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COMPARISON OF FLUVOXAMINE, IMIPRAMINE, AND PLACEBO IN THE TREATMENT OF OUTPATIENTS WITH PANIC DISORDER

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Fluvoxamine and imipramine were compared to placebo in an 8-week double-blind randomized multicentre trial comprising of 148 outpatients between 19 and 57 years of age (mean: 35) with a DSM-III-R diagnosis of Panic Disorder. Mean daily dose at endpoint was: fluvoxamine, 171.4 mg; imipramine 164.7 mg. The mean number of panic attacks per week at baseline were 10.9, 14.4 and 6.5 for fluvoxamine, imipramine and placebo, respectively. The intent-to-treat analysis of the change from baseline (difference score) of the number of panic attacks at endpoint revealed: a difference of 3.3 attacks (95% CI: –0.3, 6.8) between fluvoxamine and placebo and a difference of 6.0 attacks (95% CI: 1.5, 10.5) between imipramine and placebo. Treatment was stopped prematurely in 31 (62%) on fluvoxamine, 16 (33%) on imipramine and 29 (58%) on placebo. The number of patients withdrawing due to intolerance was 13 (26%) for fluvoxamine, 10 (21%) for imipramine and 4 (8%) for placebo. The number of patients withdrawing due to lack of efficacy was 10 (20%) for fluvoxamine, 4 (8%) for imipramine and 12 (24%) for placebo. Overall, this study demonstrated that fluvoxamine was not effective in the treatment of panic disorder but did show a strong effect for imipramine. A chance occurrence of significantly fewer number of panic attacks in the placebo group at baseline may limit the conclusions of this study. Anxiety 2:192–198 (1996). © *1996 Wiley-Liss, Inc.*

Key words: *panic attacks, tricyclic, SSRI, placebo-controlled trial, confidence intervals*

INTRODUCTION

Panic disorder affects between 2% and 5% of the general population (Regier et al., 1990; Liebowitz and Gorman, 1986). The characteristic feature of panic disorder is a series of unexpected symptoms (attacks) that occur during normal routine activities. These may include dyspnoea, palpitations, chest pain, dizziness, vertigo, sensations of otherworldliness, hot or cold flashes, sweating, faintness and fear of dying.

Previous clinical studies have demonstrated that tricyclic antidepressants are effective in the treatment of panic disorder. For example, clomipramine (Gloger et al., 1981; Den Boer et al., 1987) and imipramine (Zitrin et al., 1983) have been observed to decrease the number of panic attacks and reduce phobic avoidance in patients diagnosed with panic disorder. Although the tricyclic antidepressants are efficacious, they are problematic because their activity on noradrenergic and cholinergic systems cause unwanted side effects including sedation, hypotension and constipation.

The development of a new class of antidepressants, the serotonin selective reuptake inhibitors (SSRIs), offer a distinct advantage over the tricyclic antidepressants because they are generally devoid of sedative, cardiovascular and anticholinergic side effects. Fluvoxamine belongs to a new class of compounds, the 2-aminoethyl oximethers of aralkylketones (Claassen, 1983), and is a potent serotonin reuptake inhibitor. It is structurally unrelated to the tricyclic and polycyclic antidepressants and has a relatively low affinity for noradrenergic

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and cholinergic receptors in comparison to tricyclic antidepressant compounds. Thus, fluvoxamine should offer potential advantages to patients with panic attacks and preliminary evidence suggests that fluvoxamine is effective in reducing the number of panic attacks in patients with panic disorder (Den Boer and Westenberg, 1988, 1990; Hoehn-Saric et al., 1993).

The purpose of the present trial was to assess the relative efficacy, tolerability and safety of fluvoxamine, imipramine and placebo in outpatients with panic disorder.

MATERIALS AND METHODS

STUDY DESIGN

A double-blind, randomized, parallel group, multicentre (Montreal, Ottawa, Hamilton) trial comparing the safety, tolerability and efficacy of fluvoxamine, imipramine and placebo in outpatients with panic disorder was carried out. A 1-week placebo run-in period preceded the double-blind phase of the study. Patients who did not experience a panic attack during the 1-week placebo run-in period were allowed to have their run-in period extended for a second week. The run-in period did not exceed 2 weeks. All patients completing this run-in period were randomized to one of three treatment groups (fluvoxamine, imipramine, or placebo) for the 8-week double-blind phase. Each patient signed a written, informed consent prior to entry into the study. Study procedures and consent form were approved by each institutional ethics committee and the Canadian Health Protection Branch prior to initiation. A sample size of 50 patients per treatment group was based on an estimated response rate of 60% for the active treatments and 25% for placebo (2-tail test; α=0.05; β=0.20).

