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An open multicentre study to evaluate the efficacy and tolerance of fluoxetine 20 mg in depressed ambulatory patients

Patrick MESTERS (1), Marc ANSSEAU (2), Roger BRASSEUR (3), Georges BUSSIOS (1), Paul COSYNS (4), Marc CZARKA (1), René DE BUCK (5), Anne DE FRENNE (6), Michel DIERICK (7), Paul LINKOWSKI (8), Joseph PEUSKENS (9), Henry SCHMITT (1), Arlette SEGHERS (10)

ABSTRACT

In this study, 544 out-patients suffering from depressive disorders were enzolled in 6 weeks open study with fluoxetine 20 mg.

A statistically significant decrease of the Hamilton Rating Scale for Depression (HRS-D) score is observed during treatment.

All indivual item HRS-D scores and in particular suicidal ideation, sleep disturbances and anxiety showed the same improvement.

Side-effects were carefully recorded and presented a lower incidence rate than in other studies.

New issues in methodology management concerning ambulatory studies are discussed.

Key words : *Fluoxetine, Depression, Outpatients, Suicide, Anxiety, Efficacy, Side-effects, Safety.*

1. Introduction

Fluoxetine hydrochloride is a non-tricyclic antidepressant that specifically inhibis the re-uptake of serotonin. It differs from classical antidepressants by its absence of effect on other neurotransmitters (norepinephrine and dopamine).

(1) M.D. Eli Lilly Benelux, Brussels; (2) M.D., Ph.D. C.H.U. Sart Tilman, Liège; (3) M.D., Ste-Anne Hospital, Brussels; (4) M.D., Universitair Ziekenhuis Antwerpen; (5) M.D., Hôp. Universitaire Brugmann, Brussels; (6) Statistician. Health Care Research, Koningshooik; (7) M.D., St-Kamillus Kliniek, Ghent; (8) M.D. Ph.D., Erasmus Hospital, Brussels; (9) M.D. Ph.D., Universitair Psychiatrisch Centrum St-Jozef, Kortenberg; (10) M.D., U.C.L. St-Luc, Brussels.

These characteristics explain the virtual absence of anticholinergic side-effects with fluoxetine in contrast to classical antidepressants.

The efficacy and low side-effect profile of fluoxetine in comparison with classical antidepressants have been demonstrated in a number of studies (Bremmer, 1984; Cooper, 1988; Beasley *et al.*, 1991).

2. Methods

In this open study, performed in 1990 and 1991 in Belgium, 544 depressed outpatients received fluoxetine 20 mg qd for 6 weeks. Patients were followed up at 1 week (visit 2), 2 weeks (visit 3), and 6 weeks (visit 4).

This study was conducted by 130 Belgian psychiatrists : each enrolling 5 patients over a period of 12 months. Included in this study were male and female outpatients above 18 years old. An oral informed consent was requested.

Patients were suffering from depressive disorder according to DSM III R criteria (American Psychiatric Association, 1987) and the minimal 17 items-Hamilton Rating Scale for Depression (Hamilton, 1960) at entry was 17.

Exclusion criteria included : obvious risk of suicide, active organic pathology, history of brain disease and seizures, risk of psychotic decompensation, history of allergy to fluoxetine, pregnant or lactating women, and concomitant use of other psychotropic drugs.

In addition, the use of ECT or IMAO in the month and a tricyclic in the 2 weeks prior to the study, was an exclusion criteria. Only females who were either infertile or taking adequate contraceptive measures were eligible. Concomitant use of anxiolytics and/or sedatives with short or medium lenght of half life (oxazepam, lorazepam, temazepam) at therapeutic dosage was allowed if needed.

3. Evaluation of efficacy

The efficacy of the drug was assessed by HRS-D, clinical global impression scale (CGI-Guy 1976), and patient global impression scale (PGI) (Table I).

