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COMBINED PHARMACOLOGICAL AND BEHAVIORAL TREATMENT FOR AGORAPHOBIA

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Summary—Thirty-seven severely-disabled agoraphobics were randomly assigned to (1) Imipramine-no exposure, (2) Imipramine + exposure or (3) Placebo + exposure groups. To provide a more stringent test of the pharmacological effects of imipramine independent of exposure to phobic stimuli, *S*s in the Imipramine-no exposure condition received antiexposure instructions during the first 8 weeks of therapy. Assessments were conducted at 0, 8 and 26 weeks. At 8 weeks, the group receiving imipramine combined with exposure therapy displayed more improvement than the other two groups, and was the only group to show a reduction in panic attacks. *S*s receiving imipramine with antiexposure instructions showed little improvement on phobic indices, no reduction in panic, but significant improvement in anxiety and dysphoric mood. At 26 weeks *S*s receiving the combined imipramine + exposure treatment exhibited further improvement resulting in a significant superiority of Imipramine + exposure over Placebo + exposure across a number of different outcome indices. *S*s who had received imipramine with antiexposure instructions showed some improvement during the subsequent 18 weeks in which the antiexposure instructions were no longer in effect. However, neither this group nor the Placebo + exposure group showed a reduction in panic attacks. The results of the present trial provide support for the beneficial effects of combining intensive exposure with imipramine, but call into question the thesis that imipramine exerts its effect through a pharmacological blocking of panic attacks. Alternative hypotheses concerning the mode of action of imipramine are presented.

INTRODUCTION

There has been a recent upsurge of interest in both the etiology and treatment of agoraphobia (Mathews, Gelder and Johnston, 1981; Chambless and Goldstein, 1982; Tearnan and Telch, 1983). Advances in the application of performance-based behavioral treatments such as *in vivo* exposure and in the use of pharmacologic agents such as imipramine may account for the growing interest. Results from a large number of studies have documented the efficacy of behavioral treatments for agoraphobics (cf. Mathews *et al.*, 1981; Marks, 1978), and long-term follow-up investigations of these methods ranging from 2 to 9 yr have attested to the durability of treatment gains (Emmelkamp and Kuipers, 1979; Marks, 1971; McPherson, Brougham and McLaren, 1980; Munby and Johnston, 1980). In addition, a number of prospective double-blind studies have shown encouraging results with two classes of antidepressant medication, namely tricyclic antidepressants (most notably, imipramine) (Klein, 1967; Sheehan, Ballenger and Jacobsen, 1980; Zitrin, Klein and Woerner, 1978, 1980; Zitrin, Klein, Woerner and Ross, 1983) and monoamine oxidase inhibitors—most notably, phenelzine (Sheehan *et al.*, 1980; Mountjoy, Roth, Garside and Leitch, 1977; Lipsedge, Hajioff, Napier, Pearce, Pike and Rich, 1973; Solyom, Heseltine, McClure, Solyom, Ledwidge and Steinberg, 1973; Tyrer, Candy and Kelly, 1973).

A major methodological deficiency in the research to date, however, is the confounding of the pharmacological effects of medication with the effects of instructions encouraging *S*s to confront their phobic situations (Telch, Tearnan and Taylor, 1983). In a recent comment on the treatment of agoraphobia and panic attacks Matuzas and Glass (1983) raise the question, "How effective are the antidepressants for agoraphobia in the absence of exposure?" (p. 222). Similarly, other researchers such as Marks and Zitrin have pointed to the need to examine the effects of imipramine independent of exposure (Marks, Gray, Cohen, Hill, Mawson, Ramm and Stern, 1983; Zitrin *et al.*, 1983). It is interesting to note that the only study to include a drug no-exposure condition showed phenelzine to be no more effective than placebo (Solyom, Solyom, LaPierre, Pecknold and Morton, 1981). However, as the authors point out, inadequate drug dosage may have also been responsible for the negative results. To test the efficacy of antidepressant medication independent

of exposure to phobic situations, requires an experimental manipulation in which *S*s' exposure to feared situations is kept at a minimum while they are on the medication. Such a test would help clarify the mechanism through which antidepressant medication exerts its effects. As Marks *et al.* (1983) have suggested, "future studies might include an antiexposure condition to make certain that inadvertant self-exposure homework is not clouding the issue" (p. 161). The present study included an imipramine antiexposure instruction condition in order to better test the pharmacological effects of imipramine independent of exposure to phobic stimuli.

METHOD

Subjects

Thirty-seven individuals whose lives were severely impaired by spontaneous panic attacks and an intense fear of venturing out in public alone participated in the present study. Criteria for acceptance into the trial included the following: (a) meeting the DSM-III diagnostic definition for agoraphobia with panic attacks; (b) inability to walk unaccompanied along a specially designed test course in a major shopping center; (c) spouse or close friend willing to take an active role in the *S*'s treatment; and (d) no current use of tricyclics or MAO inhibitors. Despite relatively high initial Beck scores, none of the *S*s met the DSM-III criteria for major affective disorder. None of the *S*s had received an adequate trial of either imipramine or exposure therapy before entry to this study.

