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Specific Effects of Benzodiazepines and Tricyclic Antidepressants in Panic Disorder: Comparisons of Clomipramine with Alprazolam SR and Adinazolam SR

ROBERT L. HOLLAND[1], BRUNO C. MUSCH[2] and IAN HINDMARCH[3]*
[1]*Zeneca Pharmaceuticals, Nearside Park, Alderley Edge, Macclesfield, Cheshire, UK*
[2]*Pharmacia-Upjohn Inc., 95 Corporate Way, Bridgewater, New Jersey, USA*
[3]*HPRU-Medical Research Centre, University of Surrey, Guildford, UK*

In order to compare the efficacy and safety of tricyclic antidepressants and benzodiazepines in panic disorder, with or without agoraphobia, two studies were carried out comparing clomipramine with alprazolam sustained release (SR) or with adinazolam SR. Two hundred and fifty-seven patients received alprazolam SR (2–6 mg/day given in two divided daily doses) or clomipramine (50–150 mg/day given in two divided daily doses) for 12 weeks in a single-blind, randomised, multicentre study and 347 patients received adinazolam SR (30–90 mg/day given in two divided daily doses) or clomipramine (50–150 mg/day given in two divided daily doses) for 24 weeks in a double-blind, randomised, multicentre study. Both benzodiazepines showed an earlier onset of therapeutic efficacy than clomipramine. At the end of the treatment periods, however, clomipramine was equally as effective as alprazolam SR and more effective than adinazolam SR. Withdrawal problems were also somewhat less common with clomipramine than with alprazolam SR and adinazolam SR. Both benzodiazepines were clearly better tolerated than clomipramine. The rate of premature withdrawal was also notably higher with clomipramine than with alprazolam SR. In conclusion, the benzodiazepines alprazolam and adinazolam SR are better tolerated than the tricyclic antidepressant clomipramine in the treatment of panic disorder, but have no advantages in terms of efficacy.

KEY WORDS — benzodiazepine; panic disorder; tricyclic antidepressant; alprazolam; adinazolam; clomipramine

INTRODUCTION

Panic disorder is a relatively new nosological entity which was first included as a diagnosis in DSM-III in 1980. It is characterised by spontaneous and unexpected panic attacks, which are defined as short periods of intense anxiety or fear accompanied by physical symptoms, such as palpitations.

The tricyclic antidepressants, such as clomipramine, the monoamine oxidase inhibitors (MAOI) and the benzodiazepine alprazolam have all been found to be effective in the treatment of panic disorder (Noyes *et al.*, 1989; McTavish, 1990; Murphy, 1990). Although the tricyclic antidepressants are still considered to be the first choice therapy by many psychiatrists, they have a number of important limitations, including the emergence of anticholinergic side effects and the intensification of anxiety symptoms at the beginning of treatment. These latter symptoms, combined with a delayed onset of therapeutic effect, are responsible for a high rate of drop-outs in the first weeks of therapy; a number of studies have estimated that between a quarter and a third of patients withdraw during this time (Sheehan, 1987). Although the MAOIs are better tolerated than the tricyclic antidepressants, they are less effective (Noyes *et al.*, 1986).

Alprazolam, one of a new class of benzodiazepines, has been shown to exert clinically significant effects after only one week of treatment, blocking panic attacks and reducing the intensity of the anticipatory anxiety. Previous studies comparing alprazolam and imipramine in panic disorder have also shown that the onset of clinical activity occurs significantly earlier with alprazolam

*Correspondence to: Professor Ian Hindmarch, HPRU-Medical Research Centre, University of Surrey, Egerton Road, Guildford GU2 5XP, UK.

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than with imipramine (Noyes *et al*., 1989). As alprazolam requires administration three or four times daily, a sustained-released (SR) formulation has recently been developed in order to simplify dosing and improve compliance. Moreover, an SR formulation might prevent the occurrence of inter-dose, or breakthrough, anxiety which may be experienced by some patients. The safety and efficacy of alprazolam SR in the treatment of panic disorder has been shown to be equivalent to that of standard compressed tablets of alprazolam and significantly superior to placebo (data on file).

Adinazolam mesylate is a triazolobenzo-diazepine which has shown efficacy in depression (with and without melancholia), generalised anxiety disorder and panic disorder. In common with alprazolam, adinazolam requires multiple daily dosing and an SR formulation has now been developed which permits less frequent dosing.