CGI assessed the following two parameters :

1) Severity of depression (assessed at baseline, and at visits 2, 3 and 4). Measurement on a 7 point ordinal scale from « normal » to « belonging to the most depressive patients ».

2) Global improvement with respect to baseline (visits 2, 3, 4). Measurement on a 7 point ordinal scale ranging from « very much improved » to « much worse ».

TABLE I : *Flow Chart*

	Admission Visit 1	*Visits 2 to 4*
HRS-D (1)	X	X
DSM III R Criteria (2)	X	
CGI (3)	X	X
PGI (4)	X	X
Comedication	X	X
Somatic complaints	X	
Side-Effects		X
Weight	X	X

(1) Hamilton Rating Scale for Depression (Hamilton, 1960).
(2) American Psychiatric Association (1987).
(3) Clinical Global Impression Scale (Guy, 1976).
(4) Patient Global Impression Scale.

PGI rating (visit 2, 3, 4) concerns the patient status with respect to baseline (visit 1). Measurement is on a 7 point ordinal scale ranging from « much better » to « much worsened ». The scales were evaluated at entry (visit 1) and after 1, 2 and 6 weeks of treatment.

The success rate of the treatment was defined as the rate of patients who at visit 4, attained a more than 50 % improvement in the total HRS-D score relative to baseline, or a HRS-D value less than 10.

4. Safety

Somatic complaints at entry were recorded at visit 1.

Side-effects were recorded at visits 2, 3 and 4 and ranked as mild, moderate or serious. Body weight was measured at each visit.

Patients could withdraw from the study at any time. Physicians could also withdraw patients from the study in case of inefficacy after 3 weeks of treatment, or after serious adverse events.

The study was approved by the Erasmus Hospital's Ethical Committee (Brussels) and has been carried on following the Helsinki Declaration.

5. Statistical Analysis

Statistical analysis was performed by Health Care Research and Statistical Service, Koningshooikt, Belgium.

The data processing was performed on 537 patients (last visit carried forward) who satisfied the entry criteria (see patient population below).

The analysis of the parameters : HRS-D, CGI, and weight, was performed on the total of 537 patients, for each diagnostic subgroup and for the major depression group.

When the analysis concerned ordinal variables for which the subsequent visits were to be compared with respect to the baseline, the Wilcoxon sign rank test was applied to determine the significance of the difference.

For the quantitative variables, it was checked whether they were normally distributed. In the case of normality, the significance of the difference in subsequent visits with respect to the baseline was tested with a paired t-test. In the case of abnormality, à Wilcoxon sign rank test was applied.

All statistical tests were two sided and considered significant when the type I error was less than 5 %.

6. Results

Patient Population

Of the 544 cases in the study, 7 cases were eliminated from the analysis since they had a baseline total HRS-D score lower than 17.

321 women (60.1 %) and 213 (39.9 %) men entered the study (3 cases were not taken into account in the sex partition due to lack of information).

The mean age is 46 years for the 537 eligible patients (SD ± 13).

The mean weight is 66.7 kg (SD ± 12.5).

134 (24.6 %) patients dropped out for different reasons before visit 4, as commented below.

According to the DSM III R criteria, the following diagnoses have been confirmed :

Major depressive disorder, single episode, (n= 113; 21.5 %);
Major depressive disorder, recurrent, (n = 166; 31,6 %);
Major depressive disorder, melancholic subtype (n= 29; 5.5 %);
Dysthymic disorder (n = 124; 23.6 %);
Depressive disorder not otherwise specified, (n = 36; 6.8 %);
Adjustment disorder with depressed mood (n = 34; 6.5 %);
Major depressive disorder, bipolar (n = 24; 4.6 %).

11 patients were not diagnosed because of lack of information.

Efficacy

1) The ANOVA with the repeated measurements over time shows a highly significant time effect (p = 0.0001), no diagnosis effect over time (p = 0.39), no age effect over time (p = 0.94), no sex effect over time (p = 0.81), a depression severity effect over time (p = 0.05) and as it is significant at visit 0, 1 and not at visit 2 and 3, no interaction effect over time.