SUBJECTS

Outpatients between 18 and 65 years of age with a principal diagnosis of Panic Disorder without Agoraphobia (300.01) or Panic Disorder with Agoraphobia (300.21), as defined by DSM-III-R, were eligible for the study. Patients were required to have at least four panic attacks in the 4 weeks prior to the initial assessment or at least one attack followed by a period of at least a month of persistent fear of having another attack. In addition, patients were required to be in good physical health and able to keep weekly appointments. Patients were excluded if they had a history of major mental illness including bipolar disorder, organic brain syndrome, schizophrenia or other psychotic disorders, were considered suicidal, had a history of substance dependence, epilepsy or seizures, or received electroconvulsive therapy within the past six months. Patients were also excluded if they received either fluoxetine or monoamine oxidase inhibitors within 5 or 2 weeks, respectively, of entry into the placebo run-in period, or, if during the placebo run-in period, they experienced benzodiazepine withdrawal or did not have at least one panic attack.

TREATMENT REGIMEN

The study medication was in the form of identically appearing capsules each containing either placebo, 50 mg of fluvoxamine or 50 mg of imipramine. The medication was dispensed in bottles on a weekly basis. During the placebo run-in period, patients were instructed to take one capsule at bedtime for 1 week. Extra placebo medication was available to allow for an extension of the run-in period to a maximum of 2 weeks. During the double-blind phase of the study, medication was dispensed at weekly intervals and the patient was instructed to take one capsule at bedtime each night for 1 week. The dosage was increased to two capsules at bedtime for the second week and three capsules at bedtime for the third week, unless contraindicated by side effects. If necessary, the dosage was further increased by one capsule per week to a maximum of 6 capsules. Dosage increases above 3 capsules per day were taken in divided doses.

Oxazepam up to 60 mg daily or chloral hydrate up to 2,000 mg daily were permitted both during the placebo run-in and the first 4 weeks of the double-blind period. All other psychotropic drugs were not permitted during the study.

ASSESSMENTS

At the first visit, the psychiatric, medical and medication history of each patient was documented and the DSM-III-R criteria for Panic Disorder, the Sheehan Panic and Anticipatory Anxiety Scale (SPAAS; Sheehan, 1986; modified to DSM-III-R) and Clinical Global Impressions (CGI; Guy, 1976) were completed. Anticipatory anxiety was assessed on the SPAAS as the percentage of time spent worrying about having a panic attack or going into a situation likely to bring on an attack. The intensity of the anticipatory anxiety was rated on an 11-point scale ("0" none, "10" maximum).

Upon entry into the double-blind phase of the study, patients were assessed on a weekly basis using the SPAAS, Clinical Anxiety Scale (Snaith et al., 1982), Montgomery-Asberg Depression Rating Scale (Montgomery and Åsberg, 1979), Sheehan Disability Scale (Sheehan, 1986), Sheehan Panic Attack Diary (Sheehan, 1986; modified to DSM-III-R), Phobia Scale (Marks-Sheehan; Marks and Mathews, 1979) and Hopkins Symptom Checklist (Derogatis et al., 1974). Additional assessments included the Clinicians' Global Impression of Severity (CGIS), Improvement (CGII), Efficacy (CGIE) and Side Effects (CGISE). The CGIS was assessed on a 7-point ordinal scale ranging from normal (1) to extremely ill (7); the CGII was assessed on a 7-point ordinal scale ranging from very much improved (1) to very much worse (7); the CGIE was assessed on a 4-point ordinal scale ranging from marked improvement (1) to unchanged or worse (4); the CGISE was assessed on a 4-point ordinal scale ranging from no side effects (1) to outweighs therapeutic effect (4).

During the single-blind and double-blind phases of

the study, patients were required to maintain a daily diary of the number, duration and intensity (on a scale of 1 to 10) of their panic attacks using the Sheehan Panic Attack Diary (modified to DSM-III-R). Adverse events were documented on a weekly basis and the frequency, severity, and duration of each event was recorded. Vital signs were taken weekly and included measurements of blood pressure, heart rate, respiration, temperature and weight. At both the beginning and end of treatment, patients were given a physical examination, electrocardiogram (ECG), and a battery of laboratory tests including blood and urine.

