mechanisms involved in memory. In addition, patients who attributed improvement to medication at week 8 had more fear and avoidance of phobic situations and relapsed more subsequently (Başoğlu *et al*, 1993b).

As in other studies, the present alprazolam patients became fairly sedated and remained so even at week 8 (O'Sullivan *et al*, 1993). Next-day amnesia was noted with triazolam, a related drug (Bixler *et al*, 1991). Cerebral ventricular enlargement was found in users of long-term benzodiazepines for anxiety/panic (Lader *et al*, 1984; Schmauss & Krieg, 1987; Kellner & Uhde, 1988). Whether such effects were due to drug needs more study, but the triazolam experience bids caution.

Long-term outcome is a key issue for patients with chronic disorders. It is, therefore, not only legitimate but essential to examine outcome long after both alprazolam and exposure were discontinued. Alprazolam is like insulin or a diet, each having to continue indefinitely to maintain its effect in diabetes. Exposure is like neither insulin nor a diet; it is more like chemotherapy for neoplasia. Once patients have improved with exposure no further treatment is needed unless relapse threatens, in which case brief booster self-exposure is helpful.

The findings are generally applicable. Exposure has yielded similar results with agoraphobia/panic in many countries – the USA, Canada, England, Scotland, the Netherlands (O'Sullivan & Marks, 1990), Germany (Fiegenbaum, 1988), Spain (Echeburúa *et al*, 1993) – with different professionals (nurses (Marks *et al*, 1977; McDonald *et al*, 1988), psychiatrists and psychologists), and if instructions were by telephone (McNamee *et al*, 1989) rather than face to face. Though the present study used experienced behaviour therapists, good outcome can be obtained with little training, even just with suitable self-exposure instructions given by a computer or a manual (Ghosh & Marks, 1987). Responders to exposure for obsessive-compulsive disorder showed changes on positron emission tomography in relevant brain areas (Baxter *et al*, 1992); in time, relevant brain changes will probably be shown in responsive panic/agoraphobia patients too.

Problems with exposure therapy are the frightening and hard work patients have to do, but most manage to complete it. Of present patients who began exposure, 82% completed 8 weeks of it without drug and 85% with drug. The completion rate in a routine behaviour therapy clinic is 75% (Marks, 1987). Though our study used both therapist-accompanied and self-exposure, the effective component turns out

to be self-exposure (Ghosh & Marks, 1987; Marks *et al*, 1988; McNamee *et al*, 1989; Alkubaisy *et al*, 1992), which is easy for clinicians to supervise and learn.

Confidence in the present study's outcome is strengthened by the results across London and Toronto having been the same, whether during treatment, taper or follow-up. Moreover, the Toronto site participated in the Phase 1 trial, having few placebo drop-outs and results similar to those in the two present comparable groups (AR and PR). The high placebo drop-out rate at weeks 3–4 in the Phase 1 study came from other sites.

The present sample included fewer panic patients without phobic avoidance than did the Phase 2 study, but was similar to the samples in the Phase 1 and most other studies of panic disorder. Present results apply to the majority of patients with panic disorder. For panic without agoraphobia, too, modified exposure was superior to alprazolam (Klosko *et al*, 1988).

Current results have four implications for psychotropic drug trials. (a) Comparison is needed with useful non-drug methods as well as with other drugs and placebo. (b) Relative effect sizes as well as significance require analysis. (c) The persistence of effects after drug withdrawal needs more attention; chronic patients require chronic gains from treatment and thus studies lasting longer than one to three months. To be well informed, sufferers have to be told about effect size and duration, and side-effects of all useful treatments. (d) Conclusions are moot if the early drop-out rate is high. If FDA and CSM regulations reflected these four points, more studies would attend to them.

Conclusions

The alprazolam effect was as in previous studies. In panic disorder with agoraphobia, panic improved so much with placebo that neither alprazolam nor exposure added benefit. On most other measures, exposure was superior to alprazolam by the end of treatment and of follow-up. By eight weeks, the effect of exposure was about twice that of alprazolam, and placebo had minimal value. Combining high-dose alprazolam with exposure added little value during treatment and significantly reduced gains thereafter. During taper and follow-up, gains after exposure continued if it had not been given with alprazolam, but gains from alprazolam disappeared.