2) *Hamilton Rating Scale :*

A sustained diminution is observed from the baseline through visits 2, 3, 4 in the higher scores frequencies for the total HRS-D score and for the HRS-D individual items. This is in accordance with several other studies (Bremner, 1984; Feighner, 1985; Montgomery *et al.*, 1989, Potter *et al.*, 1991).

As a reminder item 3 concerns suicidal ideation and behaviour; items 4 to 6 concern respectively the following sleep disturbances : difficulties to fall asleep, perturbation of sleep continuity, and early awakening. Items 10 and 11 are related to psychic, and physical anxiety.

If we consider all the patients (n = 537), including those who dropped out (last visit carried forward), the total HRS-D score ranges from 17 to 46. At visit 4, however, 62.9 % of the whole population has a Hamilton score varying from 0 to 16. The improvement in the subsequent visits relative to the baseline is extremely significant for the total HRS-D score and the individual items concerning suicide, insomnia (items 3 to 6) (Fig. 1) and anxiety (items 10 and 11), (p = 0.0001). (Fig. 2 and 3).

This trend was noted for the total population and for each diagnostic subgroup. (Fig. 4).

47.7 % of the whole population (all diagnoses and drop-outs included), attain a more than 50 % improvement rate in the total HRS-D score relative to baseline, whereas, considering the Major Depressive Disorder (MDD) subgroup, 42 % present a HRS-D value lower than 10 and 50.6 % present a HRS-D value decreased by at least 50 % as compared to baseline. (Table II).

TABLE II : *Efficacy*

	HRS-D (1) < 10	50 % reduction at least on HRS-D (1)
LAST VISIT CARRIED FORWARD		
All types of depression considered (n = 537)		47,7 %
MDD (2) subgroup	42 %	50.6 %
DROP-OUT EXCLUDED		
All types of depression considered (n = 537)	52 %	61.0 %
MDD (2) subgroup	57 %	67.5 %

(1) Hamilton Rating Scale for Depression (Hamilton, 1960).
(2) Major Depressive Disorder (American Psychiatric Association, 1987).

If the drop outs are excluded, 52 % of the patients present a HRS-D score lower than 10, after 6 weeks treatment.

In 61 % of patients, HRS-D value decreases by at least 50 % of the baseline.

Considering the MDD subgroup, 57 % of the patients who completed the study, reach a HRS-D value lower than 10 and for 67.7 % of them, HRS-D value decreases by at least 50 % as compared to baseline.

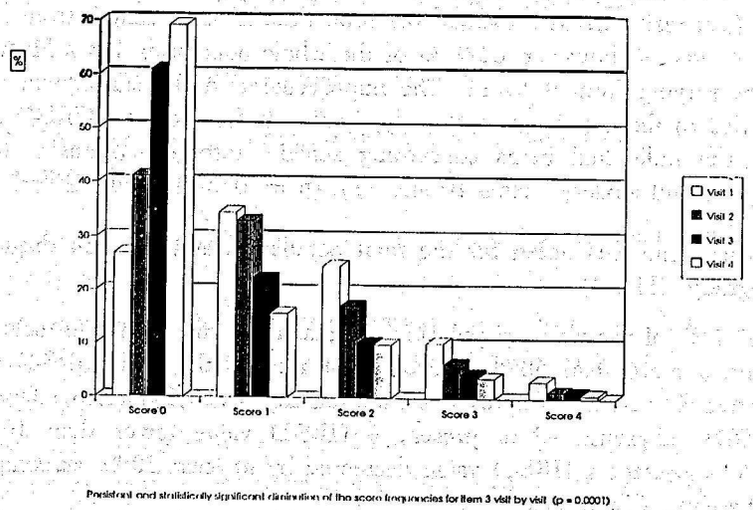

FIG. 1 : HRS-D ITEM 3 : Frequency distribution for the total population (r=537).