Experimental design

Subjects were matched according to scores on the Beck Depression Inventory (BDI) and randomly assigned to one of three treatment conditions: (1) Imipramine-no exposure, (2) Imipramine + intensive exposure and (3) Placebo + intensive exposure. During Weeks 1–4 all *S*s received medication (imipramine or placebo) under the same no-practice instructional set. During Weeks 5–8 *S*s in Groups 2 and 3 received exposure along with their medication, while *S*s in Group 1 continued to receive the no-practice instructions. During weeks 9–26 *S*s continued their medication. *S*s in the two exposure conditions (Groups 2 and 3) were instructed to continue using the skills they had learned during the exposure sessions; however no further exposure sessions were provided. The no-practice instructions given to *S*s in Group 1 were lifted during Weeks 9–26, when they were encouraged in a general way to confront phobic situations. Assessments were conducted at 0, 8 and 26 weeks. Measures in each of the three major response modalities (i.e. self-report, behavioral and physiologic) were collected.

Medication procedures

The *S*, behavior therapist, and assessor were all blind to *S*s' medication which was either imipramine or placebo during the entire course of the study. The prescribing psychiatrist was blind with respect to medication only for the first 4 weeks of the trial, after which medication status of *S*s in Group 1 (Imipramine-no exposure) became known to him due to the continued antiexposure instructions which these *S*s received. During the first 8 weeks of treatment, all *S*s were required to attend brief sessions (less than 30 min) at the clinic every 2 weeks, where they were seen by the prescribing psychiatrist for the purpose of receiving medication and evaluating medication effects. Once the dosage of medication was stabilized, these sessions were reduced to a monthly basis. The drug regimen described by Zitrin and her colleagues (Zitrin *et al.*, 1978, 1980, 1983) was used. *S*s in each of the three conditions began with 25 mg of imipramine hydrochloride (or placebo) at bedtime, with increments of 25 mg every second day up to 150 mg daily. The dosage was then increased up to a maximum of 300 mg/day for *S*s who continued to report panic attacks at the lower dosage. Those *S*s reporting intolerable side effects had their medication decreased to the last tolerable dose. Medication doses for imipramine at the 8- and 26-week assessments ranged from 50 to 300 mg. Mean prescribed medication doses at the 8-week assessment were 190 mg (SD = 54.6), 197 mg (SD = 67.1) and 183 mg (SD = 39.1) for the Imipramine-no exposure, Imipramine + exposure and Placebo + exposure groups, respectively. At 26 weeks, these mean doses were 179 mg (SD = 57.6), 181 mg (SD = 63.4) and 180 mg (SD = 43.3), respectively, for the *S*s who had continued to take their medication. Two *S*s from the first group, one from the second

group, and three from the third were dissatisfied with the medication and stopped taking it during the first 8 weeks.

Treatment conditions

Imipramine-no exposure. *S*s in this condition received imipramine hydrochloride in the manner previously described. Instructions emphasized the importance of giving the drug 'time to work' before attempting to confront feared situations. However, *S*s were instructed to continue with any activities that they could already perform. At each subsequent clinic visit during the first 8 weeks of treatment, these instructions were repeated. Following the 8-week assessment, *S*s were informed that the medication had had sufficient time to build up in their system, and that they should try to venture out into previously feared situations. However, *S*s were given no therapist-aided exposure, or instructions on *how to confront* phobic situations, nor were they provided manuals outlining self-directed exposure methods.

Imipramine + exposure. *S*s in this condition were administered imipramine on the same dosage schedule and with the same antiexposure instructions as *S*s in the Imipramine-no exposure condition. However, beginning at Week 5 the no-practice instructions were dropped, and *S*s were given intensive group exposure as described by Hand, Lamontagne and Marks (1975). *S*s were treated in small groups ranging from 4 to 6 *S*s per group. A total of 9 session hours (3 hr on each of 3 consecutive days) were devoted to therapist-assisted *in vivo* exposure. The treatment rationale stressed how the agoraphobics' fears had been strengthened by their avoidance of fearful situations. *S*s were told that by confronting their phobic situations while tolerating their emotional reaction, they would eventually experience a reduction of anxiety. *S*s were asked to see the therapist as an instructor who would teach them how to use this method. It was emphasized that *S*s view their role as active participants rather than as passive recipients of help.

Once in the phobic situation, emphasis was placed on teaching *S*s to tolerate their emotional arousal. *S*s were instructed to describe to themselves their actual emotional state, anticipating neither phobic nor unreal positive consequences of the situation.