Acknowledgements

We are indebted to the late Dr Gerald Klerman for his great help as scientific adviser, to Dr Matig Mavissakalian for rating the

integrity of the psychological treatment, to Dr David Greenblatt's laboratory for analysis of drug plasma levels, and, for valuable comments on the manuscript, to Raimund Buller, Graham Dunn, Edna Foa, John Greist, Jeff Jefferson, Malcolm Lader, Wolfgang Maier, Matig Mavissakalian, Randy Nesse, and Adolf Tobeña.

The study was supported by grants from the Upjohn Company for the treatment phase and the Dunhill Medical Trust for analysis of the data.

References

- ALKUBAISY, T., MARKS, I. M., LOGSDAIL, S., *et al* (1992) The role of exposure homework in phobia reduction: A controlled study. *Behavior Therapy*, **23**, 599–621.
- ANDERSCH, S., ROSENBERG, N. K., KULLINSJÖ, H., *et al* (1991) Efficacy and safety of alprazolam, imipramine and placebo in the treatment of panic disorder: a Scandinavian multicenter study. *Acta Psychiatrica Scandinavica*, (suppl. 365), 18–27.
- BALLENGER, J. C., BURROWS, G. D., DUPONT, R. L., *et al* (1988) Alprazolam in panic disorder and agoraphobia: results from a multicenter trial: I. Efficacy in short-term treatment. *Archives of General Psychiatry*, **45**, 413–422.
- BAŞOĞLU, M., LAX, T., KASVIKIS, Y., *et al* (1988) Patterns and predictors of improvement in obsessive compulsive disorder. *Journal of Anxiety Disorders*, **2**, 299–317.
- , MARKS, I. M., KILIC, C., *et al* (1993a) The relationship between panic, anticipatory anxiety, agoraphobia, and global involvement in panic disorders with agoraphobia treated with alprazolam and exposure. (Submitted for publication.)
- , ——, ——, *et al* (1993b) Alprazolam and exposure for panic disorder with agoraphobia: attribution of improvement to medication predicts subsequent relapse. (Submitted for publication.)
- BAXTER, L., SCHWARTZ, J. R., BERGMAN, K. S., *et al* (1992) PET scan changes after successful drug and behavioral treatment. *Archives of General Psychiatry*, **49**, 681–689.
- BECK, A. T., WARD, C. H., MENDELSON, M., *et al* (1961) An inventory of measuring depression. *Archives of General Psychiatry*, **4**, 561–571.
- BIXLER, E. O., KALES, A., MANFREDI, R. L., *et al* (1991) Next-day memory impairment with triazolam use. *Lancet*, **337**, 827–831.
- BOUTON, M. E., KENNEY, F. A. & ROSENGARD, C. (1990) State-dependent fear extinction with two benzodiazepine tranquilizers. *Behavioral Neuroscience*, **104**, 44–55.
- BROWN, J. L. & HAGUE, K. J. (1986) A review of alprazolam withdrawal. *Drug Intelligence and Clinical Pharmacology*, **20**, 837–841.
- CHOUINARD, G., ANNABLE, L., FONTAINE, R., *et al* (1982) Alprazolam in the treatment of GAD and panic disorders: a double-blind placebo-controlled study. *Psychopharmacology*, **77**, 229–233.
- CROSS-NATIONAL COLLABORATIVE PANIC STUDY, SECOND PHASE INVESTIGATORS (CNCPS, SPI) (1992) Drug treatment of panic disorders. Comparative efficacy of alprazolam, imipramine and placebo. *British Journal of Psychiatry*, **160**, 191–202.
- DEROGATIS, L. R., LIPMAN, R. S. & COVI, L. (1973) An out-patient psychiatric rating scale: preliminary report. *Psychopharmacological Bulletin*, **9**, 13–28.
- DUNNER, D. L., ISHIKI, D., AVERY, D. H., *et al* (1986) Effect of alprazolam and diazepam on anxiety and panic attacks in panic disorder: a controlled study. *Journal of Clinical Psychiatry*, **47**, 458–460.
- ECHEBURÚA, E., DECORRAL, P. & BAJOS, E. G. (1993) Self-exposure and alprazolam in the treatment of agoraphobia without current panic. *Behavioural Psychotherapy* (in press).
- FIGENBAUM, W. (1988) Long-term efficacy of ungraded versus graded massed exposure in agoraphobia. *Panic and Phobias 2* (eds I. Hand & H.-U. Wittchen), pp. 83–88. New York: Springer-Verlag.