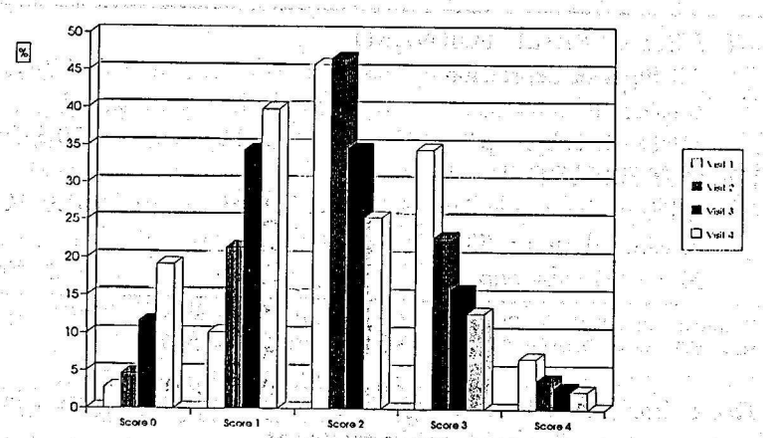

FIG. 2 : HRS-D ITEM 10 : Frequency distribution for the total population (n=537)

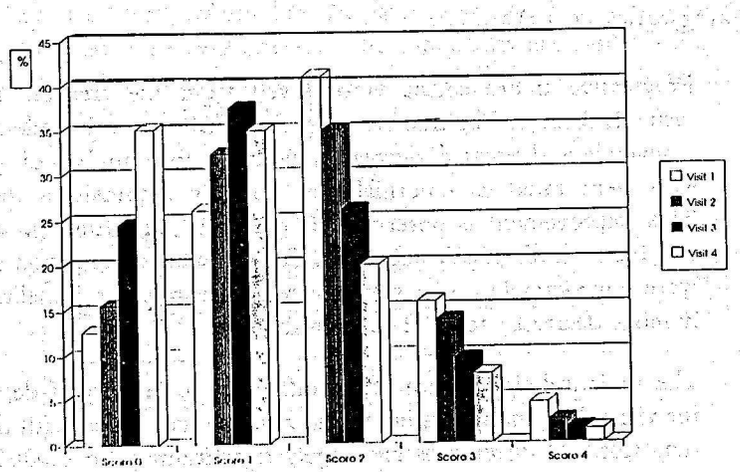

FIG. 3 : HRS-D ITEM 11 : Frequency distribution for total population (n=537)

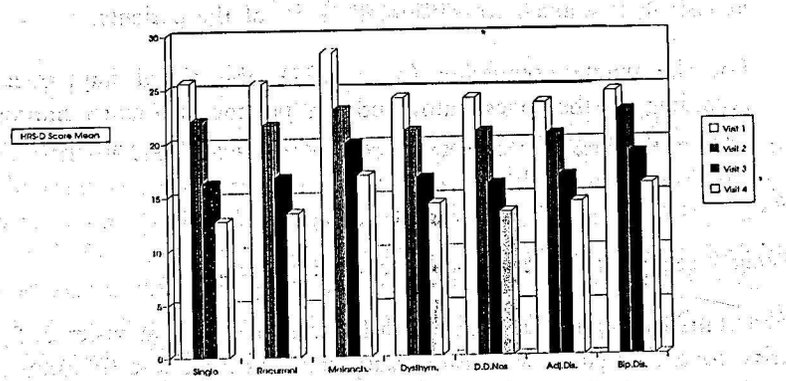

FIG. 4 : HRS-D Total score evolution by diagnosis (n=537)

3) *Clinical Global Impression Scale :*

a) Severity of depression :

Progressive improvement is observed from the baseline through visits 2, 3 an 4. The number of patients who were « moderate » to « severely » depressed decreases, whereas the number of patients who were rated as « normal » or « mildly depressive » increases. This improvement is observed for the total population (n = 537) and for each diagnostic subgroup. For the whole population 90.5 % were « moderately » to « very severely » depressed at baseline. This number decreases to 37.2 % at visit 4.