On the first day, *S*s were escorted to a nearby park in the downtown area of Palo Alto and encouraged to gradually confront phobic situations under maximal mutual support while following the speed of the slowest in the group. After Day 1, *S*s were encouraged to achieve independence from the instructor and other group members. To facilitate independence, the therapist remained at predesignated 'check points'. *S*s were asked to check in with the therapist every 30 min, at which time the group members briefly discussed their progress and shared with other group members strategies that were helpful in overcoming specific obstacles. During Day 3, *S*s were encouraged to confront more difficult situations unaccompanied. These included crossing busy streets, waiting in lines in banks and grocery stores etc. At the end of Day 3, *S*s were provided with slightly modified versions of the agoraphobic and partner home-based treatment manuals developed by Mathews *et al.* (1981). They were informed that the purpose of the manuals was to insure that the progress made in the previous 3 days be transferred to the home environment. The *S*s manual provided a step-by-step description of the method of practice with specific instructions about coping with feelings of panic while practising. The partner manual included sections covering the partner's role in reinforcing phobic behavior, partner's use of contingent attention to reinforce *S*'s practice, and suggestions on how the partner might help plan targets for practice. *S*s and their partners were instructed to read over both the agoraphobic and partner manuals very carefully and answer each set of questions at the end of each section. In addition, *S*s were instructed to practise confronting phobic situations for at least 1 hr each day during the next 4 weeks. Partners were asked to provide support and encouragement during *S*s' practice efforts.

During Weeks 6–8, *S*s and their partners met in small groups with the therapist to discuss the structured home-practice, Each weekly 90-min clinic session was devoted toward: (a) reinforcing homework completion; (b) pinpointing specific areas of difficulty with the use of the manuals in directing home-practice; (c) problem-solving solutions to problems in homework exercises; and (d) assuring that each group member and their partner had set homework targets for the following week. Marital problems were discussed only if they were serving as obstacles for home-practice.

Placebo + exposure. This treatment condition was identical to the previous one with the exception that *S*s were administered a lactose placebo in place of the imipramine hydrochloride.

Assessments

Phobia ratings. The Fear Questionnaire (FQ) developed by Marks and Mathews (1979) was administered to all *S*s at each assessment. *S*s rated their main phobia on a 0–8 scale and three sets of five questions concerning agoraphobia, blood–injury phobia and social phobia.

Mood. Mood was assessed using the following scales: (a) 21-item BDI (Beck, 1967); (b) Zung (1965) Self-Rating Depression Scale; and (3) FQ-Depression—a 1-item, 0–8 scale, in which *S*s rate the degree to which they feel miserable or depressed.

Behavioral approach test (BAT). To obtain a direct behavioral assessment of phobic severity, *S*s were asked to walk a specially designed course (approx. 1.0 km) along the major walkway of the Stanford Shopping Center. The course was broken down into 12 landmarks or stations consisting of well-known stores (e.g. Macy's, Woolworth's). Each consecutive station was approx. 25–50 yd further from the starting point. *S*s were informed that the purpose of the test walk was to obtain an objective measure of their fear. Each *S* was provided a detailed map of the course and instructed to walk unaccompanied along the course as far as they could without stopping. *S*s were instructed to place a red tape marker on the ground at the farthest point reached. The number of stations reached served as the index of performance on the test walk. Those individuals who completed the course at the pretreatment assessment ($N = 7$) were viewed as insufficiently phobic and were excluded from the study.

Anticipated anxiety. Just prior to the start of the BAT walk, *S*s examined a map of the course and rated their anticipated level of anxiety at each point along the course on a 0–10 scale with 0 representing complete calmness and 10 representing extreme anxiety. *S*s' ratings were averaged across stations to provide an overall index of anticipated anxiety.

Performance anxiety. Subjective reports of performance anxiety during the test walk were assessed by having *S*s record their subjective level of anxiety at each point along the walk on a 0–10 scale with 0 representing complete calmness and 10 representing extreme anxiety. *S*s' self-report of fear at each of the completed stations was averaged to yield an overall index of fear arousal during the test walk.

Heart rate (HR). *S*s' HR during the behavioral test walk was measured continuously with a Vitalog MC-2 device (Vitalog Corporation) and an R-wave detector connected to the chest by electrocardiograph electrodes. The MC-2 is a solid-state ambulatory microcomputer which stores data on HR and physical activity on a minute-by-minute basis and quickly transfers these data to a microcomputer for data analysis (Taylor, Kramer, Bragg, Miles, Rule, Savin and Debusk, 1982; Taylor, Telch and Haavik, 1983). The device measures $4 \times 8 \times 12$ cm, weighs 0.5 kg and is worn on the belt. Prior to the BAT walk, the device was attached by an undergraduate research assistant. *S*s were told that the purpose of the assessment was to study how *S*s' HR changes during encounters with phobic situations. After the electrodes were attached, a 5-min reating baseline was obtained while the *S* remained seated in a comfortable chair in the clinic. Following the baseline recording, *S*s were driven to the Stanford Shopping Center and instructed to begin the BAT walk. *S*s' HR during the walk was stored on the Vitalog and later transferred to an Apple II computer for data analysis. The HR index was calculated by subtracting each *S*'s average resting HR from their average HR during the BAT walk. HR was only collected at the 0- and 8-week assessments.