In order to compare the efficacy and safety of tricyclic antidepressants and benzodiazepines in panic disorder with or without agoraphobia, two studies were carried out comparing clomipramine with alprazolam SR or with adinazolam SR.

ALPRAZOLAM SR VERSUS CLOMIPRAMINE IN PANIC DISORDER

Patients and methods

Patients of either sex (age 18–65 years) meeting DSM-III-R criteria for panic disorder with or without agoraphobia, and with at least one panic attack in the 4 weeks prior to the study, were enrolled in this single-blind (evaluator-blind), parallel group, randomised, flexible-dose study carried out in 22 centres. Patients were excluded if they had a past serious suicide attempt or current suicidal ideation, a lifetime diagnosis of DSM-III-R mania, psychosis or dementia, concurrent or recent generalised anxiety disorder, substance abuse, drug psychosis, obsessive–compulsive disorder, hypomania, paranoia, major depression, bipolar disorder or cyclothymic disorder, or if they required psychotherapy or behaviour therapy during the study or had received it in the 2 weeks prior to the study. All patients gave their informed consent.

Following a 1-week placebo run-in period, patients received alprazolam SR (2–6 mg/day given in two divided daily doses) or clomipramine (50–150 mg/ day given in two divided daily doses) for 12 weeks; gradual dose escalation was performed over the first 3 weeks. Efficacy criteria included the proportion of patients who completed the first 4 weeks of treatment, the change from baseline in the number of total panic attacks (situational and unexpected) from the Panic Attack and Anticipatory Anxiety scale, and the Clinical Global Impression (CGI) Global Improvement Score and Severity of Illness Score which were assessed at weeks 1, 2, 4, 8 and 12 (the Panic Attack and Anticipatory Anxiety Scale was also assessed at week 3).

At the end of the 12-week treatment period, patients entered a 6- or 12-week taper period, after which they were monitored for a further 2 weeks. Variables measured during this period included the Panic Attack and Anticipatory Anxiety scale and the CGI Global Improvement Score and Severity of Illness.

Statistical analyses were performed by a two-way analysis of variance for continuous variables and chi-square contingency methods for categorical variables.