The statistical significance of the difference in severity of depression for visits 2, 3 and 4 relative to the baseline was tested with the sign rang test. All differences are largely significant (p = 0.0001).

b) Clinical Global Impression - Global Improvement (Investigator/ Patient) :

The difference in the severity of depression for visit 2, 3, 4 in regards to the investigator's and thre patient's perception of improvement was assessed. A gradual increase from visit 2 through visits 3 and 4 in the frequency of patients with « much improvement » is observed. However for the melancholic subgroup, the PGI at visit 4, is « much worse » for 20.7 % of the patients.

For the whole population (n = 537), the global improvement according to the investigator and the patient is « much improvement » for respectively 60.5 % and 59.6 % of the patients.

Weight

Weight relative to baseline decreases during treatment.

The statistical significance of the difference in weight at visits 2, 3, 4 relative to the baseline, was tested with the sign rank test (p value for each visit respectively : 0.0001, 0.0001, and 0.01).

However, the absolute mean difference is relatively low, 0,252 kg at visit 2; 0.410 kg at visit 3; and 0.249 kg at visit 4.

Side Effects

Evaluation of tolerance includes data from all patiens.

237 patients reported events at visit 2, 167 at visit 3 and 101 at visit 4. Nausea, nervousness (agitation) and epigastric discomfort were the most common adverse events reported by the patients at visit 2, with percentages of 12.9, 3.87 and 3.29 respectively. The complaints decreased during the therapy. At the last visit, the percentage of each of these symptoms dropped to 3.73, 1.49 and 1.74 (Fig. 5).

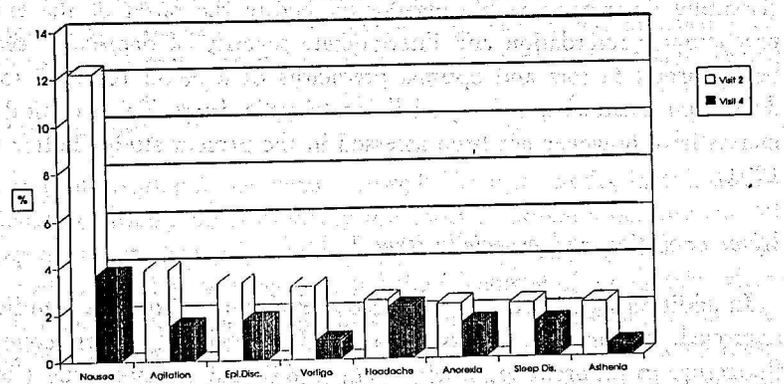

FIG. 5 : Evolution of percentage of side effects at visit 2 and 4 (n=537)

Discussion

Efficacy

Previous published studies have demonstrated the efficacy of fluoxetine in the treatment of depression, in comparison with classical antidepressants (clomipramine, amitryptiline, and imipramine) (Feighner, 1985; Ropert, 1989; Loeb *et al.*, 1989). Two double blind studies, indicate that fluoxetine significantly improved the HRS-D total score after 1 week of treatment whereas the same effect took place after 2 weeks with classical antidepressants (Feighner, 1985; Ropert, 1989).

In this study, patients show a good clinical response with a decrease in mean HRS-D score greater than 50 % after 6 weeks of treatment among 61 % of patients suffering from depressive disorder who completed the study, and among 67.7 % of those who were specifically suffering from MDD, according to the DSM III R criteria. The CGI and PGI scores also significantly improve during therapy.

The observed HRS-D response rate is similar to that observed in other studies conducted during the last years with outpatients suffering from MDD. (Feighner, 1985 : 55 %; Fabre and Putman, 1987 : 67 %; Beasley, 1991 : 62.3 %). However, the pattern of improvement of HRS-D score seems to be specific for the different diagnoses subgroups.

