Efficacy and tolerability of citalopram in comparison with fluvoxamine in depressed outpatients: a double-blind, multicentre study

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In 16 depression clinics in hospitals and outpatient facilities in the Netherlands, a study was performed to evaluate and compare the efficacy and tolerability of citalopram and fluvoxamine and to determine the difference in the incidence of gastrointestinal side-effects. A total of 217 patients with a depressive disorder (DSM-III-R criteria) and a score of at least 16 on the Hamilton rating scale for depression were randomized to treatment. The results of this study indicate that the two drugs are equally effective. The adverse events occuring during treatment show a similar pattern between the two drugs, but citalopram is better tolerated than fluvoxamine. Citalopram induces fewer gastrointestinal adverse events compared with fluvoxamine. However, this did not affect the drop-out rates.

Keywords: Citalopram – Depression – Fluvoxamine – Gastrointestinal side-effects

INTRODUCTION

The involvement of serotonin (5-HT) in the development of depressive disorders was first postulated about 25 years ago (Lapin and Oxenkrug, 1969). Since that time, laboratory studies and studies in depressed patients, post-mortem studies and the clinical use of serotonin precursors have supported the involvement of serotonin in the development of depressive illness (Curzon, 1982). Many drugs used as antidepressant treatments potentiate serotonin transmission, which resulted in the suggestion that depression is correlated with a serotonin deficiency syndrome (Asberg *et al.*, 1986).

The group of drugs which specifically inhibit serotonin uptake appear to be the most clinically useful (Burrows, *et al.*, 1988) and are as effective as standard tricyclics (Bech and Cialdella, 1992). Although no clinical evidence has emerged to suggest that these drugs are more effective or have a faster onset of action than the older, tricyclic antidepressants, the major advantage of the SSRIs (selective serotonin reuptake inhibitors) appears to be a relative lack of anticholinergic effects and as a consequence a lack of cardiovascular toxicity in overdose (Leonard, 1988). Furthermore they lack sedative properties, making them more suitable for use in ambulant patients (Montgomery, 1988). This potential improvement in therapeutic effect may represent an important advance in the treatment of depression (Montgomery, 1989).

Fluvoxamine is a SSRI which has been in clinical

use in the Netherlands for some years. The anti-depressant efficacy of fluvoxamine has been shown to be comparable to that of tricyclic antidepressants, but as expected, it presents a different profile of side-effects (Burrows *et al.*, 1988). Despite the low inci-dence of adverse anticholinergic effects, fluvoxamine does cause, in about one-third of the patients, a high incidence of gastrointestinal side-effects such as nau-sea and vomiting (Benfield and Ward, 1986; Bateman and Chaplin, 1988).

Citalopram is the most selective SSRI marketed (Hyttel, 1982, 1988, 1993; Hyttel and Larsen, 1985). The efficacy of citalopram has been established in placebo-controlled studies both in the long and short term (DUAG, 1986; Gravem *et al.*, 1987; Timmer-man *et al.*, 1987; Bech and Cialdella, 1992; Mont-gomery, *et al.*, 1992; Nyth *et al.*, 1992; Silverstone, 1992) at doses between 20 mg and 60 mg/day. It causes few anticholinergic and cardiovascular side-effects. Like other SSRIs, gastrointestinal symptoms seem to be the most frequently observed side-effects. Clinical trial data on citalopram suggest the incidence of nausea to be about 20% (Dencker and Høpfner Petersen, 1988).

Although superior efficacy has not been demon-strated for any of the SSRIs, the structural diversity of this group is reflected in emerging qualitative and quantitative differences in side-effects and drug inter-action potential (Lane *et al.*, 1995). Thus, this study was designed to compare and contrast the efficacy but more specifically the tolerability of citalopram with fluvoxamine in outpatients with a major depres-sive disorder. The tolerability recording had special emphasis on the incidence of gastrointestinal side-effects, such as nausea and vomiting.

METHODS

Design
This was a 6-week, double-blind, multicentre, ran-domized parallel group comparison of citalopram and fluvoxamine in outpatients with a major depres-sion according to DSM-III-R criteria.