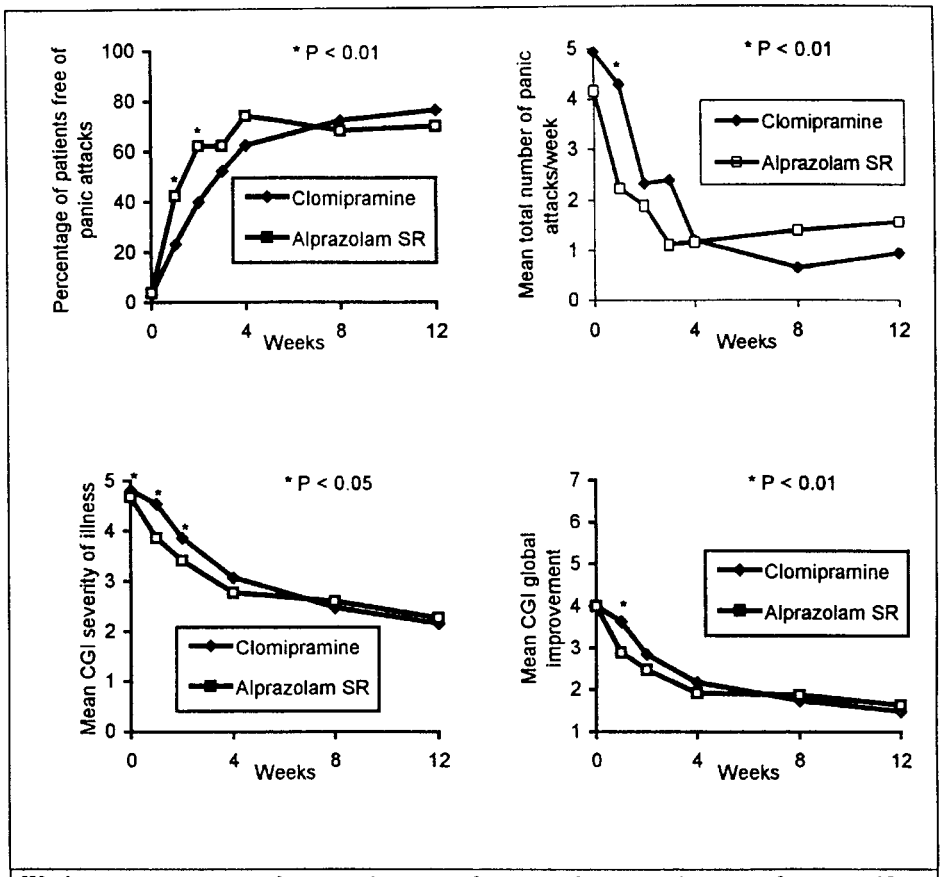
Results

Two hundred and fifty-seven patients were enrolled in the study, 129 in the alprazolam SR group and 128 in the clomipramine group. The groups were well matched with respect to demographic and baseline characteristics; 34 per cent of patients in the alprazolam SR group and 38 per cent in the clomipramine group were male and the mean age was 35·3 years in the alprazolam SR group and 34·3 years in the clomipramine group. As shown in Table 1, more patients withdrew prematurely in the clomipramine group than in the alprazolam SR group (42 versus 17). The percentage of patients who completed the first 4 weeks of treatment was significantly higher with alprazolam SR than with clomipramine (95 per cent versus 80 per cent).

Both drugs resulted in a marked improvement after 12 weeks of treatment. At week 12, the mean

Table 1. Reasons for premature withdrawal from alprazolam SR or clomipramine

	Alprazolam SR ($N = 129$)	Clomipramine ($N = 128$)
Lack of efficacy	4	11
Adverse events	7	18
Other	6	13
Total	17	42



Weeks	0	1	2	3	4	8	12
Clomipramine (N)	128	121	103	96	90	86	71
Alprazolam SR (N)	129	125	116	111	108	113	96

Figure 1. Efficacy of alprazolam SR and clomipramine during 12 weeks of treatment

total number of panic attacks had fallen from 4·16 at baseline to 2·02 in the alprazolam SR group and from 4·93 to 1·79 in the clomipramine group. Similarly, 61·7 per cent of patients in the alprazolam SR group and 64·8 per cent of patients in the clomipramine group were free of panic attacks. The mean CGI severity of illness score fell from 4·67 to 2·62 in the alprazolam SR group and from 4·81 to 2·76 in the clomipramine group, whilst the CGI Improvement scores were 1·98 and 2·13 in the alprazolam SR and clomipramine groups, respectively. There were no statistically significant differences between the treatments for any parameter. However, alprazolam SR was significantly ($p < 0·05$) more effective than clomipramine in the initial weeks of treatment in terms of the percentage of patients free of panic attacks, the total number of panic attacks, and the CGI severity of illness and global improvement (Figure 1). Alprazolam SR resulted in fewer adverse events than clomipramine; the most common events are shown in Table 2 and included somnolence (31 per cent) in the alprazolam SR group and dry mouth (32 per cent) and diaphoresis (26 per cent) in the clomipramine group. Serious adverse events occurred in four patients treated with alprazolam

Table 2. Adverse events* occurring with alprazolam SR and clomipramine

	Alprazolam SR ($N = 129$)	Clomipramine ($N = 128$)
Somnolence	40 (31·0 per cent)	17 (13·3 per cent)
Anxiety	20 (15·5 per cent)	10 (7·8 per cent)
Headache	18 (14·0 per cent)	22 (17·2 per cent)
Insomnia	16 (12·4 per cent)	15 (11·7 per cent)
Depressive symptoms	13 (10·1 per cent)	6 (4·7 per cent)
Dizziness	13 (10·1 per cent)	20 (15·6 per cent)
Dry mouth	10 (7·8 per cent)	41 (32·0 per cent)
Constipation	9 (7·0 per cent)	20 (15·6 per cent)
Nausea	8 (6·2 per cent)	15 (11·7 per cent)
Diaphoresis	7 (5·4 per cent)	33 (25·8 per cent)
Tremor	7 (5·4 per cent)	23 (18·0 per cent)

*Adverse events occurring in more than 10 per cent of patients in either group.

SR and three treated with clomipramine. Neither treatment had any clinically relevant effects on laboratory parameters or vital signs.