DATA ANALYSIS

Two patient samples were identified for analyses and reporting purposes prior to unblinding: an all-patient analysis and an intent-to-treat (ITT) analysis. The all-patient sample was defined as those randomized to double-blind treatment and who provided at least some drug safety and tolerance data. The primary safety variable was the incidence of treatment emergent signs and symptoms (TESS; the appearance for the first time, or those which worsened if present at baseline). Laboratory tests, vital signs and electrocardiographic data were assessed and values outside the normal range were analyzed.

The main efficacy analysis of the study was based on the last observation carried forward (LOCF) of the ITT sample. Patients were included in the ITT sample if they entered the double-blind phase of the study, took at least one dose of study drug, and provided at least some valid (efficacy) data.

The primary "panic" efficacy variables were the percentage of patients free of panic attacks at endpoint, the number of panic attacks per week, the number of limited symptom attacks per week and the percentage and intensity of anticipatory anxiety. The primary "global measures" efficacy variables were the CGI severity, CGI improvement, CGI efficacy, CAS and MADRS total scores.

A priori, it was decided that separate analyses of variance, repeated measures model be used to compare each active drug to placebo. Each analyses was carried out to determine group and time main effects and group by time interactions. In addition, individual analyses of variance at each week were carried out. Comparisons by Chi-square and Fisher's exact test were carried out for categorical data. Finally, 95% confidence intervals (95CI) of differences between means were calculated.

The Panic Factor (a composite measure of the number of full panic attacks times the intensity of the attack times the duration) has been proposed as a more sensitive measure of treatment-specific improvement (Pecknold et al., 1993). The Panic Factor was found to violate usual parametric assumptions and was analyzed by the Mann-Whitney U test, corrected for ties. Statistical analysis was carried out using the SAS and SPSS statistical packages.

RESULTS

In total, 168 patients entered the single-blind placebo run-in period. Twenty patients were discontinued prior to randomization to the double-blind period; therefore, 148 patients were included in the all-patient sample for reporting safety and tolerability to treatments. Sixteen patients were excluded (from the intent-to-treat sample) before unblinding due to protocol violations or invalid data.

The demographic data were similar for the three treatment groups; males and females were equally represented (Table 1). The mean duration of treatment for the ITT sample was 37 days for fluvoxamine, 49 days for imipramine and 41 days for placebo. Table 2 presents the reasons for premature withdrawal from the study overall. Treatment was stopped prematurely in 31 (62%) on fluvoxamine, 16 (33%) on imipramine, and 29 (58%) on placebo. The number of patients withdrawing due to intolerance was 13 (26%) for fluvoxamine, 10 (21%) for imipramine, and 4 (8%) for placebo. The number of patients withdrawing due to lack of efficacy was 10 (20%) for fluvoxamine, 4 (8%) for imipramine, and 12 (24%) for placebo. The difference in drop out rates between fluvoxamine and placebo was 4% (95% CI: -15%, 23%), Chi-square=0.17, ns. The difference between imipramine and placebo was 25% (95% CI: 6%, 44%), Chi-square=5.92, $p < 0.05$.

The mean daily dose of medication at termination of study was 171.4 mg for fluvoxamine-treated patients, 164.7 mg for imipramine-treated patients and four capsules for patients in the placebo group. Overall, the majority of patients received prior or concurrent medication but there was no difference between the three treatment groups (fluvoxamine: 80%, imipramine: 81%, placebo: 90%).

SAFETY

All-Patient Sample. One hundred and forty-eight patients (50 fluvoxamine, 48 imipramine, 50 placebo) were randomized to double-blind treatment and provided at least some postbaseline safety or tolerance data. For patients receiving fluvoxamine, 90% reported treatment emergent signs and symptoms. The most frequently occurring complaints were nausea (62%), headache (34%), somnolence (34%), dizziness (32%), dry mouth and constipation (26% each). Thirteen patients were discontinued for adverse experiences and there were no serious adverse events.

For the imipramine group, 100% of the patients reported treatment emergent events. The most frequently reported events were dry mouth (85%), headache (42%), constipation (40%), dizziness (40%), nausea (29%), and sweating (27%). Ten patients withdrew prematurely due to adverse experiences. There were no serious adverse events.

