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Short-Term and Long-Term Evaluation of Selective Serotonin Reuptake Inhibitors in the Treatment of Panic Disorder: Fluoxetine vs Citalopram

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This double-blind study evaluates the efficacy and tolerability of fluoxetine and citalopram in the acute and long-term treatment of panic disorder in 42 patients meeting DSM-IV criteria for panic disorder with or without agoraphobia. Fluoxetine and citalopram showed similar efficacy in the treatment of panic disorder patients. On the basis of HRSA and PASS mean score evaluation, fluoxetine was more rapid than citalopram in reducing generalized anxiety symptoms, spontaneous panic attacks and anticipatory anxiety. Fluoxetine appeared to be effective at a dosage of 10 mg/day, while citalopram reached the same efficacy at a dosage of 30 mg/day. Long-term evaluation has demonstrated high rates of persistent full remission with both drugs. Copyright © 1999 John Wiley & Sons, Ltd.

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

INTRODUCTION

The ever-growing body of evidence indicating a crucial role of a dysregulation of the 5-HT neuronal systems in the pathophysiology of anxiety states (Kahn *et al*., 1986; Charney *et al*., 1987) has supported the use of selective serotonin reuptake inhibitors (SSRIs) in the treatment of panic disorder (PD). In fact, clomipramine was first approved for use in PD in Europe on the basis of its serotonin reuptake inhibitory properties (Gloger *et al*., 1981). However, the drug showed the typical disadvantages of tricyclic antidepressants: some delay before the onset of an antipanic action, an initial exacerbation of symptoms in about 20 per cent of patients with PD and the well-known side-effects profile that includes anticholinergic effects, weight gain, memory difficulties and orthostatic hypotension.

Later on, Sheehan *et al*. (1988) recommended the use of more selective agents (SSRIs) which demonstrated fewer and less troublesome side-effects. More recently, Boyer (1995) and Johnson *et al*. (1995) showed that SSRIs were significantly superior to imipramine and alprazolam in the treatment of PD. Among SSRIs, a significant efficacy of fluoxetine and fluvoxamine in patients with PD has been demonstrated (Westenberg, 1996). Paroxetine (Dunbar *et al*., 1995; Oehrberg *et al*., 1995; Steiner *et al*., 1995; Sheehan and Harnett-Sheehan, 1996; Lecrubier *et al*., 1997a,b; Ballenger *et al*., 1998) and fluvoxamine (Den Boer *et al*., 1987; Den Boer and Westenberg, 1988; Black *et al*., 1993; Hoehn-Saric *et al*., 1993; Woods *et al*., 1994) remain, however, the most extensively investigated SSRIs in PD treatment. On the contrary, less information is available on the usefulness of fluoxetine (Gorman *et al*., 1987; Schneier *et al*., 1990; Solyom *et al*., 1991; Louie *et al*., 1993; Bystritsky *et al*., 1995) and citalopram (Humble and Wistedt, 1992; Lepola *et al*., 1994; Wade *et al*., 1997; Lepola *et al*., 1998).

The aim of this study was to evaluate and compare the efficacy of fluoxetine and citalopram in the short-term and long-term treatment of PD patients.

SUBJECTS AND METHODS

The study, performed at the Institute of Psychiatry of the University of Bologna, followed the ethical

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

All patients included in the study were aged between 18 and 65 years and suffered 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, be cooperative and compliant and be able to attend weekly visits. History of Psychosis, current major depression, organic brain syndromes, significant neurological disorders, seizures, presence of relevant cardiovascular, hepatic, renal or haematological diseases, alcohol or drugs abuse, or a known allergy to one of the study drugs were the exclusion criteria. Women who were pregnant or lactating, or of childbearing potential and not using adequate contraception were also excluded. Eighty-nine consecutive patients were screened.

All patients meeting inclusion criteria entered a 10-day washout period during which they had to experience at least one panic attack in order to be eligible for the double-blind phase of the study. Physical health was determined through physical examination and a careful evaluation of medical history, and laboratory testing.

Before baseline evaluation, all patients had to have discontinued treatment with any psychotropic drug for at least two weeks; patients already treated with fluoxetine and citalopram had to have discontinued their treatment for two months. Throughout the study the only permitted psychoactive drug was oxazepam, up to a maximum daily dose of 30 mg.

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 compliance with medications. Forty-two patients still meeting the selection criteria after the washout period were randomly assigned to a double-blind drug treatment phase, receiving either fluoxetine ($n = 21$) or citalopram ($n = 21$) at flexible doses within a fixed dose range. Initial dose for the first week of active treatment was either 10 mg of fluoxetine or 20 mg of citalopram once each morning.