Patients treated with clomipramine experienced somewhat fewer problems during withdrawal (50 per cent and 67 per cent had no problems during short- and long-term taper, respectively) than those treated with alprazolam SR (corresponding percentages of 32 per cent and 38 per cent, respectively). However, less than 15 per cent of patients in either group experienced severe problems. The percentage of patients free of panic attacks and the total number of panic attacks during the taper and post-taper assessments did not differ significantly between the treatment groups, except for a higher percentage of patients free of panic attacks in the clomipramine group at the final long-term taper assessment. The most common adverse events during discontinuation in the alprazolam SR group were anxiety (14·7 per cent), depressive symptoms (8·5 per cent) and insomnia (8·5 per cent), whilst clomipramine was associated most frequently with diaphoresis (8·6 per cent), headache (7·8 per cent) and dizziness (7·0 per cent).

ADINAZOLAM SR VERSUS CLOMIPRAMINE IN PANIC DISORDER

Patients and methods

Patients of either sex (age 18–65 years) meeting DSM-III-R criteria for panic disorder with or without agoraphobia, and with a score of less than two on the 'suicide', 'depressed mood' and 'feelings of guilt' questions on the Hamilton Rating Scale for Depression (HAMD), were enrolled in this double-blind, parallel group, randomised, flexible-dose study carried out in 24 centres. Patients were excluded if they had a past serious suicide attempt or current suicidal ideation, a lifetime diagnosis of DSM-III-R mania, psychosis or dementia, concurrent or recent DSM-III-R generalised anxiety disorder, substance abuse, drug psychosis, obsessive–compulsive disorder, hypomania, paranoia or major depression, or if they required psychotherapy or behaviour therapy during the study or had received it in the 12 weeks prior to the study. All patients gave their informed consent.

Patients received adinazolam SR (30–90 mg/day given in two divided daily doses) or clomipramine (50–150 mg/day given in two divided daily doses) for 24 weeks; gradual dose escalation was performed over the first 2 weeks. At the end of the 24-week treatment period, patients entered a 6-week taper period, after which they were monitored for a further 2 weeks. Efficacy criteria included the total number of panic attacks (situational and unexpected) from the Panic Attack and Anticipatory Anxiety scale, the CGI Global Improvement Score, the Phobic Anxiety Dimension of the SCL-90 and the Sheehan Disability Scale, which were assessed at weeks 1, 2, 4, 8, 12, 16, 20 and 24 (the SCL-90 was assessed only at weeks 8 and 24) of the treatment period and weekly during the discontinuation period.

Statistical analyses were performed by a two-way analysis of variance for normally distributed continuous variables and the Kruskal–Wallis test for non-normally distributed continuous variables.

Results

Three hundred and forty-seven patients were enrolled in this study, 166 in the adinazolam SR group and 149 in the clomipramine group. The groups were well matched with respect to demographic and baseline characteristics; 36 per cent of patients in the adinazolam SR group and 38 per cent in the clomipramine group were male and the mean age was 36·5 years in the adinazolam SR group and 35·8 years in the clomipramine group. The study was completed by 108 patients in the adinazolam SR group and 113 patients in the clomipramine group; the main reason for premature termination in both groups was withdrawal of

Table 3. Efficacy of adinazolam SR and clomipramine at week 24 (last observation carried forward)

		Adinazolam SR	Clomipramine
Total panic attacks	Mean (SD)	3·1 ± 6·49	1·5 ± 5·31
	Mean (SD) change from baseline	−2·1 ± 7·68	−3·6 ± 7·50
SCL-90 Phobic anxiety cluster	Mean (SD)	7·8 ± 7·16	3·7 ± 4·95
	Mean (SD) change from baseline	−5·4 ± 6·37	−8·6 ± 6·06
CGI Improvement	Mean (SD)	2·7 ± 1·67	1·7 ± 1·10
Disability scale — work	Mean (SD)	2·4 ± 3·03	1·4 ± 2·48
	Mean (SD) change from baseline	−2·3 ± 3·66	−3·9 ± 3·49
Disability scale — social	Mean (SD)	3·0 ± 3·19	1·7 ± 2·45
	Mean (SD) change from baseline	−2·8 ± 3·51	−4·4 ± 3·20
Disability scale — family	Mean (SD)	2·8 ± 3·15	1·4 ± 2·35
	Mean (SD) change from baseline	−2·2 ± 3·24	−3·2 ± 3·39

consent (12 per cent in the adinazolam SR group and 9 per cent in the clomipramine group).