Perceived self-efficacy. To assess *S*s' self-judged competence concerning their ability to reach each station of the BAT walk, *S*s were administered a Self-efficacy scale modeled after that of Bandura and his colleagues (Bandura and Adams, 1977; Telch, Bandura, Vinceguerra, Agras and Stout, 1982). Following a detailed description of the test course, *S*s were presented with a list of the 12 stations on the course and asked to judge for each station whether they could successfully reach it. For each station that *S*s judged they could reach, they were asked to rate their degree of certainty in that judgment on a 100-point scale ranging from complete uncertainty to complete certainty. Strength of self-efficacy was computed by averaging each *S*s' certainty ratings across all stations.

Panic. Two measures of panic were used. *S*s' frequency of panic attacks was assessed by having them record each episode of panic on a home daily panic diary form. *S*s were instructed to indicate the date, time of the attack, setting in which attack occurred and their coping method. In addition to the diary form, *S*s completed a Panic Questionnaire (PQ) at each assessment. On this scale *S*s were asked to rate the presence of panic within the last month, outcome expectations concerning

the likelihood of panic attacks in the future and efficacy ratings concerning their ability to cope with future panic attacks without avoidance.

Unaccompanied excursions from home. *S*s were instructed to log in their diary each time they left the house unaccompanied.

RESULTS

Subject demographics and dropouts

Seven *S*s (all females) were excluded from the trial because they were able to walk the entire BAT course at pretest. A one-way ANOVA indicated that these 7 individuals scored significantly less phobic on the Main Phobia and Agoraphobia subscales of the FQ than those individuals who were unable to complete the course ($P < 0.05$).

Demographic information on the 37 *S*s who were accepted into the trial and successfully met the entry criteria is presented in Table 1. There were no significant differences between groups on any of the demographic variables at baseline. Eight *S*s (2 in the Imipramine-no exposure, 3 in the Imipramine + exposure and 3 in the Placebo + exposure conditions) dropped out during the first 8-week phase of the study. Adverse side effects of the medication were responsible for all dropouts in the two imipramine conditions and 1 dropout in the Placebo + exposure group. Two other *S*s in the Placebo + exposure condition were unable to comply with scheduling requirements and were thus terminated from the study. Two additional *S*s, 1 in each of the two imipramine conditions, could not be located at the 26-week follow-up assessment. A one-way ANOVA performed on the pretreatment scores revealed no significant differences between the 27 completers and the 10 noncompleters.

Treatment effects

One-way ANCOVAs adjusted for pretreatment scores were performed on all continuous variables at the 8- and 26-week assessments. One-tailed *a priori* linear contrast comparisons were performed on the adjusted group means at the 8- and 26-week assessments. Within-group changes over time were tested separately for each group with two-tailed *t*-tests for dependent samples. χ^2-analyses were performed on all dichotomous variables. Means and standard deviations for each measure at Weeks 0, 8 and 26 are presented in Table 2.

Eight-week assessment

A summary of the statistical findings at the 8-week assessment is presented in Table 3 and in Fig. 1. *S*s assigned to the Imipramine + exposure condition showed statistically significant

Table 1. *S* demographics

	Imipramine no exposure ($N = 12$)	Imipramine + exposure ($N = 13$)	Placebo + exposure ($N = 12$)
Sex			
Male (%)	8.3	15.4	0.0
Female (%)	91.7	84.6	100
Age at screening (yr)			
$\bar{X}$	43.5	42.2	38.7
SD	11.3	12.5	9.5
Marital status			
Never married (%)	8.3	7.3	16.7
Married (%)	58.3	69.2	58.3
Separated/divorced (%)	33.3	23.1	25.0
Education			
Did not complete high school (%)	25.0	23.0	0.0
Graduated from high school (%)	50.0	46.2	41.7
Some college (%)	25.0	15.4	41.7
College graduate or beyond (%)	0.0	15.4	16.6
Employment status			
Housewife/unemployed (%)	91.6	92.3	91.6
Employed (%)	8.4	7.7	8.4
Duration of fear (yr)			
$\bar{X}$	12.5	12.8	11.3
SD	11.4	10.7	10.1
*S*s having prior treatment (%)	83.3	76.9	75.0

Table 2. Means and standard deviations for each outcome measure at the 0-, 8- and 26-week assessments