In the placebo group, 90% of the patients reported treatment emergent signs and symptoms. The most commonly reported events were headache (42%), nau-

TABLE 1. Demographic data

		Treatment group			
		Fluvoxamine	Imipramine	Placebo	Total
Sex					
Male	N (%)	19 (44)	21 (50)	26 (55)	66
Female	N (%)	24 (56)	21 (50)	21 (45)	66
Age (yrs)	Mean	34.5	34.5	35.5	34.9
	Range	19–57	21–52	21–52	
DSM-III-R					
300.01	N (%)	14 (33)	11 (26)	14 (30)	39
300.21	N (%)	29 (67)	31 (74)	33 (70)	93
Course of illness					
One episode	N (%)	13 (30)	14 (33)	16 (34)	43
Several episodes	N (%)	9 (21)	9 (21)	12 (26)	30
Several years	N (%)	21 (49)	19 (45)	19 (40)	59
Duration of illness (yrs)	Mean	9.0	7.6	7.0	7.8

sea (32%), dry mouth (24%), constipation (22%), and dizziness (20%). Four patients were discontinued for adverse experiences.

Analysis of variance, repeated measures model, of the CGI Side Effect scores between fluvoxamine and placebo revealed a significant time effect overall ($F=3.62$, $p < 0.001$) and a significant difference between the two groups ($F=5.45$, $p=0.02$). Similarly, the analysis between imipramine and placebo revealed a significant time effect ($F=5.07$, $p < 0.0001$) and a significant difference between the two groups ($F=16.1$, $p=0.0001$). The interaction terms for both above analyses were not significant. Analyses of variance by week showed that fluvoxamine was tolerated significantly less well at weeks 1, 5 and 8 ($p=0.03$ to $p=0.005$), with a trend at weeks 3, 4 and 6 ($p < 0.1$) compared to placebo. Analyses of variance by week showed that imipramine was tolerated significantly less well at every week from week 1 to 8 ($p=0.01$ to $p=0.0001$) compared to placebo. The mean difference at week 8 (LOCF) between fluvoxamine and placebo-treated patients was 0.39 (95% CI: 0.04, 0.74) and between imipramine and placebo-treated patients was 0.47 (95% CI: 0.14, 0.79).

TABLE 2. Reasons for premature withdrawal before and after week 4, patients

	Fluvoxamine (n=50)	Imipramine (n=48)	Placebo (n=50)
Intolerance	12	7	3
Inefficacy	1	1	2
Protocol violation	2	0	3
Others	4	1	6
Total	19	9	14
Mandatory withdrawal of oxazepam and chloral hydrate at week 4			
Intolerance	1	3	1
Inefficacy	9	3	10
Protocol violation	1	0	2
Others	1	1	2
	12	7	15
Total	31	16	29

No consistent effects were noted in the electrocardiograms or laboratory test results. Most values outside the lab reference ranges at the end of study had also been elevated at baseline, with the exception of elevated alanine aminotransferase levels in one fluvoxamine and a few imipramine-treated patients. One placebo-treated patient was discontinued because of elevated liver enzymes. There were significantly more imipramine-treated patients (n=11) with increased heart rate than fluvoxamine or placebo-treated patients (n=1 each).

EFFICACY

Of the 132 patients in the intent-to-treat sample, treatment was stopped prematurely in 65 patients; 25 (58%) on fluvoxamine, 13 (31%) on imipramine and 27 (57%) on placebo. The difference in drop out rates between fluvoxamine and placebo was 1% (95% CI: -20%, 21%), Chi-square=0.01, ns. The difference between imipramine and placebo was 27% (95% CI: 7%, 46%), Chi-square=6.34, $p < 0.05$. Table 3 presents the mean scores at baseline and week 8 (LOCF) of the main efficacy variables of the study and the 95% confidence intervals around the differences between each active treatment group and placebo.

Responders. The percentage of patients free of panic attacks at week 8 (LOCF) was 37% for fluvoxamine, 64% for imipramine and 47% for placebo. The difference between fluvoxamine and placebo was -10% (95% CI: -30%, 11%), Chi-square=0.88, ns. The differences between imipramine and placebo was 18% (95% CI: -3%, 38%), Chi-square=2.77, $p=0.10$.