Both treatments resulted in an improvement in all efficacy parameters. Adinazolam SR was somewhat more effective than clomipramine during the initial weeks of treatment. However, as shown in Table 3, clomipramine was significantly more effective than adinazolam SR at week 24. Adinazolam SR was considerably better tolerated than clomipramine (Table 4). The most common events were sedation (15 per cent) and dry mouth (15 per cent) in the adinazolam SR group and dry mouth (52 per cent) and constipation (31 per cent) in the clomipramine group. Neither treatment had a clinically relevant effect on laboratory parameters or vital signs, with the exception of a significant decrease in serum uric acid levels in the adinazolam SR group.

During the withdrawal period, more patients in the clomipramine group than in the adinazolam SR group remained in remission (86·7 per cent versus 71·8 per cent), whilst more patients in the adinazolam SR group than in the clomipramine group experienced relapse (25·4 per cent versus 12·2 per cent); there were no differences between the groups in the percentage of patients who experienced rebound. Adverse events which occurred in 5 per cent or more of patients during discontinuation included panic attacks and sweating in the adinazolam SR group and lightheadedness, parasthesia, sleep disorder, irritability, anxiety and depression in the clomipramine group.

Table 4. Adverse events* occurring with adinazolam SR and clomipramine

	Adinazolam SR ($N = 166$)	Clomipramine ($N = 149$)
Dry mouth	24 (14·5 per cent)	77 (51·7 per cent)
Sedation	24 (14·5 per cent)	17 (11·4 per cent)
Constipation	20 (12·0 per cent)	46 (30·9 per cent)
Light-headedness	17 (10·2 per cent)	23 (15·4 per cent)
Nausea	15 (9·0 per cent)	17 (11·4 per cent)
Fatigue	12 (7·2 per cent)	16 (10·7 per cent)
Sleep disorder	11 (6·6 per cent)	29 (19·5 per cent)
Sweating	6 (3·6 per cent)	27 (18·1 per cent)
Tremor	3 (8·1 per cent)	37 (24·8 per cent)

*Adverse events occurring in more than 10 per cent of patients in either group.

DISCUSSION

The aim of these two studies was to compare the efficacy and safety of standard tricyclic antidepressant treatment (clomipramine) with sustained-release benzodiazepines (alprazolam and adinazolam) in panic disorder. Both studies were carried out in patients with DSM-III-R diagnosed panic disorder, with or without agoraphobia. Although neither study was carried out in the USA, all the patients met the more rigorous DSM-III-R criteria for panic disorder which is employed in the USA in place of the International Classification of Diseases (ICD-10), the accepted diagnostic system in Europe. The DSM-III-R classifies panic disorder as a distinct condition and places a heavy emphasis on the specific number of panic attacks.

The benzodiazepines and the tricyclic antidepressant were all safe and effective in the treatment of panic disorder. Both benzodiazepines showed an earlier onset of therapeutic efficacy than clomipramine. At the end of the treatment periods, however, clomipramine was found to be equally as effective as alprazolam SR and more effective than adinazolam SR. Withdrawal

problems were also somewhat less common with clomipramine than with alprazolam SR and adinazolam SR.

Both benzodiazepines were clearly better tolerated than clomipramine. The most common adverse effects with clomipramine were dry mouth, which affected between one-third and one-half of patients, constipation, diaphoresis and tremor. The incidence of adverse events was considerably lower with both benzodiazepines, the most common adverse events being somnolence (31 per cent) with alprazolam SR and dry mouth and sedation (both 15 per cent) with adinazolam SR. Moreover, the rate of withdrawal due to adverse events was notably higher with clomipramine than with alprazolam SR. The lower incidence of adverse events, combined with the simplified dosing schedule associated with SR benzodiazepine preparations, should result in improved compliance compared with clomipramine.

In conclusion, the benzodiazepines alprazolam and adinazolam SR are better tolerated than the tricyclic antidepressant clomipramine in the treatment of panic disorder, but have no advantages in terms of efficacy.

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