	Imipramine-no exposure ($N = 10$)	Imipramine + exposure ($N = 10$)	Placebo + exposure ($N = 9$)
Fear Questionnaire (FQ)			
Main Phobia (0–8)			
0 Weeks	7.0 (1.3)	7.6 (1.0)	7.8 (0.4)
8 Weeks	6.2 (2.1)	2.5 (2.2)	4.0 (2.1)
26 Weeks	5.4 (2.5)	2.0 (1.9)	4.4 (2.4)
Agoraphobia scale (0–40)			
0 Weeks	31.0 (6.3)	36.0 (5.7)	35.1 (6.8)
8 Weeks	28.4 (11.2)	17.3 (10.3)	23.3 (7.8)
26 Weeks	23.8 (9.3)	12.6 (8.1)	25.6 (8.8)
Total Phobia score (0–120)			
0 Weeks	76.6 (13.1)	72.1 (20.4)	81.3 (18.4)
8 Weeks	63.6 (27.6)	31.7 (15.5)	60.0 (21.9)
26 Weeks	53.1 (13.1)	19.3 (13.1)	59.7 (21.6)
Test walk measures			
Approach behavior (0–12)			
0 Weeks	6.2 (3.1)	5.2 (2.8)	2.6 (2.3)
8 Weeks	7.8 (4.0)	11.2 (2.2)	9.0 (3.7)
26 Weeks	8.2 (3.5)	11.4 (1.7)	9.6 (3.7)
Anticipatory anxiety (0–10)			
0 Weeks	7.3 (2.3)	8.0 (1.2)	8.8 (1.3)
8 Weeks	4.4 (2.7)	2.5 (0.80)	2.9 (1.0)
26 Weeks	3.1 (2.1)	1.0 (2.1)	3.7 (2.8)
Performance anxiety (0–10)			
0 Weeks	7.4 (2.2)	7.9 (1.4)	8.4 (1.9)
8 Weeks	4.0 (3.7)	1.1 (1.6)	3.0 (2.3)
26 Weeks	2.9 (2.0)	0.8 (2.0)	2.8 (3.2)
Self-efficacy strength (0-100)			
0 Weeks	34.0 (33.7)	23.3 (14.7)	23.7 (20.9)
8 Weeks	52.8 (35.6)	81.0 (32.3)	61.9 (35.4)
26 Weeks	55.4 (36.0)	90.7 (20.9)	66.1 (37.2)
Change in HR			
0 Weeks	21.0 (6.1)	24.4 (10.9)	19.2 (11.1)
8 Weeks	21.3 (9.7)	15.9 (10.7)	25.2 (17.4)
Depression measures			
BDI			
0 Weeks	25.3 (12.6)	25.3 (7.7)	20.1 (12.6)
8 Weeks	14.7 (14.1)	13.4 (5.7)	13.0 (11.9)
26 Weeks	15.2 (10.1)	4.7 (4.4)	13.4 (14.1)
Zung			
0 Weeks	66.9 (13.1)	68.4 (9.5)	63.5 (13.6)
8 Weeks	53.7 (18.3)	51.8 (10.2)	51.4 (16.3)
26 Weeks	56.9 (14.8)	40.9 (7.0)	55.0 (16.5)
FQ-Depression			
0 Weeks	6.6 (2.5)	5.6 (2.2)	3.9 (2.6)
8 Weeks	3.4 (3.3)	2.6 (1.9)	3.0 (2.2)
26 Weeks	3.9 (2.7)	1.1 (1.4)	2.6 (2.4)
Diary measures			
Excursions from home			
0 Weeks	1.7 (1.2)	1.6 (1.4)	2.0 (2.8)
8 Weeks	1.0 (0.87)	3.7 (3.5)	4.4 (3.6)
26 Weeks	4.3 (2.6)	5.0 (5.0)	2.2 (2.4)
Panic frequency/week			
0 Weeks	1.8 (1.8)	1.9 (2.2)	3.4 (4.9)
8 Weeks	0.75 (1.0)	0.60 (1.1)	0.78 (0.74)
26 Weeks	2.8 (3.5)	0.1 (0.3)	2.3 (3.2)

improvements from before to after treatment on all measures with the exception of HR; and those in the Placebo + exposure group showed significant improvements on all measures except HR, panic and two of the indices of depression. *S*s receiving imipramine with antiexposure instructions (Group 1) showed significant improvement for anticipated anxiety, performance anxiety during the BAT walk and dysphoric mood.

Between-group comparisons of the adjusted posttest means demonstrated that Imipramine + exposure group was significantly superior to the Imipramine-no exposure group on Main Phobia (FQ), Agoraphobia (FQ), Total Phobia (FQ), approach behavior, anticipated anxiety, performance anxiety and self-efficacy during the BAT walk, as well as on the number of unaccompanied excursions from home. Comparisons between Imipramine + exposure and Placebo + exposure groups yielded a consistent trend toward more improvement for those receiving

Table 3. Significance of overall treatment effects, between-group comparisons and within group changes for each measure at the 8-week assessment[a,b]

