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Panic Disorder. A Long-Term Treatment Study: Fluoxetine vs Imipramine

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This double-blind study evaluates the efficacy and tolerability of fluoxetine and imipramine in the acute and long-term treatment of panic disorder in 38 patients meeting DSM-IV criteria for panic disorder with or without agoraphobia. On the basis of HRSA mean scores evaluation, fluoxetine was found to be quicker than imipramine in reducing generalized anxiety at the end of the first week of treatment. However, through PASS and CGI mean scores evaluation, no statistically significant differences were found at any time in the efficacy of fluoxetine and imipramine on the total number of panic attacks, anticipatory anxiety or phobia severity. Fluoxetine has also turned out to be better tolerated than imipramine and to be effective at dosages low enough to avoid the event of an activation syndrome. Long-term evaluation has shown high rates of persistent remission with both drugs. Copyright © 1999 John Wiley & Sons, Ltd.

KEY WORDS — panic disorder; fluoxetine; imipramine; long-term treatment

INTRODUCTION

Panic disorder (PD) is a serious and disabling disease which exhibits a chronic and often fluctuating course. PD is also characterized by high rates of relapse after remission, irrespective of associated agoraphobia (Faravelli and Albanese, 1987; Keller *et al*., 1994). Due to the chronic course of PD, long-term treatment is generally necessary. Current treatment options for PD include benzodiazepines, tryciclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs). The use of benzodiazepines long-term is associated with several disadvantages, including sedation, reduced coordination, impaired cognition, and, most importantly, development of dependence with associated withdrawal symptoms (Salzman, 1993). TCAs have a delayed onset of action, cause side-effects, particularly anticholinergic ones, that compromise tolerance and compliance and, in some cases, cause a transient exacerbation of symptoms during the first two weeks of treatment (Westenberg, 1997). MAOIs have established efficacy as antipanic drugs (Bakish *et al*., 1993), although the body of research supporting this statement is not overwhelming (Jefferson, 1997).

More recent studies have been demonstrating the efficacy of serotonin selective reuptake inhibitors (SSRIs) and their better tolerability profile compared with classic TCAs (Hoehn-Saric *et al*., 1993; Oehrberg *et al*., 1995; Sheehan and Harnett-Sheehan, 1996). Paroxetine (Oehrberg *et al*., 1995; Steiner *et al*., 1995; Sheehan and Dunbar, 1996; Lecrubier *et al*., 1997) and fluvoxamine (Hoehn-Saric *et al*., 1993; Den Boer *et al*., 1987; Woods *et al*., 1994; Bakish *et al*., 1996) are the most extensively investigated SSRIs in PD treatment. Little is known however about the efficacy of fluoxetine; in fact, few previous open studies (Gorman *et al*., 1987; Schneier *et al*., 1990; Solyom *et al*., 1991; Louie *et al*., 1993) and only one double-blind study (Bystritsky *et al*., 1995) have been performed to evaluate the efficacy of fluoxetine in the treatment of PD.

The aim of the present study was to evaluate the efficacy and tolerability of fluoxetine in acute and long-term treatment of PD with or without agoraphobia compared with imipramine.

SUBJECTS AND METHODS

This was a double-blind study performed at the Institute of Psychiatry of the University of Bologna. The study followed the ethical guidelines

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laid down by the Declaration of Helsinki (with amendments) and was approved by the local Ethics Committee.

Patients eligible for inclusion could be either sex, aged between 18 and 65 years, suffering from PD with or without agoraphobia according to DSM-IV criteria. They had to give written informed consent to enter into the trial after a full discussion of the requirements and aims of the study. All patients had to be compliant and able to attend weekly visits. Exclusion criteria were: history of psychosis, current major depression, organic brain syndromes or significant neurological disorders, seizures, a known allergy to one of the study drugs, presence of clinically relevant cardiovascular, hepatic, renal or haematological diseases, alcohol or drug abuse, or narrow angle glaucoma. Women who were pregnant, lactating or of childbearing potential and not using adequate contraception were also excluded. Eighty-three consecutive patients were screened.

All patients meeting inclusion criteria entered a 10-day washout period during which physical health was determined through medical history, physical examination and laboratory testing. During the washout period the eligible patients had to experience at least one panic attack.