The selected outpatients were attending 16 depres-sion clinics in hospitals or other outpatient facilities in the Netherlands. These patients were randomly assigned to double-blind treatment with either citalo-pram or fluvoxamine. The treatment period was 6 weeks. The starting dose was either 20 mg of citalo-pram or 100 mg of fluvoxamine. Both treatments were to be taken once a day in the evening. After 1 week the dosage was to be increased to 30 mg of citalopram (once a day, in the evening) or 150 mg of

fluvoxamine (50 mg at noon and 100 mg in the even-ing). These dosage regimes were to be continued for 3 weeks, thus completing the 4-week, fixed-dose treat-ment regime. After the 4-week treatment period, the dosage was either continued at the same level, or in case of insufficient response, increased to 40 mg of citalopram (once a day, in the evening) or 200 mg of fluvoxamine (100 mg at noon and 100 mg in the even-ing; the advised therapeutic dose in the Netherlands in 1992, range 100–200 mg/day). The selected dose was then continued for a further 2 weeks thus com-pleting the 6 weeks of study treatment. The original fluvoxamine and citalopram tablets were packed into identical capsules. Placebo capsules were used to ensure that the same number of capsules were received in each treatment group. Patients attended for assessment at the beginning of the study and after 1, 2, 4 and 6 weeks on study treatment. At each visit, the Clinical Global Impressions (CGI; Guy, 1976), Hamilton depression rating scale (HAMD; Hamil-ton, 1967; Bech *et al.*, 1989) and the UKU side-effect rating scale (Lingjaerde *et al.*, 1987) were to be assessed. The patients were asked to complete the Zung self-rating depression scale (20 items; Zung, 1965; Dijkstra, 1974; Zitman *et al.*, 1989) just prior to the entry visit and during the treatment period just prior to each visit after 1, 2, 4 and 6 weeks.

Patients
Cooperative outpatients of either sex with a reason-able knowledge of the Dutch language and aged between 18 and 70 years, who met the DSM-III-R criteria for (i) major depression, single episode (296.2), (ii) major depression, recurrent (296.3), or (iii) bipolar disorder, depressed (296.5), with a score of at least 16 on the HAMD (17 items) and after having given written informed consent, were eligible for the study. Excluded were patients who had been treated with monoamine oxidase (MAO) inhibitors or fluoxetine within the last 3 weeks or with other psychotropic drugs within the last week, with the exception of benzodiazepines. Furthermore, patients with another primary psychiatric diagnosis than the above mentioned, or with a history of epilepsy, alco-hol and/or drug abuse, pregnant or lactating women and women of childbearing potential failing to use standard birth control methods, as well as patients with renal, hepatic, cardiovascular, neurological or somatic disorders, and/or significant abnormal laboratory findings, were excluded.

Assessments
The primary efficacy variable was the 17-item Hamil-ton depression rating scale total score (HAMD). As

secondary efficacy variables, the Clinical Global Impression (CGI, severity of illness), the Zung Self-rating Scale for Depression, the HAMD factors and the HAMD total score (50% reduction of baseline score) were used. Severity of adverse events and the influence of these events on daily functioning were assessed by means of the UKU side-effect scale (0 = none, 1 = mild, 2 = moderate, 3 = marked; Lingjaerde et al., 1987; Kamp and Haffmans, 1989). Spontaneously reported adverse events were also recorded.

Clinical laboratory tests and physical examinations were carried out at the beginning and end of the study treatment period. Physical examinations included body weight, height, blood pressure and heart rate. Selected benzodiazepines as permitted concomitant medication at baseline could be continued during the study. Patients who were receiving other benzodiazepines were switched to one of the following permitted drugs. The maximum doses of the benzodiazepines which could be given during the study were: oxazepam at 50 mg daily, lormetazepam at 4 mg daily, temazepam at 20 mg daily, lorazepam at 4 mg or flurazepam at 15 mg daily. Preferably, the daily dosage was stable during the study period. All non-psychotropic medication was allowed but the regime was to be kept stable. In case of severe nausea and/or vomiting, domperidone could be given.

Joint rating sessions were held at an investigator meeting before the start of the study and at three investigator meetings during the study. The interrater reliability was > 0.80.