Variable	Treatment effects (F-test)	Between-group comparisons: Group 1 vs Group 2 (t-test)	Between-group comparisons: Group 1 vs Group 3 (t-test)	Between-group comparisons: Group 2 vs Group 3 (t-test)	Within-group comparisons: Group 1 ($N = 10$) (t-test)	Within-group comparisons: Group 2 ($N = 10$) (t-test)	Within-group comparisons: Group 3 ($N = 9$) (t-test)
Fear Questionnaire (FQ)							
Main Phobia	8.02**	3.99***	2.45**	1.43†	1.15	7.76***	4.97***
Agoraphobia	5.33**	3.27**	1.75*	1.55†	0.78	5.39***	7.18***
Total Phobia	5.31*	3.09**	0.52	2.44**	1.45	4.65***	4.87***
Test walk measures							
Approach behavior	3.26*	2.54**	1.48†	0.75	1.51	5.75***	4.49**
Change in HR	1.19	0.93	0.63	1.54†	0.12	1.65	0.84
Anticipatory anxiety	4.62*	3.04**	1.68*	1.19	4.02**	8.71***	6.40***
Performance anxiety	3.96*	2.81**	1.35†	1.36†	3.13*	10.81***	8.14***
Self-efficacy strength	3.56*	2.67**	1.20	1.42†	1.94	5.91***	4.11**
Depression							
BDI	0.16	0.31	0.27	0.56	3.00*	4.75***	1.76
Zung	0.21	0.55	0.05	0.57	4.03**	3.96**	2.61*
FQ-Depression	0.92	0.23	1.03	1.31	3.40**	4.11**	1.65
Diary measures							
Excursions	4.16*	2.35*	2.64**	0.36	1.51	2.47*	2.32*
Panic attacks	0.06	0.33	0.12	0.21	1.37	2.75*	1.66

[a]Group 1 = Imipramine-no exposure; Group 2 = Imipramine + exposure; Group 3 = Placebo + exposure.
[b]All between-group comparisons are one-tailed; all other analyses are two-tailed.
†$P < 0.10$; *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

imipramine which reached statistical significance on all three FQ subscales, HR, performance anxiety during the BAT walk and self-efficacy. No significant differences were found between the groups on panic attack frequency as measured by panic diaries or presence of panic as measured by the PQ. The Placebo + exposure condition proved superior to the Imipramine-no exposure

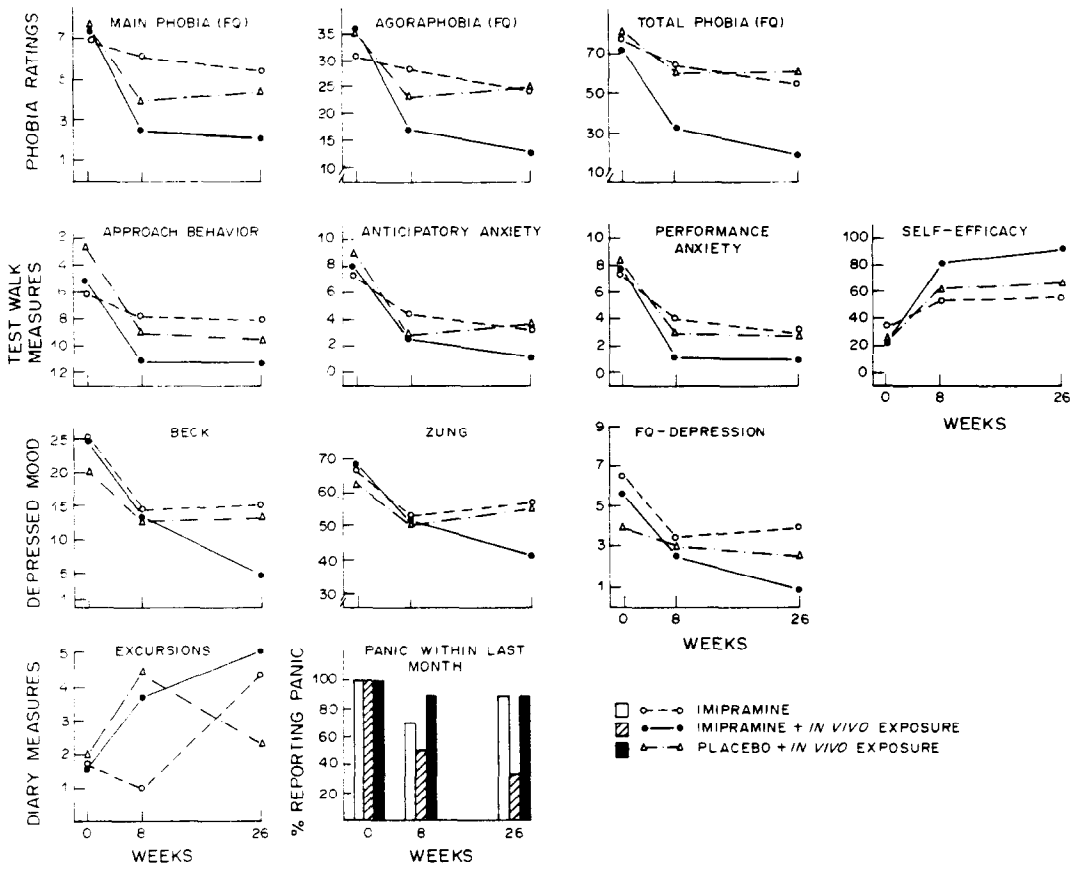

Fig. 1

condition on Main Phobia (FQ), Agoraphobia (FQ), approach behavior anticipated and performance anxiety on the BAT walk and unaccompanied excursions from home (see Table 3).