During the following weeks, 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. Citalopram was titrated up to 10 mg every week to a maximum of 60 mg/day if the clinical response was inadequate. Mean dosage was $20 \text{ mg} \pm 10$ for fluoxetine and $40 \text{ mg} \pm 10$ for citalopram.

All patients underwent weekly evaluation for the first 16 weeks, every two weeks between week 17 and 24. Later on the evaluations were performed on a monthly basis. The evaluation was performed by using the Panic-Associated Symptoms Scale (PASS), the Hamilton Rating Scale for Anxiety (HRSA), the Clinical Global Impression (CGI) and the Dosage Records and Treatment-Emergent Symptoms Scale (DOTES). 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. CGI evaluated global functioning (both efficacy and safety information). Safety and tolerability were assessed through a careful physical examination. Side-effects were recorded using DOTES.

At the end of the 24 weeks of active treatment (acute and continuation phase), responders entered the 6-month maintenance phase.

SAMPLE SIZE AND STATISTICAL ANALYSIS

We recruited 21 patients treated with fluoxetine compared with 21 patients treated with citalopram. Patients to treatment groups were randomly assigned. The results are expressed as mean $\pm$ SD.#

Significant differences in the comparison between groups were obtained by Mann-Whitney U test; differences between two related samples by Wilcoxon test and multiple comparison methods (Stanton Glantz, 1987). The Chi-square test or, when appropriate, Fisher's Exact test provided a statistical assessment of whether there was an association between two variables. The p-values $<0{\cdot}05$ were considered significant. 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

Forty-two patients entered the study. By week 2, two patients dropped out: one from the fluoxetine group because of nausea and one from the citalopram group due to increased agitation.

Table 1. Demographic and clinical information

	Fluoxetine ($n = 21$)	Citalopram ($n = 21$)
Gender		
M	9 (42·9 per cent)	8 (38·1 per cent)
F	12 (57·1 per cent)	13 (61·9 per cent)
Age (years)	37·2 ± 7·0	36·7 ± 7·4
Age at onset of panic	31·6 ± 7·8	30·8 ± 8·0
Duration of illness	5·6 ± 4·9	5·9 ± 5·3
Marital status		
Married	10 (47·6 per cent)	9 (42·9 per cent)
Divorced	4 (19·1 per cent)	7 (33·3 per cent)
Never married	7 (33·3 per cent)	5 (23·8 per cent)
Phobic avoidance		
None	7 (33·3 per cent)	6 (28·6 per cent)
Mild to moderate	5 (23·8 per cent)	8 (38·1 per cent)
Severe	9 (42·9 per cent)	7 (33·3 per cent)
CGI, illness severity	5 ± 2	5 ± 2
No prior psychiatric treatment	13 (61·9 per cent)	12 (57·1 per cent)
No drug therapy in the past 3 months	18 (85·7 per cent)	17 (80·9 per cent)
HRSA (baseline)	21·6 ± 5·9	20·1 ± 5·2
Drop-out	1	1
Non-responders	4	7
Relapse	4	3

(Mean ± SD)

Two patients in the fluoxetine group and two in the citalopram group took 15 mg/day of oxazepam for the first two weeks of treatment. Forty patients completed then the acute phase of treatment. Sixteen (out of 20) (80 per cent) patients were responders in the fluoxetine group, and 13 (out of 20) (65 per cent) patients were responders in the citalopram group, and entered the maintenance phase.

In our series a full remission was reached at the end of the 4th week in the fluoxetine group and at the end of the 6th week in the citalopram group. According to the criteria of Yonkers *et al.* (1998), full remission was defined as the total absence of anxiety symptoms or the absence of attacks although the patient sometimes may feel on the verge of an attack but he/she is able to control it. There could also be some slight anxiety in the situation (or in anticipation of the situation) but no avoidance symptoms (Keller *et al.*, 1994).

HRSA mean scores show that fluoxetine was more effective than citalopram in reducing generalized anxiety at the end of the first ($p < 0{\cdot}05$) and the second week ($p < 0{\cdot}03$) of treatment. Fifty per cent reduction in HRSA mean scores was reached at the end of the second week of treatment in the fluoxetine group and at the end of the third week in the citalopram group.

If particular attention is devoted to the evaluation of the single sections of PASS, it can be noted that in the fluoxetine group PASS 3 score (spontaneous panic attacks) significantly improves ($p < 0{\cdot}03$) through the second and the third week of treatment and PASS 7 score (anticipatory anxiety) significantly improves ($p < 0{\cdot}03$) through the second and the third week of treatment.