Number of Panic Attacks. Analysis of variance revealed that fluvoxamine-treated patients had significantly

TABLE 3. Mean scores at week 8 (LOCF) and differences between means of three treatment groups

	Fluvoxamine (n=43)		Imipramine (n=42)		Placebo (n=47)		Difference,[a] 95% CI, between groups: Fluvoxamine vs. placebo			Imipramine vs. placebo		
	Baseline	Endpoint	Baseline	Endpoint	Baseline	Endpoint	Mean	95%	CI	Mean	95%	CI
Full panic attacks/week[b]	10.9	5.8	10.3	2.5	6.5	4.6	3.3	−0.3,	6.8	6.0	1.5,	10.5
Limited panic attacks/week[b]	11.9	6.7	14.1	6.4	11.3	8.0	1.9	−4.1,	7.8	4.4	−1.8,	10.5
Anticipatory anxiety (%)	45.7	35.7	38.0	18.6	38.1	35.0	−0.6	−12.7,	11.5	16.4	5.9,	26.9
Anticipatory intensity	5.0	4.1	4.7	3.0	4.1	3.7	−0.4	−1.4,	0.7	0.8	−0.2,	1.76
CGI severity	4.2	3.4	4.1	2.6	4.2	3.3	−0.2	−0.8,	0.4	0.6	0.1,	1.1
CGI improvement	3.8	3.0	3.4	2.0	3.4	2.8	−0.2	−0.9,	0.4	0.7	0.1,	1.3
CGI efficacy	3.4	2.6	3.2	1.9	3.2	2.6	−0.1	−0.6,	0.5	0.7	0.2,	1.2
CAS	13.4	9.0	13.0	5.9	12.6	9.0	0.0	−2.5,	2.6	3.1	0.8,	5.5
MADRS	17.0	11.6	16.9	7.4	16.0	11.2	−0.4	−4.1,	3.3	3.8	0.1,	7.6

[a] *Differences favoring active drug.*
[b] *Change from baseline; see text for abbreviations and description of scales.*

more panic attacks at baseline (mean ± S.D.=10.9 ± 9.8) than the placebo-treated group (mean ± S.D.=6.4 ± 6.6; F=6.4; p=0.013); additionally, imipramine-treated patients (mean ± S.D.=10.3 ± 14.4) tended to have more panic attacks than placebo-treated patients (F=2.7; p=0.10). Since patients in both active treatment groups had more panic attacks at baseline than those in the placebo group and since no obvious errors in randomization could be detected, an unfortunate chance occurrence seems likely. To statistically adjust for baseline difference in number of panic attacks, a change score (baseline score minus weekly score) was calculated for each week for the three treatment groups.

Analysis of variance, repeated measures model, of the change from baseline number of full panic attacks between fluvoxamine and placebo revealed a significant time effect overall (F=4.40, $p < 0.0001$), and a trend towards a group by time interaction (F=1.92, p=0.064). Analyses of variance of the weekly change scores revealed a trend in favour of fluvoxamine from week 4 to 8 (p=0.06 to p=0.09; week 6 difference p=0.04). The analysis of variance between imipramine and placebo revealed a significant time effect (F=3.31, $p < 0.002$), a significant difference between the two groups (F=7.54, p=0.007) and a significant group by time interaction (F=2.54, p=0.014). Analyses of variance of the weekly change scores revealed a statistically significant difference in favour of imipramine from weeks 2, 3, 5 to 8 (p=0.04 to p=0.009), though not at week 4 (p=0.50).

Anticipatory Anxiety (Percent). At baseline, the mean ± S.D. levels of anticipatory anxiety on SPAAS for the three groups were not significantly different: fluvoxamine, 45.5 ± 29.1%; imipramine 48.4 ± 25.8%; placebo 44.0 ± 27.3%. Analysis of variance, repeated measures model, of the anticipatory anxiety scores (percent) between fluvoxamine and placebo revealed only a significant time effect (F=3.10, p=0.003) with no difference between the two groups or group by time interaction. The analysis of the anticipatory anxiety scores between imipramine and placebo revealed a significant time effect (F=8.77, p=0.0001), a significant difference between the two groups (F=8.1, p=0.006) and a significant interaction (F=5.8, p=0.0001). Analyses of variance of anticipatory anxiety by week revealed significant differences in favour of imipramine from week 3 to 8 (p=0.002 to p=0.008).