Twenty-six week assessment

A summary of the statistical findings at the 26-week assessment is presented in Table 4. *S*s assigned to Imipramine + exposure (Group 2) showed significant improvement from 0 to 26 weeks on all 12 continuous outcome variables, while those assigned to Placebo + exposure (Group 3) showed improvement on all outcome measures except panic attacks, excursions from home unaccompanied and one index of dysphoric mood (FQ-Depression). Those *S*s assigned to Group 1 (Imipramine-no exposure) and who from week 9 were given general encouragement to face their feared situations, showed significant improvement from 0 and 26 weeks on Total Phobia (FQ), anticipated anxiety, performance anxiety during the BAT walk, each of the three indices of depression and unaccompanied excursions from home. However, only the *S*s assigned to the Imipramine + exposure condition demonstrated significant reductions in the presence of panic attacks within the last month ($\chi^2 = 11.97$, $P = 0.02$), within the last week ($\chi^2 = 13.77$, $P = 0.008$) and panic almost every day ($\chi^2 = 11.04$, $P = 0.03$). Moreover, the combined treatment demonstrated further improvements from the 8- to 26-week assessment on agoraphobia (FQ, $t = 2.15$, $P < 0.10$), depression (FQ, $t = 1.90$, $P < 0.10$; BDI, $t = 3.57$, $P < 0.01$; Zung, $t = 3.67$, $P < 0.01$) and anticipated anxiety ($t = 2.45$, $P < 0.05$). Whereas *S*s assigned to the Placebo + exposure group showed no further gains from 8 to 26 weeks, and those assigned to Group 1 showed significant improvement from 8 to 26 weeks on unaccompanied excursions ($t = 5.29$, $P < 0.001$).

Between-group comparisons at the 26-week assessment revealed a consistent superiority of the Imipramine + exposure condition over either the Placebo + exposure or Imipramine-no exposure conditions (see Table 4). The combined treatment achieved significantly greater treatment gains than the Imipramine-no exposure group on all continuous outcome measures except unaccompanied excursions, and significantly greater improvement than the Placebo + exposure group on all continuous outcome measures except the BAT walk. Imipramine + exposure yielded a significantly greater reduction in the presence of panic within the last month as compared to the Placebo + exposure group ($\chi^2 = 9.71$, $P < 0.05$).

Contrary to the findings at the 8-week assessment, comparisons between Groups 1 and 3 (Imipramine-no exposure vs Placebo + exposure) yielded few differences at the 26-week assessment. *S*s receiving imipramine without exposure (Group 1) reported significantly more unaccompanied excursions from home than *S*s receiving placebo with exposure (Group 3). On the other hand, *S*s assigned to Placebo + exposure were significantly less phobic on the Main Phobia scale (FQ) compared to Imipramine-no exposure *S*s. No other differences were significant (see Table 4).

Table 4. Significance of treatment effects, intergroup differences and within-group changes for each measure at the 26-week assessment[a,b]

		Intergroup comparisons			Within-group comparisons (0–26 weeks)		
Variable	Treatment effects (*F*-test)	Group 1 vs Group 2 (*t*-test)	Group 1 vs Group 3 (*t*-test)	Group 2 vs Group 3 (*t*-test)	Group 1 (*N* = 9) (*t*-test)	Group 2 (*N* = 9) (*t*-test)	Group 3 (*N* = 9) (*t*-test)
Fear Questionnaire (FQ)							
Main Phobia	10.08***	4.43***	2.05*	2.72**	2.22	9.64***	4.59**
Agoraphobia	6.57**	2.98**	0.10	3.28**	1.90	7.98***	3.51**
Total Phobia	14.10***	4.26***	0.73	4.88***	3.30*	6.14***	2.99*
Test walk measures							
Approach behavior	2.70*	2.14*	0.85	1.04	1.32	5.31***	4.20**
Anticipatory anxiety	3.21	2.24*	0.21	2.02*	4.54**	9.90***	5.85***
Performance anxiety	2.37	2.12*	0.66	1.42†	5.43***	14.22***	5.13***
Self-efficacy strength	4.09*	2.84**	1.20	1.68*	1.36	9.99***	3.77**
Depression							
BDI	5.47**	2.96**	0.04	2.82**	4.29**	3.59**	3.64**
Zung	9.12***	3.65***	0.17	3.75***	3.13*	6.56***	3.24*
FQ-Depression	5.74**	2.91**	0.07	2.84**	3.60**	6.62***	2.07
Diary measures							
Excursions	1.82	0.41	1.41†	1.82*	3.14*	2.98*	0.32
Panic attacks	3.58*	2.67**	1.25	1.36†	0.96	2.30*	1.89

[a]Group 1 = Imipramine-no exposure; Group 2 = Imipramine + exposure; Group 3 = Placebo + exposure.
[b]All between-group comparisons are one-tailed; all other analyses are two-tailed.
†$P < 0.10$; *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