No differences were recorded in the evaluation of frequency and severity of adverse effects in both groups. The most common side-effects were: insomnia, increased agitation, nausea and headache. Four patients in the fluoxetine group and three in the citalopram group relapsed during the maintenance phase (third and fourth month).

DISCUSSION

The SSRIs are rapidly emerging newcomers in the PD field. Their clinical acceptance has actually preceded well-designed research studies that support their efficacy (Jefferson, 1997).

In fact some previous reports have suggested that SSRIs provide an effective and well-tolerated alternative to older pharmacological agents such as TCAs in the treatment of PD. In particular, a meta-analysis of 32 studies including 2300 patients (Boyer, 1995) concluded that SSRIs should be considered as drugs of first choice in PD treatment. Several trials on sertraline (Gorman and Wolkow, 1994; Baumel *et al*., 1996), paroxetine (Ballenger *et al*., 1998), and fluvoxamine (Hoehn-Saric *et al*., 1993; Black *et al*., 1993) have confirmed the efficacy and good tolerability of SSRIs showing in particular a statistically significant superiority to placebo.

Fluoxetine has been evaluated in two open studies by Gorman *et al*. (1987) and Schneier *et al*. (1990), showing positive results at low doses (10 mg/day) cutting down the side-effect rate in the first weeks of treatment. Furthermore, a multicentric double-blind randomized trial (Lydiard *et al*., 1997) demonstrated that fluoxetine was significantly superior to placebo at only 20 mg/day.

The efficacy of citalopram in PD has been evaluated by Wade *et al*. (1997) and Lepola *et al*. (1998), who demonstrated that citalopram is more effective than placebo and that it appears to be most effective at low doses (20–30 mg/day), thus significantly reducing adverse effects.

As far as we know, this is the first report in which two SSRIs are compared in a double-blind study in the long-term. In fact, studies on maintenance drug treatments in PD are scarce and are often in the form of naturalistic follow-ups after acute treatment trials.

We have chosen to evaluate the efficacy of citalopram and fluoxetine because these drugs, among the available SSRIs, have been subjected to less extensive studies. Our study shows that fluoxetine and citalopram are both effective in the treatment of PD. Fluoxetine was more rapid than citalopram in reducing generalized anxiety symptoms (assessed by HRSA), spontaneous panic attacks and anticipatory anxiety (assessed by PASS); it also appeared to be effective at a dosage of 10 mg/day, while citalopram reached the same efficacy at a dosage of 30 mg/day. It is possible that the different onset of the therapeutic effect observed between the two drugs could have been reduced or annulled if citalopram had been administered at higher doses from the beginning, as reported by other studies (Wade *et al*., 1997; Lepola *et al*., 1998).

The response rates obtained at week 8 do not significantly differ from those obtained later. In fact, in our study, full remission, observed after four weeks of treatment in the fluoxetine group and after six weeks in the citalopram group, was generally maintained during the maintenance phase.

The small number of patients composing our sample represents the short-coming of the study. In fact it has limited its power in making a more precise distinction between the therapeutic effects of the two drugs.

CONCLUSION

PD is a syndrome with a chronic and recurrent pattern, which requires long-term treatment. Therefore the pharmacological agents used to treat it should be both effective and well-tolerated over a prolonged time course.

Benzodiazepines and TCAs, currently used in PD treatment, have demonstrated some limitation in their long-term use. In particular, benzodiazepines show sedative properties and can lead to dependency. The tolerability of TCAs is greatly limited by anticholinergic side-effects.

Most reports have demonstrated the usefulness of SSRIs in PD treatment over short-term periods. Recently, paroxetine and citalopram have been demonstrated to be effective in PD over a period of 36 weeks (Lecubrier *et al*., 1997a, b) and 1 year (Lepola *et al*., 1998).

Therefore we would emphasize that our report confirms the efficacy of SSRIs in PD treatment over short- and long-term periods in the absence of adverse effects, thus suggesting that for long-term periods SSRIs could be the drugs of first choice. Furthermore, we hope that more efforts will be made to recognize among the SSRIs the pharmacological agent that would be the most effective and best tolerated in the maintenance phase.

REFERENCES

Argyle, N., Deltito, J., Allerup, P., Maier, W., Albus, M., Nutzinger, D., Rasmussen, S., Ayuso, J. L. and Bech, P. (1991). The Panic-Associated Symptom Scale: measuring the severity of panic disorder. *Acta Psychiatrica Scandinavica*, **83**, 20–26.