Intensity of Anticipatory Anxiety. At baseline, the mean ± S.D. levels of intensity of anticipatory anxiety scores on SPAAS for the three groups were not significantly different: fluvoxamine 5.5 ± 2.1; imipramine 4.6 ± 1.9; placebo 4.7 ± 2.3. Analyses of variance, repeated measures model, of the intensity of anticipatory anxiety scores revealed a significant time effect overall and a significant group by time interaction between imipramine and placebo (F=4.3, p=0.0001). Over the course of the study, patients on imipramine decreased their anticipatory anxiety intensity levels more than those on placebo. Nevertheless, no significant differences were found in the weekly analyses between any of the usual comparisons, except for a difference (p=0.05) between fluvoxamine and placebo at week 1, which was considered spurious.

Panic Factor. The Mann-Whitney U test of the Panic Factor revealed a tendency towards a lower ranking of placebo-treated patients compared to fluvoxamine-treated patients at baseline (U=807.5, p=0.10), weeks 3 (U=776, p=0.05) and 4 (U=794.5, p=0.08), with a statistically significant difference at week 1 (U=755, p=0.04). Although imipramine had a tendency towards a higher ranking at week 1 (U=874.5, p=0.09) than placebo, the ranking was reversed at week 5 (U=785) and week 7 (U=795), both p=0.08.

A percentage change score (calculated as baseline factor score minus each weekly factor score, divided by baseline score times 100%) was analyzed to determine whether adjusting for initial values revealed any significant differences between groups. Significantly

greater improvement on this measure was revealed on the Mann-Whitney *U* test for placebo compared to fluvoxamine at week 1 (U=763.5, p=0.05). A tendency towards significantly greater change on this measure was revealed on the Mann-Whitney *U* test for imipramine compared to placebo at weeks 2 (U=781, p=0.09) and weeks 5 to 8 (U=763, p=0.05 to U=799, p=0.09).

Clinical Global Impression: Severity. At baseline, the mean ± S.D. CGI Severity scores for fluvoxamine (4.2 ± 1.0) and imipramine (4.1 ± 0.7) groups were not significantly different from placebo (4.2 ± 0.7). Analysis of variance, repeated measures model, of the CGI Severity scores between fluvoxamine and placebo revealed a significant time effect overall (F=21.3, p<0.0001) with no difference between the two groups (F=0.9, p=0.34) or interaction (F=0.76, p=0.64) effect. The analysis between imipramine and placebo revealed a significant time effect overall (F=44.53, p<0.0001) and a significant group by time interaction (F=3.40, p=0.001). Analyses of variance by week showed that the imipramine-treated patients were less severely ill at weeks 5, 7 and 8 (p=0.032 to p=0.047), with a trend at weeks 4 and 6 (p<0.1) compared to placebo.

Clinical Global Impression: Improvement. Analysis of variance, repeated measures model, of the CGI Improvement scores between fluvoxamine and placebo revealed a significant time effect overall (F=137.0, p<0.0001) with no difference between the two groups (F=.9, p=0.36) or group by time interaction (F=0.38, p=0.9) effect. The analyses between imipramine and placebo revealed a significant time effect overall (F=131.0, p<0.0001), a significant difference between the two groups (F=6.42, p=0.013) and a significant interaction (F=3.07, p=0.002). Analyses of variance by week between imipramine and placebo revealed significant differences at week 2, and weeks 4 to 8 (p=0.042 to p=0.005).

Clinical Global Impression: Efficacy. Analysis of CGI Efficacy followed the same pattern as the CGI Improvement (above), with significant differences between imipramine and placebo found from week 2 onwards (p=0.03 to p=0.003).

Clinical Anxiety Scale. At baseline, the mean ± S.D. CAS total scores for fluvoxamine (13.4 ± 4.1) and imipramine (13.0 ± 3.7) groups were not significantly different from placebo (12.6 ± 3.9). Analysis of variance, repeated measures model, of the CAS scores between fluvoxamine and placebo revealed a significant time effect overall (F=18.7, p<0.0001) with no difference between the two groups (F=0.02, p=0.9) or interaction (F=1.2, p=0.3) effect. The analysis between imipramine and placebo revealed a significant time effect (F=34.6, p<0.0001), significant group effect (F=3.9, p=0.05) and significant group by time interaction (F=5.7, p=0.0001). Analyses of variance by week showed that the imipramine patients were less anxious at weeks 5, 6, 7, and 8 (p=0.01 to p=0.003), with a trend at week 4 (p=0.07) compared to placebo.