DISCUSSION

Results of the present investigation lend strong support for the combined use of imipramine and intensive exposure in the treatment of agoraphobia. *S*s' response to the combined treatment was superior to either exposure without imipramine, or imipramine without exposure, on a wide array of symptom indices including avoidance behavior, phobic anxiety, anticipated anxiety, panic and dysphoric mood. Of particular theoretical interest was the finding that the combined treatment was the only condition to show a significant reduction in report panic attacks at the 26-week assessment. Moreover, it was also the only condition to show a further reduction in dysphoric mood from the 8- to 26-week assessments. This favorable response to the combined use of imipramine and exposure is consistent with the findings reported by Zitrin *et al.* (1983) and Sheehan *et al.* (1980), showing that imipramine is superior to placebo when combined with a psychological treatment encouraging exposure to phobic situations. However, it differs from the study reported by Marks *et al.* (1983) who found no synergistic effect. This may be due to two reasons. First, the *S*s in the latter study showed lower initial scores on measures of depression than those in the present study or in the studies of Zitrin *et al.* (1978, 1980) or Sheehan *et al.* (1980). Second, the medication dosage used in that study was markedly lower than that used in our or other studies demonstrating an additive effect of imipramine to exposure.

One aim of the present study was to examine the effectiveness of imipramine in the absence of exposure and hence shed light on the mechanism of action of this drug in the treatment of agoraphobia with panic. To do this we used antiexposure instructions to control for the effects of inadvertent self-exposure. The used of antiexposure instructions deserves comment. Although it is clear that no clinician would consider using such instructions, their use helped us separate the effects of imipramine and exposure therapy. Could such instructions have been antitherapeutic, encouraging a passive attitude in *S*s assigned to this group? While we cannot entirely discount this possibility, two considerations make this explanation unlikely. First, post-study interviews revealed that *S*s perceived such instructions to be credible and consistent with the widely used prescription to allow medication time to work. Second, in the second phase of the study, despite the removal of such instructions, no further benefit upon panic attacks was observed in this group.

Results from the 8-week assessment demonstrated that imipramine given in conjunction with antiexposure instructions resulted in reductions in depression and in anticipated anxiety. While some reduction in panic attack frequency occurred (see Table 2), It was not statistically significant, and 70% of *S*s reported an attack within the last month and 40% an attack within the last week (see Table 5). Even when *S*s were encouraged to confront their feared situations in the second phase of the study, albeit without specific exposure treatment, no further reduction in panic was found.

These data fail to support the position that imipramine's mechanism of action is the blocking of panic attacks (Klein, 1967; Zitrin *et al.*, 1978). Nor do they suggest that exposure treatment alone produces a beneficial effect upon panic. Only *S*s who were given the combined therapy showed significant reductions in panic attacks. It should be noted, however, that this test of the panic suppression hypothesis was weakened by two limitations of the study, namely the small sample size, and the failure to include a Placebo + antiexposure condition. A further possible limitation was the setting of the maximum dose of imipramine at 300 mg/day. It is possible that higher dosage in the Imipramine-no exposure group would have revealed an antipanic effect.

Marks (1983) has proposed an alternative mechanism to account for the clinical effectiveness of imipramine. He contends that imipramine exerts a positive effect on agoraphobia mainly through its beneficial effect on depressed mood. However, our data fail to support this hypothesis since Imipramine-no exposure *S*s displayed marked reductions in depressed mood with little improvement on phobic avoidance or phobic anxiety. Our findings suggest, therefore, that imipramine and exposure therapy have either an additive or interactive effect upon panic and phobic behavior. An alternative hypothesis concerning the mode of action of antidepressants in treating agoraphobia has been put forth by Telch *et al.* (1983). In brief, it was suggested that the alteration in dysphoric mood brought about by the drug, affects the process by which exposure therapy achieves its results. Two possible pathways are considered. First, alleviation of depressed mood may increase the likelihood that agoraphobics will engage in self-directed exposure. Second, alleviation of dysphoric mood may help correct any devaluation of self-observed gains during exposure therapy, thus promoting an increase in self-efficacy. The postulated dysphoria–efficacy hypothesis might be tested

by employing a nonpharmacological method for alleviating dysphoric mood (e.g. Beck's cognitive therapy) both alone and in combination with an exposure treatment. These two conditions could be compared to an exposure only condition. To the extent that the alternative depression treatment is effective in reducing agoraphobics' dysphoric mood, our hypothesis would predict that the combined treatment approach would result in higher self-efficacy and significantly more improvement on phobia outcome measures.

The favorable results from imipramine found in the present study should be interpreted in the light of several issues. First, a substantial number of agoraphobics are fearful of taking medications. Nearly 20% of the individuals who responded to our recruitment notices were unwilling to undergo pharmacological treatment and thus were not accepted into the study. Second, of those willing to take imipramine, a sizeable number cannot tolerate the drug's side effects and thus drop out. Dropout rates from the antidepressant trials published to date consistently average between 35 and 40%, well above the mean of 10% for drug-free behavioral treatment (Mavissakalian and Barlow, 1981). However, the combination of imipramine with an exposure treatment appears to offer added benefit for those agoraphobics who are willing to take medication and who can tolerate the drug's side effects.

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