The study was performed in accordance with the Declaration of Helsinki. The study was approved by the appropriate institutional review board and ethics committee.

Statistical considerations

Sample size and study power

A prospective sample size estimate was made, which had a priority of assessing the between-group comparisons of side-effects for citalopram and fluvoxamine treatment groups. The hypothesis to be tested was: citalopram would give a 50% lower incidence of gastrointestinal side-effects in comparison with fluvoxamine at the equivalent level of efficacy. Statistical significance was to be assessed at the 5% level ($p = 0.05$) using two-tailed tests. The study design chosen with a specific side-effect questionnaire was expected to give a relatively high incidence of reported side-effects. The side-effect reporting expected with fluvoxamine was 35% and required a sample size of 115 patients in each treatment group (in total 230

patients) to detect with an 80% power ($1 - \beta = 0.80$) and an alpha of 0.05 ($a = 0.05$) for the difference between the two treatment groups.

Analysis population

The intention-to-treat population (ITT) included all patients who had been allocated a randomization number on entry of double-blind treatment.

Specific statistical procedures

The ordered categorical data (e.g. HAMD, CGI) were analysed using the Cochran–Mantel–Haenszel test, with modified scores that allow adjustment for baseline differences where appropriate. Confidence intervals for the treatment difference were calculated using a non-parametric method (Armitage and Berry; Statistical Methods in Medical Research, third edn, in press). Two-by-two tables (e.g. improved/not improved) were analysed using either the χ^2 test or Fisher's exact test, depending upon the characteristics of the data.

The Zung score has been summarized in a similar manner to that suggested by Zung (1965). The Zung score was not to be used to investigate the difference between the efficacy of the two treatment groups, but to determine whether the patient's assessment of efficacy was related to that of the investigator. The analysis of the Zung index included tests for a correlation with the HAMD and CGI scores, using Pearson and Spearman rank correlation methods.

Multiple regression methods, with entry and deletion levels set at 0.1, were used to examine the effects of the following covariates on the total HAMD score: centre, age, sex, previous psychiatric history, severity at entry, gastrointestinal (GI) adverse events.

RESULTS

Patients
Between May 1990 and July 1992, a total of 217 patients were entered into the study. One hundred and eight patients (45 M, 63 F; median age 44.2 years) were randomized to citalopram and 109 patients (44 M, 65 F; median age 40.2 years) to fluvoxamine.

Approximately 60% of the patients had a history of clinically significant somatic disorders and about half of them had a family history of psychiatric disorders. Forty-six out of 108 patients treated with citalopram and 59 out of 109 patients treated with fluvoxamine had experienced a previous depressive

TABLE I. Psychiatric data on the current depressive episode (*n* = 217)

Current depressive episode	ITT		Efficacy	
	Citalopram (*n* = 108)	Fluvoxamine (*n* = 109)	Citalopram (*n* = 87)	Fluvoxamine (*n* = 80)
Severity				
Mild	3	1	3	1
Moderate	38	45	30	33
Severe				
(i) without psychotic features	66	60	53	44
(ii) with psychotic features	1	3	1	2
DSM-III-R diagnosis Major depression single episode 296.2	67	54	54	44
Major depression recurrent episode 296.3	38	52	30	34
Bipolar disorder (depressed) 296.5	3	3	3	2
Duration (weeks)				
Median	26	26	26	34, 5
Range	3–400	2–312	3–400	2–312
Antidepressant treatment received within 3 weeks of starting study (no. of patients)	70	80	57	55

episode. A summary of the diagnosis, according to the DSM-III-R classification, as well as the severity, duration and treatment of the current depressive episode is presented in Table 1. The depressive episode was assessed as severe in about 60% of the patients. Approximately 60% of the patients were receiving treatment for their depression at the start of the trial, and most patients had responded poorly. The intention-to-treat population (ITT) consisted of all 217 patients. Twenty-one patients treated with citalopram and 29 treated with fluvoxamine were withdrawn from the study due to adverse events (*n* = 15; 13.9% and *n* = 23; 21.1%, respectively), noncompliance (*n* = 4; 3.7% and *n* = 3; 2.8% respectively) and unallowed comedication (*n* = 2 and *n* = 3). These 50 patients were excluded from the ITT sample for the efficacy analysis. There was no significant difference between the treatment groups when the reasons for withdrawal were examined. Similarly, analysing time to withdrawal, no significant differences between the two treatment groups emerged.