Before baseline evaluation, all patients should have discontinued treatment with any psychotropic drug (except benzodiazepines), for at least two weeks. MAOIs should have been discontinued for at least three weeks and fluoxetine or imipramine for at least two months. Oxazepam (up to a maximum daily dose of 30 mg) was the only permitted psychotropic drug during the washout phase and the first four weeks of double-blind treatment.

After the washout period, 38 patients still met the selection criteria and entered the blind phase. They were then randomly assigned to fluoxetine ($n = 19$) or imipramine ($n = 19$) treatment at flexible doses within a fixed dose range. Initial dose for the first week of active treatment was either 10 mg of fluoxetine or 25 mg of imipramine once each morning. Fluoxetine was raised by 10 mg weekly increments to a maximum of 50 mg/day (b.i.d.) on the basis of clinical improvement unless unacceptable side-effects appeared. Imipramine was raised up to 50 mg/day at the end of the first week of treatment. During the following weeks, dose levels were titrated up with increments of 50 mg every week to a maximum of 250 mg/day (b.i.d.), unless unacceptable side-effects appeared. At the end of the 24 weeks of active treatment (acute and continuation phase), responders entered the 6-month maintenance phase.

Several clinical and demographic variables of interest (Table 1) were collected directly from the patient and from a relative who was also involved in the control of the compliance with medications. The patients underwent weekly evaluation for 16 weeks, every two weeks between week 17 and 24 and later monthly. The evaluation was performed by using the Panic-Associated Symptoms Scale (PASS), the Hamilton Rating Scale for Anxiety (HRSA), the Hamilton Rating Scale for Depression (HRSD) and the Clinical Global Impression (CGI).

The PASS (Argyle *et al*., 1991) was used to measure the core symptoms of PD. In fact, PASS assesses the number of spontaneous and situational panic attacks, limited symptoms attacks, anticipatory anxiety and phobia score. HRSA was used to evaluate the overall severity of anxiety and HRSD to measure affective symptoms. CGI evaluated global functioning (both efficacy and safety information). Safety and tolerability were assessed by physical examination. Side-effects were recorded by using the Dosage Records and Treatment-Emergent Symptoms Scale (DOTES).

SAMPLE SIZE AND STATISTICAL ANALYSIS

Nineteen patients treated with fluoxetine were compared with 19 patients treated with imipramine. The assignment of patients to treatment groups was random. Results were expressed as mean $\pm$ S.D. The p-values $< 0{\cdot}05$ were considered significant.

The Chi-square test or, when appropriate, Fisher's Exact test provided a statistical assessment of whether there was an association between two variables and change between two groups after treatment. Differences between two independent samples were evaluated by Mann-Whitney test, differences between two related samples by Wilcoxon test and multiple comparison methods (Stanton Glantz, 1987). Statistical analysis was performed using the Statistical Analysis System (SAS) version 6.04 (SAS, 1990) and the Statistical Package for Social Sciences (SPSS), version 6.0 (Norusis, 1994).

RESULTS

There were no statistically significant differences between the two treatment groups in any demographic and clinical parameters (Table 1).

Table 1. Demographic and clinical information

	Fluoxetine ($n = 19$)	Imipramine ($n = 19$)
Gender		
M	8 (42·11 per cent)	12 (63·16 per cent)
F	11 (57·89 per cent)	7 (36·84 per cent)
Age (years)	$37·0 \pm 7·1$	$37·2 \pm 8·2$
Age at onset of panic (years)	$31·4 \pm 8·0$	$31·7 \pm 8·4$
Duration of illness (years)	$5·6 \pm 5·1$	$5·5 \pm 4·2$
Marital status		
Married	8 (42·11 per cent)	9 (47·37 per cent)
Divorced	4 (21·05 per cent)	6 (31·58 per cent)
Never married	7 (36·84 per cent)	4 (21·05 per cent)
Phobic avoidance		
None	9 (47·37 per cent)	10 (52·63 per cent)
Mild to moderate	7 (36·84 per cent)	7 (36·84 per cent)
Severe	3 (15·79 per cent)	2 (10·53 per cent)
CGI, illness severity	5 ± 2	5 ± 2
No prior psychiatric treatment	15 (78·95 per cent)	14 (73·68 per cent)
No drug therapy in the past 3 months	17 (89·47 per cent)	16 (84·21 per cent)
Drop-out	1 (5·26 per cent)	2 (10·53 per cent)
Non-responders	4 (22·22 per cent)	4 (23·53 per cent)
Relapse	3 (21·43 per cent)	3 (23·08 per cent)

(mean $\pm$ S.D.)