Ballenger, J. C., Wheadon, D. E., Steiner, M., Bushnell, W. and Gergel, I. P. (1998). Double-blind, fixed-dose, placebo-controlled study of paroxetine in the treatment of panic disorder. *American Journal of Psychiatry*, **155**, 36–42.

Baumel, B., Bielski, R., Carmen, J., Hegel, M., Houck, C., Linden, R., Nakra, B., Ota, K., Pohl, R. and

Wolkow, R. (1996). Double-blind comparison of sertraline and placebo in patients with panic disorder. Poster presented at the 20th Collegium Internationale Neuro-Psychopharmacologicum. Melbourne, Australia.

Black, D. W., Wesner, R., Bowers, W. and Gabel, J. (1993). A comparison of fluvoxamine, cognitive therapy, and placebo in the treatment of panic disorder. *Archives of General Psychiatry*, **50**, 44–50.

Boyer, W. (1995). Serotonin uptake inhibitors are superior to imipramine and alprazolam in alleviating panic attacks: a meta-analysis. *International Clinical Psychopharmacology*, **10**, 45–49.

Bystritsky, A., Rosen, R. M., Murphy, K. J., Bohn, P., Keys, S. A. and Vapnik, T. (1995). Double-blind pilot trial of desipramine versus fluoxetine in panic patients. *Anxiety*, **1**, 287–290.

Charney, D. S., Woods, S. W., Goodman, W. K. and Heninger, G. R. (1987). Serotonin function in anxiety, II: effects of the serotonin agonist mCPP in panic disorder patients and healthy subjects. *Psychopharmacology*, **92**, 14–24.

Den Boer, J. A. and Westenberg, H. G. M. (1998). Effect of serotonin and noradrenaline uptake inhibitor in panic disorder: a double-blind comparative study with fluvoxamine and maprotiline. *International Clinical Psychopharmacology*, **3**, 59–74.

Den Boer, J. A., Westenberg, H. G. M., Kamerbeek, W. D. J., Verhoeven, W. M. A. and Kahn, R. S. (1987). Effect of serotonin uptake inhibitors in anxiety disorders: a double-blind comparison of clomipramine and fluvoxamine. *International Clinical Psychopharmacology*, **2**, 21–32.

Dunbar, G., Steiner, M. and Oakes, R. *et al*. (1995). A fixed dose study of paroxetine and placebo in the treatment of panic disorder. Poster presented at the VIIIth Congress of the European College of Neuropsychopharmacology, Venice, Italy.

Gloger, S., Grunhaus, L., Birmacher, B. and Troudart, T. (1981). Treatment of spontaneous panic attacks with clomipramine. *American Journal of Psychiatry*, **138**, 1215–1217.

Gorman, J. M. and Wolkow, R. (1994). Sertraline as a treatment for panic disorder (abstract). *Neuropsychopharmacology*, **10**(35 part 2), 1975.

Gorman, J. M., Liebowitz, M. R., Fyer, A. J., Goetz, D., Campeas, R. B., Fyer, M. R., Davies, S. O. and Klein, D. F. (1987). An open trial of fluoxetine in the treatment of panic attacks. *Journal of Clinical Psychopharmacology*, **7**, 329–332.

Hoehn-Saric, R., McCleod, D. R. and Hipsley, P. A. (1993). Effect of fluvoxamine on panic disorder. *Journal of Clinical Psychopharmacology*, **13**, 321–326.

Humble, M. and Wistedt, B. (1992). Serotonin, panic disorder and agoraphobia: short-term and long-term efficacy of citalopram in panic disorders. *International Clinical Psychopharmacology*, **6**(suppl. 5), 21–39.

Jefferson, J. W. (1997). Antidepressants in panic disorder. *Journal of Clinical Psychiatry*, **58**(suppl. 2), 20–24.

Johnson, M. R., Lydiard, R. B. and Ballenger, J. C. (1995). Panic disorder. Pathophysiology and drug treatment. *Drugs*, **49**, 328–344.

Kahn, R. J., McNair, D. M., Lipman, R. S. and Covi, L. (1986). Imipramine and clordiazepoxide in depressive and anxiety disorders II: efficacy in anxious outpatients. *Archives of General Psychiatry*, **43**, 79–85.

Keller, M. B., Yonkers, K. A., Warshaw, M. G., Pratt, L. A., Gollan, J. K., Massion, A. O., White, K., Swartz, A. R., Reich, J. and Lavori, P. W. (1994). Remission and relapse in subjects with panic disorder and panic with agoraphobia. *Journal of Nervous and Mental Disease*, **182**(5), 290–296.