- FYER, A. J., LIEBOWITZ, M. R., GORMAN, J. M., *et al* (1987) Discontinuation of alprazolam in panic patients. *American Journal of Psychiatry*, **144**, 303–308.
- GELDER, M. G. & MARKS, I. M. (1966) Severe agoraphobia: a controlled trial. *British Journal of Psychiatry*, **112**, 309–319.
- GHOSH, A. & MARKS, I. M. (1987) Self-treatment of agoraphobia by exposure. *Behavior Therapy*, **18**, 3–16.
- GRAY, J. A. (1987) Interactions between drugs and behavior therapy. *Theoretical Foundations of Behavior Therapy* (eds H. J. Eysenck & I. Martin), pp. 433–447. New York: Plenum.
- HAMILTON, M. (1959) The assessment of anxiety states by rating. *British Journal of Medical Psychology*, **32**, 50–55.
- (1960) A rating scale for depression. *Journal of Neurology, Neurosurgery and Psychiatry*, **23**, 56–62.
- KELLNER, C. H. & UHDE, T. W. (1988) CT scanning in panic disorders. Abstract No. 37A. *APA Abstracts, Montreal, May 10*. Washington, DC: APA.
- KLOSKE, J. S., BARLOW, D. H., TASSINARI, R. B., *et al* (1988) Alprazolam vs cognitive behaviour therapy in panic disorder: in *Panic and Phobias 2* (eds I. Hand & H. U. Wittchen), pp. 54–65. New York: Springer-Verlag.
- LADER, M. H., RON, M. & PETURSSON, H. (1984) Computed axial brain tomography on long-term benzodiazepine users. *Psychological Medicine*, **14**, 203–206.
- LAVORY, P. W., KELLER, M. B. & KLERNAN, G. L. (1984) Relapse in affective disorders: reanalysis of the literature using life table methods. *Journal of Psychiatric Research*, **18**, 13–25.
- LELLIOTT, P. T., MARKS, I. M., MONTEIRO, W. O., *et al* (1987) Agoraphobics 5 years after imipramine and exposure: outcome and predictors. *Journal of Nervous and Mental Disease*, **175**, 599–605.
- LESSER, I. M., RUBIN, R. T., PECKNOLD, J. C., *et al* (1988) Secondary depression in panic disorder and agoraphobia. *Archives of General Psychiatry*, **45**, 437–443.
- MAIER, W., ROTH, M., ARGYLE, N., *et al* (1991) Avoidance behaviour: a predictor of the efficacy of pharmacotherapy in panic disorder? *European Archives of Psychiatry and Clinical Neuroscience*, **241**, 151–158.
- MARKS, I. M. (1978) *Living with Fear*. New York: McGraw-Hill.
- (1985) *Psychiatric Nurse Therapists in Primary Care. Research Series*. London: Royal College of Nursing.
- (1986) *Behavioural Psychotherapy: Maudsley Pocketbook of Management*. Available from Prof. Marks, Institute of Psychiatry, London SE5 8AF.
- (1987) *Fears, Phobias and Rituals*. New York: Oxford University Press.
- , HALLAM, R. S., PHILPOTT, R., *et al* (1977) *Nursing in Behavioural Psychotherapy*. London: Royal College of Nursing.
- & MATHEWS, A. M. (1979) Brief standard self-rating for phobic patients. *Behavior Research and Therapy*, **17**, 263–267.
- , GRAY, S., COHEN, S. D., *et al* (1983) Imipramine and brief therapist-aided exposure in agoraphobics having self-exposure homework: a controlled trial. *Archives of General Psychiatry*, **40**, 153–162.
- , LELLIOTT, P. T., BAŞOĞLU, M., *et al* (1988) Clomipramine and exposure for obsessive-compulsive disorder. *British Journal of Psychiatry*, **152**, 522–534.
- , ALBUQUERQUE, A., COTTRAUX, J., *et al* (1989) The 'efficacy' of alprazolam in panic disorder and agoraphobia: a critique of recent reports. *Archives of General Psychiatry*, **46**, 668–669.