A total of 69 patients in the citalopram group and 65 in the fluvoxamine group received the higher doses during the last 2 weeks. Of the patients who completed the 6-week, double-blind study, 57 patients of the citalopram group and 46 patients of the fluvoxamine group continued treatment. In addition, four patients on citalopram and one patient on fluvoxam-

ine, who did not complete the 6-week trial period, continued treatment.

Benzodiazepines were given to 18 (17%) patients on citalopram and 24 (22%) patients on fluvoxamine. The difference between the groups is not statistically significant. The antiemetic agent domperidone was given to 10 (9%) of the citalopram group and 23 (21%) of the fluvoxamine group. The difference is significant (*p* = 0.02, χ^2 test).

Efficacy

The primary efficacy variables was the HAMD total score. All patients had a HAMD total score of at least 16 at entry into the trial. In Table II, the data show a substantial decrease of the total score in both treatment groups during the study. The mean total score dropped from about 25 at baseline to approxi-

TABLE II. HAMD total scores at baseline and after 2, 4 and 6 weeks of treatment with citalopram or fluvoxamine

	Citalopram		Fluvoxamine	
	Mean	Range	Mean	Range
Baseline	24.7	17–35	24.5	17–38
Week 2	21.2	5–38	22.3	5–39
Week 4	19.0	4–39	20.0	2–39
Week 6	16.6	2–38	18.0	2–39

TABLE III. Number of complete and partial responders and non-responders after 6 weeks of treatment

HAMD score	Citalopram ($n = 108$)	Fluvoxamine ($n = 109$)
0–7	15	9
8–15	30	34
>15	63	66

mately 17 at week 6. There were no significant differences between the two treatments.

In Table III the number of patients showing complete response (HAMD total score 0–7), partial response (HAMD total score 8–15), and non-response (HAMD total score greater than 15) at week 6, are presented. Two patients in the fluvoxamine group could not be included in this analysis because of missing data. Fifteen citalopram patients (14%) and 9 fluvoxamine patients (8%) showed complete response. The difference is not significant. The mean percentage reduction in score at week 6 was 33% in the citalopram group and 26% in the fluvoxamine group. Thirty-three out of 108 patients on citalopram and 31 out of 109 patients on fluvoxamine showed a reduction in total score of 50% or more.

Multiple regression revealed that there was a significant difference between centres and showed that the final HAMD total score was closely related to gastrointestinal adverse events, baseline HAMD total score and age. No relation was found between the final HAMD score and psychiatric history or sex. There was no indication of a treatment difference ($p > 0.01$).

HAMD factors (Table III)
The mean scores between baseline and at week 6 of the HAMD factor scores show a clear reduction in melancholia, retardation and anxiety/somatization for both treatment groups. The difference between the

TABLE IV. Differences in incidence of adverse events—excess incidence versus comparator

Symptom	Citalopram %	Fluvoxamine %
Diarrhoea		+ 13.6
Nausea		+ 16.0
Vomiting		+ 9.1
Tachycardia		+ 10.8
Tremor		+ 11.7
Paraesthesia	+ 10.4	
Suicide attempt		+ 4.6

groups was not statistically significant. The sleep disturbance factor scores were also reduced in both treatment groups during the 6-week study, but less markedly as for the other factors.

Clinical Global Impression (CGI)
At baseline the majority of patients scored 3 or 4 (moderately ill). At the end of the study, 37 of the citalopram group (34%) and 35 of the fluvoxamine group (32%) and 35 of the fluvoxamine group (32%) had score 1 (no illness/mild illness). The analysis of severity of illness score at end-point, adjusting for baseline score, showed a median difference between treatment groups of –0.26 with 95% confidence interval, –0.64 to 0.11 ($p = 0.13$).