Thirty-eight patients entered the study. By week 3, three patients dropped out: two from the imipramine group because of severe anticholinergic effects, one from the fluoxetine group because of nausea and increased agitation. Three patients (two in the fluoxetine group and one in the imipramine group) had been taking oxazepam (15 mg/day) during the first two weeks of treatment.

Thirty-five patients completed the acute phase of treatment; 14 (out of 18) patients (77·78 per cent) in the fluoxetine group were responders and 13 (out of 17) patients (76·47 per cent) were responders in the imipramine group. They all entered the six-month maintenance period. Responder is a patient who has reached the full remission criteria, i.e. the total absence of anxiety symptoms or the absence of attacks, although the patient sometimes feels on the verge of an attack but he/she is able to control it. There could also be some slight anxiety present in a situation (or in anticipation of the situation), but no avoidance (Keller *et al*., 1994). A persistent full remission was reached between week 6 and 7 of treatment.

In our responder group, mean dosage of fluoxetine was 20 mg/day $\pm$ 10 and mean dosage of imipramine was 150 mg/day $\pm$ 25. Four patients (22·22 per cent) in the fluoxetine group and four patients (23·53 per cent) in the imipramine group were non-responders. These patients remained non-responders even if drug doses were progressively incremented to the maximum planned unless unacceptable side-effects appeared.

No statistically significant differences were found at any week in the efficacy of fluoxetine and imipramine on limited symptoms attacks, spontaneous panic attacks, situational panic attacks, total number of panic attacks or anticipatory anxiety and phobia severity evaluated through single PASS items.

HRSA mean scores evaluation shows that fluoxetine was quicker than imipramine in reducing generalized anxiety at the end of the first week of treatment ($p < 0·02$). In fact, in the fluoxetine group, patients' mean HRSA score at baseline was 32 and at the end of the first week of treatment it was 22·8. Conversely, in the imipramine group, patients' mean HRSA score at baseline was 31·4 and at the end of the first week of treatment it was 26·3. However, imipramine reached the same antianxiety effect as fluoxetine by the end of the third week of treatment. At this time a 50 per cent of mean HRSA score reduction (Figure 1) and a score of much or very much improved on the CGI were registered with both drugs.

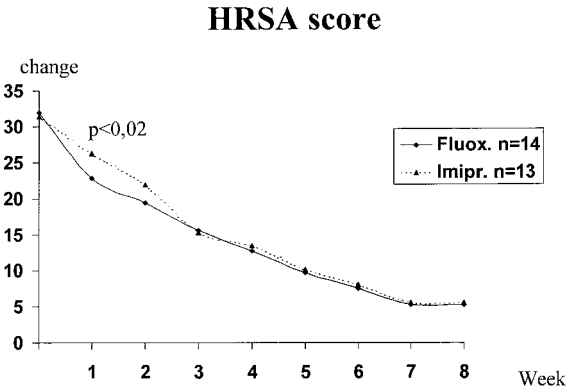

Figure 1. Changes in severity scores for HRSA (mean scores for each period)

If particular attention is devoted to the evaluation of the single sections of the PASS, we can note that in the fluoxetine group, compared with the imipramine group, PASS 1 score (situational panic attacks) improves significantly quicker ($p < 0{\cdot}03$) through the first and the second week of treatment; in the same way, fluoxetine-induced improvement in PASS 7 score (anticipatory anxiety) is significantly superior ($p < 0{\cdot}03$) through the second and the fourth week of treatment compared with the imipramine-induced improvement. Furthermore, considering CGI and all PASS items, there is a trend for a greater fluoxetine-induced improvement, although statistically non-significant.