- , GREIST, J., BAŞOĞLU, M., NOSHIRVANI, H., *et al* (1992) Comment on the second phase of the Cross-National Panic Study. *British Journal of Psychiatry*, **160**, 202–205.
- MAVISSAKALIAN, M. & MICHELSON, L. (1986) Agoraphobia: therapist-assisted in vivo exposure and imipramine. *Journal of Clinical Psychiatry*, **47**, 117–122.
- MCDONALD, R., MARKS, I. M. & BLIZARD, R. (1988) Quality assurance of outcome in mental health care in clinical settings. *Health Trends*, **20**, 111–114.
- MCMAMEE, G., O'SULLIVAN, G., LELLIOTT, P., *et al* (1989) Telephone-guided treatment for housebound agoraphobics with panic disorder: exposure vs relaxation. *Behavior Therapy*, **20**, 491–497.
- MELLMAN, T. A. & UHDE, T. W. (1986) Withdrawal syndrome with gradual tapering of alprazolam. *American Journal of Psychiatry*, **143**, 1464–1466.
- MUNJACK, D. J., CROCKER, B., CABE, D., *et al* (1989) Alprazolam, propranolol and placebo in the treatment of panic disorder and agoraphobia with panic attacks. *Journal of Clinical Psychopharmacology*, **9**, 22–27.
- O'SULLIVAN, G. & MARKS, I. M. (1990) Long-term outcome of phobic and obsessive compulsive disorders after exposure: a review chapter. *Handbook of Anxiety, Vol. 4* (eds R. Noyes, M. Roth & G. Burrows). Amsterdam: Elsevier.
- , —, BAŞOĞLU, M., *et al* (1992) Side effects of alprazolam. (Submitted for publication.)
- PECKNOLD, J. C., SWINSON, R. P., KUCH, K., *et al* (1988) Alprazolam in panic disorder and agoraphobia: results from a multicenter trial: III. Discontinuation effects. *Archives of General Psychiatry*, **45**, 429–436.
- SCHMAUSS, C. & KRIEG, J. C. (1987) Enlargement of CSF spaces in benzodiazepine abusers. *Psychological Medicine*, **17**, 869–873.
- SHEEHAN, D. V., RAJ, A. B., HARNETT-SHEEHAN, K., *et al* (1990) Adinazolam sustained release in panic disorder: a pilot study. *Irish Journal of Psychological Medicine*, **7**, 124–128.
- SPITZER, R. L., WILLIAMS, J. B. W. (1983) *Structured Clinical Interview for DSM-III, Upjohn version (SCID-UP)*. Biometric Research Division, New York State Psychiatric Institute.
- TESAR, G. E., ROSENBAUM, J. F., POLLACK, M. H., *et al* (1987) Clonazepam vs alprazolam in the treatment of panic disorder: interim analysis of a prospective, double-blind, placebo-controlled trial. *Journal of Clinical Psychiatry*, **48** (suppl. 10).
- WOLPE, J. & LAZARUS, A. (1966) *Behaviour Therapy Techniques*. Oxford: Pergamon.

*Isaac M. Marks, MD, FRCPsych, *Professor of Experimental Psychopathology, Institute of Psychiatry and Bethlem-Maudsley Hospital, London SE5 8AF*; Richard P. Swinson, MD, *Toronto General Hospital and University of Toronto, Canada*; Metin Başoğlu, MD, *Institute of Psychiatry, London*; Klaus Kuch, MD, *Toronto General Hospital and University of Toronto*; Homa Noshirvani, MD, MRCPsych, *Institute of Psychiatry, London*; Geraldine O'Sullivan, MRCPsych, MB, BS, *Institute of Psychiatry, London*; Paul T. Lelliott, MRCPsych, MB, BS, *Institute of Psychiatry, London*; Marlene Kirby, MA, *Toronto General Hospital and University of Toronto*; Gary McNamee, RMN, *Institute of Psychiatry, London*; Seda Sengun, MD, *Institute of Psychiatry, London*; Kim Wickwire, RN, *Toronto General Hospital and University of Toronto*

*Correspondence