Zung self-rating depression scale
For each visit the patients completed the Zung self-rating depression scale. The mean indices at baseline were very similar in the two treatment groups, and the values decreased during the 6-week trial period in both groups. A correlation analysis showed a highly significant correlation between the Zung indices, the HAMD scores and the CGI scores for the week 6 data, with Pearson correlation coefficients of 0.73 and 0.65, respectively.

Tolerability (Table IV)
The objective behind using the UKU side-effect rating scale in this trial was to allow a more accurate comparison of the most critical complaints made by patients when treated with 5-HT uptake inhibitors. As expected, at baseline, a high incidence of 'side-effects' was reported (spontaneously reported and UKU scores) by 57% of the patients.

The incidence of treatment-emergent diarrhoea was higher in patients receiving fluvoxamine ($p = 0.026$) as was the incidence of nausea ($p = 0.017$). Furthermore, there was a trend towards a higher incidence of vomiting in the fluvoxamine group ($p = 0.052$; Table V).

The incidence of diarrhoea at the end of the study, after dose increment for many patients, was similar for citalopram and fluvoxamine with eight mild reports in each group corresponding to an incidence of 7.4% and 7.3%, respectively. In contrast, the incidence of nausea remained higher on fluvoxamine throughout the study period, confirming a clinically important difference. Mild nausea was reported in eight and twelve patients and moderate nausea in one and six patients for citalopram and fluvoxamine, respectively. At week 6 vomiting was only recorded in the fluvoxamine group.

TABLE V. Incidence and course of the main side-effects in percentages after 1, 2, 4 and 6 weeks of treatment with citalopram (Cit) or fluvoxamine (Flu)

	Week							
	1		2		4		6	
	Cit %	Flu %	Cit %	Flu %	Cit %	Flu %	Cit %	Flu %
Nausea	25.0	34.8	23.1	30.2	17.6	20.1	8.3	16.5
Headache	14.8	14.7	11.3	15.6	14.0	14.9	7.3	11.1
Tachycardia	10.2	12.0	5.5	10.3	7.4	11.9	5.6	7.3
Paraesthesia	11.1	7.3	7.4	5.5	4.6	4.6	5.6	4.7
Vomiting	7.4	11.9	—	—	0	1.8	0	4.6
Diarrhoea	9.3	13.7	6.5	11.9	5.6	15.6	7.4	7.3
Tremor	11.1	29.2	12.0	17.5	9.3	13.8	4.6	11.1

Serious adverse events

Four serious adverse events were reported in patients treated with citalopram. These included suicide ($n = 1$), a fatal myocardial infarction ($n = 1$), a diagnosis of multiple sclerosis whilst continuing citalopram treatment ($n = 1$) and a pregnancy ($n = 1$). Six serious adverse events were reported for the fluvoxamine group. These included suicide attempts ($n = 2$), suicidal tendencies ($n = 2$), aggressive reaction and agitation in a psychotic patient ($n = 1$) and aggravation of depression ($n = 1$), all resulting in hospitalization. The causal relationship to test treatment was in all 10 cases assessed as either no relationship or unlikely.

UKU, assessment of adverse events

At baseline, about 50% of the patients had adverse events with either moderate or marked interference with daily functioning (score 2 or 3). After 1 week of treatment, the percentages of patients with scores 2 or 3 remained constant in the citalopram group, whereas the percentage of patients with score 3 was almost doubled in the fluvoxamine group. Later in the trial period, the relative number of patients with score 3 decreased in both treatment groups.

Safety results

Concerning the vital signs data or laboratory data, no obvious differences between the treatment groups could be detected, either at entry or end-point and no changes were seen over the duration of the study.

DISCUSSION

Most newer antidepressants including the SSRIs have been compared with the tricyclic antidepressants, but few comparative studies of two different SSRIs have been published (Lane *et al.*, 1995). This report describes the results of a comparative clinical

trial of the two SSRIs citalopram and fluvoxamine. The aim of the trial was to compare the efficacy and specifically the tolerability of the two antidepressant drugs in a double-blind, parallel group study with flexible dose-ranges within the ranges recommended by the manufacturers of the two drugs.