Lecrubier, Y., Bakker, A., Dunbar, G. and Judge, R. (1997a). A comparison of paroxetine clomipramine and placebo in the treatment of panic disorder. *Acta Psychiatrica Scandinavica*, **95**, 145–152.

Lecrubier Y, Judge R, and the Collaborative Paroxetine Panic Study Investigators (1997b). Long-term evaluation of paroxetine, clomipramine and placebo in panic disorder. *Acta Psychiatrica Scandinavica*, **95**, 153–160.

Lepola, U., Leinonen, E., Turtonen, J. and Pertinen, J. (1994). The effect of citalopram in panic disorder and agoraphobia. *Nord Journal of Psychiatry*, **48**(1), 13–17.

Lepola, U., Wade, A. G., Leinonen, E. V., Koponen, H. J., Frazer, J., Sjodin, I., Penttinen, J. T., Pedersen, T. and Lehto, H. J. (1998). A controlled, prospective, 1-year trial of citalopram in the treatment of panic disorder. *Journal of Clinical Psychiatry*, **59**, 528–534.

Louie, A. K., Lewis, T. B. and Lannon, R. A. (1993). Use of low-dose fluoxetine in major depression and panic disorder. *Journal of Clinical Psychiatry*, **54**, 435–438.

Lydiard, R. B., Pollack, M. H., Judge, R., Michelson, D. and Tamura, R. (1997). Fluoxetine in panic disorder: a placebo-controlled study. Presented at the 10th Congress European College of Neuropsychopharmacology, Vienna.

Norusis, M. J. (1994). SPSS/PC+ Advanced Statistics, Version 6·0. SPSS Inc., Chicago.

Oehrberg, S., Christiansen, P. E., Behnke, K., Borup, A. L., Severin, B., Soegaard, J., Calberg, H., Judge, R., Ohrstrom, J. K. and Maniiche, P. M. (1995). Paroxetine in the treatment of panic disorder. *British Journal of Psychiatry*, **167**, 374–379.

SAS (1990). *SAS User's Guide; Statistics, Version 6·04*. SAS Institute Inc, Cary, NC.

Schneier, F., Liebowitz, M. R., Davies, S. O., Faierbanks, J., Hollander, E., Campeas, R. and Klein, D. F. (1990). Fluoxetine in panic disorder. *Journal of Clinical Psychopharmacology*, **10**, 119–121.

Sheehan, D. V. and Harnett-Sheehan, K. (1996). The role of SSRIs in panic disorder. *Journal of Clinical Psychiatry*, **57**(suppl. 10), 51–58.

Sheehan, D. V., Zak, J. P., Miller, J. A. and Fanous, B. S. L. (1988). Panic disorder: the potential role of serotonin reuptake inhibitors. *Journal of Clinical Psychiatry*, **49**(suppl. 8), 30–36.

Solyom, L., Solyom, C. and Ledwidge, B. (1991). Fluoxetine in panic disorder. *Canadian Journal of Psychiatry*, **36**, 378–380.

Stanton Glantz, A. (1987). *Primer of Biostatistics*. McGraw Hill, New York.

Steiner, M., Oakes, R., Gergel, I. P., Burnham, D. B. and Wheadon, D. E. (1995). A fixed dose study of paroxetine and placebo in the treatment of panic disorder. In *New Research Program and Abstracts of the 148th Annual Meeting of the American Psychiatric Association*, Abstract NR355, 150, Miami, FL.

Wade, A. G., Lepola, U., Koponen, H. J., Pedersen, V. and Pedersen, T. (1997). The effect of citalopram in panic disorder. *British Journal of Psychiatry*, **170**, 549–553.

Westenberg, H. G. M. (1996). Developments in the drug treatment of panic disorder: what is the place of selective serotonin reuptake inhibitors? *Journal of Affective Disorders*, **40**, 85–93.

Woods, S., Black, D., Brown, S., Asnis, G., Potkin, S., Hameedi, F. and Goddard, A. (1994). Fluvoxamine in the treatment of panic disorder in outpatients: a double-blind, placebo-controlled study. *Neuropsychopharmacology*, **10**(suppl. 3), 103.

Yonkers, K. A., Zlotnick, C., Allsworth, J., Warshaw, M., Shea, T. and Keller, M. B. (1998). Is the course of Panic Disorder the same in women and men? *The American Journal of Psychiatry*, **155**, 596–602.