Montgomery-Asberg Depression Rating Scale (MADRS). At baseline, the mean ± S.D. MADRS total scores for fluvoxamine (17.0 ± 7.3) and imipramine (16.9 ± 7.3) groups were not significantly different from placebo (16.0 ± 8.1). Analysis of variance, repeated measures model, of the MADRS scores between fluvoxamine and placebo revealed a significant time effect overall (F=11.3, p<0.0001) with no difference between the two groups (F=0.2, p=0.64) or interaction (F=1.1, p=0.34) effect. The analysis between imipramine and placebo revealed a significant time effect (F=24.6, p<0.0001) and significant group by time interaction (F=4.3, p=0.0001) but no significant group effect (F=1.8, p=0.18). Analyses of variance by week showed that the imipramine patients were significantly less depressed at week 5 and termination (p=0.05), with a trend at weeks 6 and 7 (p<0.08) compared to placebo.

DISCUSSION

At the end of treatment, fluvoxamine failed to produce a greater reduction in the number of full panic attacks compared with placebo. In addition, there was essentially no difference between fluvoxamine and placebo on Anticipatory Anxiety and Intensity, the Clinical Global Impression scales of Severity, Improvement and Efficacy or on overall measures of depression (MADRS) and anxiety (CAS). This result is in contrast to previous studies reporting a superior efficacy of fluvoxamine to placebo in the treatment of panic disorder (Den Boer and Westenberg, 1990; Hoehn-Saric et al., 1993).

There are several possible explanations for fluvoxamine's weak therapeutic effect. First, the patients in the fluvoxamine group had, by chance, significantly more mean panic attacks at baseline than patients in the placebo group. A second explanation is the requirement for patients to discontinue anxiolytic treatment after the fourth week of treatment. This may have contributed to a higher than expected drop out rate, especially in the fluvoxamine and placebo groups. In hindsight, a more suitable plan would have required patients to be weaned off benzodiazepines prior to the run-in period. Third, patients in the fluvoxamine group received, on average, 37 days of treatment, whereas patients in the imipramine group received 49 days of treatment. It is possible that fluvoxamine works more slowly than imipramine and requires more time to be effective. Fourth, it is possible that the average dose of fluvoxamine (171.4 mg/d) was not sufficient to display a strong therapeutic effect. Hoehn-Saric et al. (1993) found that fluvoxamine at a dose of 206.8 mg/d was significantly more effective than placebo in reducing the number of major panic attacks.

The present study supports the consistent finding in the literature that imipramine is more effective than placebo in the treatment of Panic Disorder (e.g.,

Rosenberg, 1993). Apart from the limited attack change score, all the 95% CI for the outcome variables are positive and in favour of imipramine compared to placebo. At the end of treatment, imipramine produced a significantly greater mean reduction in the number of full panic attacks. Additionally, imipramine was judged to be significantly improved on the CGI subscales of Severity, Improvement and Efficacy and on overall measures of depression (MADRS) and anxiety (CAS). Imipramine-treated patients spent significantly less time worrying about having a panic attack or going into a situation likely to bring on an attack, although the intensity of the worry was not significantly reduced.

In this study, the 47% placebo response rate, while higher than expected, is similar to a recently completed large study, reporting 48% (Pecknold et al., 1994). The number of patients free of panic attacks at end of study was higher for those in the imipramine-treated group compared to either fluvoxamine or placebo-treated groups.

In the present study, patients treated with imipramine reported adverse events more often than patients in either the fluvoxamine or placebo groups. A significantly higher proportion of imipramine-treated patients reported anticholinergic events compared with fluvoxamine or placebo. Patients in the fluvoxamine group reported nausea and somnolence more often than patients in the imipramine or placebo groups. Overall, at the end of treatment, physician ratings of the Clinical Global Impression of Side Effects showed that placebo-treated patients had a significantly higher level of tolerance compared with patients treated with both active drugs. Relatively fewer imipramine-treated patients withdrew for ineffectiveness, and fewer patients in the placebo group dropped out owing to adverse experiences.

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