The demographic characteristics were similar in the two groups. It is remarkable that the median duration of the present depressive episode in both groups was 26 weeks with a range of 3 weeks to 8 years in the citalopram group and 2 weeks to 6 years in the fluvoxamine group. The efficacy of treatment using the HAMD, the CGI severity of illness, and the Zung self-rating depression scale indicated that the response rate was rather low. The reason for this poor response may be related to the fact that many of the patients had a long duration of their present episode as mentioned above (Scott *et al.*, 1992) and 60% of the patients were receiving unsuccessful antidepressant therapy before entry into the study, indicating a possible therapy resistance (Guscott and Grof, 1991). Other reasons may be the short duration of the trial (6 weeks) in combination with the slow increment of the dosage and the fact that the patients were not treated with the currently accepted maximal dosages of the SSRIs (fluvoxamine 300 mg/day; citalopram 60 mg/day). However, no rationale for this variability in dosage could be determined, as moderate dosages of approximately 150 mg/day or 40 mg/day were shown to be effective in the treatment of depression (Kaspar *et al.*, 1992). Furthermore, there are more patients in the fluvoxamine group who are treatment resistant and have a longer duration of their current depressive episode.

The results of the ratings on the HAMD total score, HAMD factors and the Zung self-rating scale were supported by the global ratings, which showed that about one-third of the patients in each group

had a score of 0 or 1, indicating no depression or only mild depression at end-point. The finding that the sleep disturbance factor was less markedly reduced might be explained by the fact that SSRIs are not sedative.

The severity of the depression at entry as well as the relatively small sample size and the lack of a placebo control group might limit the conclusions on the efficacy results. However, the sample size was estimated on the main purpose of this study, i.e. to compare the type, severity and frequency of the adverse events.

Adverse events were recorded by using the UKU side-effect rating scale (Lingjaerde *et al.*, 1987). The incidence of adverse events was recorded at baseline and, as expected, many adverse events were assessed. The comparison between treatments comprised treatment-emergent adverse events defined as adverse events not present at baseline or, that recur, with at least one visit without the adverse event.

A significantly higher incidence of diarrhoea and nausea was recorded in patients receiving fluvoxamine. In addition, there was a definite trend that vomiting was seen more frequently in the patients in the fluvoxamine group than in the citalopram group. This is in good agreement with the fact that significantly more patients in the fluvoxamine group were prescribed the antiemetic drug domperidone. Domperidone has peripheral antidopaminergic activity and crosses the blood–brain barrier only to a limited extent.

The recording of adverse events per assessment point showed that nausea and vomiting were reported most frequently at the beginning of treatment, particularly in the citalopram group. Although citalopram has a higher serotonin affinity, these differences in side-effects might be due to the different selectivity of serotonin reuptake inhibition. In this outpatient study, dosages of fluvoxamine and citalopram were chosen at a maximum of 200 mg/day and 40 mg/day, respectively. Higher initial dosages of fluvoxamine resulted in an increased incidence of adverse effects without any concomitant improvement (Kaspar *et al.*, 1992). A lower initial dose of fluvoxamine (< 100 mg) might have resulted in less initial side-effects.

Tachycardia is a known adverse reaction of tricyclic antidepressants, but is uncommon in patients treated with 5-HT uptake inhibitors. The incidence of tachycardia in this study was surprisingly high (citalopram 20.4% and fluvoxamine 31.2%), maybe as a somatic symptom of anxiety. The difference between treatments did not reach the level of statistical significance.

Symptoms classified as paraesthesia were recorded slightly, but not significantly, more frequently in patients receiving citalopram than in patients receiving fluvoxamine, whereas the incidence of tremor tended to be higher in the fluvoxamine group.

Suicide or suicide tendencies is a niche of special interest in clinical trials in depression. Suicide attempt (WHO preferred term) was recorded in 1 out of 108 patients on citalopram and in 6 out of 109 patients on fluvoxamine. Due to the very small numbers, this finding may be incidental.

CONCLUSION

The results of this double-blind comparative study of citalopram and fluvoxamine indicate that the two SSRIs are equally effective. In the population of patients entered into the study, the response rate in both treatment groups was rather low. The adverse events occurring during treatment show a similar pattern between the two drugs at these dosages, in favour of citalopram.

Acknowledgements

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