The adverse effects seen in the fluoxetine group were not troublesome and consisted of insomnia, increased agitation and nausea. In the imipramine group, the adverse effects were quite severe: sweating, blurred vision, insomnia, increased agitation, constipation and dry mouth.

The rates of relapse (one or more panic attacks per week following a remission (Keller *et al.*, 1994) were 21·43 per cent for the fluoxetine group and 23·08 per cent for the imipramine group; all episodes of relapse occurred in the maintenance phase through the fourth and the fifth month.

DISCUSSION

This study shows that fluoxetine is as effective as imipramine in treating PD. In fact, full remission was recorded in 77·78 per cent and 76·47 per cent of patients in the fluoxetine and in the imipramine group respectively.

On the basis of HRSA mean scores, fluoxetine was found to be quicker than imipramine in reducing generalized anxiety at the end of the first week of treatment ($p < 0{\cdot}02$), while imipramine reached the same antianxiety efficacy at the end of the third week of treatment.

Furthermore, fluoxetine was safer and better tolerated than imipramine regarding side-effects profile. In fact in the imipramine group, anticholinergic effects lead to greater distress making two patients drop out. In the fluoxetine group, however, side-effects were quite few and scarcely relevant. This point is crucial, as it can influence compliance with medication which is often a core factor in the success or failure of an antipanic therapy both in acute and long-term treatment.

It is important to emphasize the better efficacy that fluoxetine demonstrated over imipramine in reducing HRSA mean scores at the end of the first week of treatment, that is when patients consumed low dosage of drug (10 mg/day). In fact, it could be very useful to have the chance to use a drug which can be effective at relatively low doses, particularly in PD patients who, when given high doses of SSRIs, can often experience anxiety-like symptoms, including increased agitation, restlessness, and jitteriness (Gorman *et al.*, 1987), probably because of their increased sensitivity to new physical sensations, especially those which mimic anxiety symptoms.

The rates of acute response seen in both treatment groups may be related to the high prevalence of patients with moderate to severe forms of disease, as indicated by CGI baseline scores (Table 1). Moreover, we have to highlight that, in our sample, 19 patients out of 38 showed no phobic avoidance, and 14 out of 38 suffered from mild to moderate phobic avoidance (Table 1). These aspects could have favourably influenced treatment response (Rosenberg *et al.*, 1991).

Studies on maintenance drug treatments in panic disorder are scarce and are often in the form of naturalistic follow-ups after the acute treatment trials (Lepola *et al.*, 1998). The usefulness of long-term treatment of PD has been recently questioned by Davidson (1988). In particular, continuation of improvement with prolonged administration of antipanic drugs was demonstrated by Katschnig *et al.* (1995) and Lecrubier *et al.* (1997), but few data are available to state whether a reduced maintenance dose is sufficient after short-term treatment or whether better management is achieved with the original dose.

Although prolonged treatment is appropriate for most patients, there is a reluctance to consider

long-term medication. Therefore the recognition of prognostic factors can provide useful information on treatment outcome. A low baseline score in HRSA and completion of 8 months treatment are considered major predictors of a panic-free outcome (Rickels *et al*., 1993). Furthermore, all follow-up studies present problems on the interpretation of the results because the number of patients remaining in a treatment group is generally decreased by many factors.

In our study high rates of persistent full remission are recorded. In fact, during the maintenance period, and more precisely through the fourth and the fifth month, 21·43 per cent of relapses were observed in the fluoxetine group and 23·08 per cent in the imipramine group. However, all patients did well in two weeks time when dosage of medication was increased (up to 50 mg/day of fluoxetine and 250 mg/day of imipramine). This seems to demonstrate a better efficacy of higher doses over a long-term period.

Finally our study presents some shortcomings; the small number of patients composing our sample has limited the power of the study in making a more precise distinction between the therapeutic effects of the two drugs, i.e. between the action of the two drugs on the single sections of the rating scales employed. It was also impossible to identify statistically significant differences between any characteristics of relapsed and non-relapsed patients. Furthermore, some unanswered questions on long-term treatment, such as the appropriate to reduce maintenance therapy dosage, remain and require further research. The available literature offers some suggestions on the efficacy of fluoxetine in PD treatment. However, as far as we know, this double-blind study represents an original report principally devoted to stimulate future research in which sample size should be increased.

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