Indeed, in addition to the expected effect on severity of depression, the prognosis generally depends on the presence of other additional factors, classically described : stable personality before the onset of the episode, psychomotor retardation and intermediate severity of depression seem to be important factors and optimal predictors of a better response to antidepressant treatment, and especially to tricyclic drugs. These clinical parameters have however not been assessed in the present study (Potter *et al.*, 1991).

Items evolution and especially item 3.

In addition to the HRS-D total score evolution, anxiety is significantly improved, confirming results obtained in previous studies comparing fluoxetine to imipramine (Loeb *et al.*, 1989) and clomipramine (Ropert, 1989). The evolution of item 3 shows that suicidal ideation or behaviour significantly decreases during fluoxetine treatment, as previously described by Beasley in a meta analysis (17 double blind trials : 1765 patients with fluoxetine, 731 patients with tricyclics and 569 patients with placebo). Beasley concluded also that « the data do not show that fluoxetine is associated with an increased risk of suicidal acts or emergence of substantial suicidal thoughts among depressed patients ». (Beasley *et al.*, 1991).

Safety

No serious adverse event has been recorded. Mainly gastro-intestinal side-effects were described (nausea : 12.9 %, epigastric discomfort : 3.3 %, anorexia : 2.3 %). The percentage of the side-effects, during the 6 weeks of treatment, decreases rapidly to reach a low incidence rate (respectively : 3.7 %, 1.7 % and 1.5 %).

Cooper has reviewed all adverse events form comparative clinical trials in which 2938 patients were treated by fluoxetine (Cooper, 1988). Nausea was reported at least once by 23 % of patients. However, its severity was mild and its incidence decreased with continuation of therapy. Other side-effects are described by Cooper, in higher proportions than those observed in our Belgian study (nervousness : 10 vs 3.9 %; vertigo : 6 % vs 3 %, insomnia : 13 % vs 2.3 %). A significant decrease of weight is also observed during treatment, that may improve patient compliance. This decrease in weight parallels the conclusion of Cooper that weight loss is proportional to patient's body weight before therapy (Cooper, 1988).

Drop-Out.

134 patients have dropped out from the study (24.6 %).

The reasons are described in table III. As published in the literature, time spent with out-patients to foresee their needs and enhance their involvement is a significant variable that affects compliance (Rickels, 1986).

Treatment duration.

Efficacy of treatment has been assessed during 6 weeks in this study. This length of follow up is probably too short to obtain a definite cure of the depressive episode and could only sedate acute symptoms. (Beasley *et al.*, 1991). Frank *et al.* (1990), noted the advantage of a long term treatment at therapeutic doses during the treatment of depression, rather than to decrease the dosage (or the intake frequency) to a maintenance therapeutic level after the disappearance of the acute symptomatology. This new approach of longterm maintenance should be viewed as a medical improvement, reducing the risk of relapse and new episodes of depression. (Montgomery *et al.*, 1989).

TABLE III : *Reasons for Dropping Out.*

Lack of Efficacy :	6.0 %	(n = 33)
Lack of Efficacy and Adverse Reaction :	1.6 %	(n = 9)
Adverse Reaction :	9.3 %	(n = 51)
Lost to Follow up without explanation :	4.2 %	(n = 23)
Clinician's Decision without Explanation :	2.0 %	(n = 10)
Patient's Decision without Explanation :	1.5 %	(n = 8)

24.6 % of the included patients (n = 134) dropped out.

Conclusions

This large open multicentric study, performed in Belgium, confirms previous published data on the efficacy and safety of fluoxetine 20 mg in the treatment of depressive disorders.

One of the main interests of a study with outpatients is, that the population is different from hospitalized patients, usually studied in trials, in

terms of history, cause of illness, social and professional insertion and clinical profile.

In order to track the evolution of these patients, specific tools are needed. Specific methodologies oriented to the assessment of the quality of the patient/clinician relationship, psychological and social patient environment, long term treatment, quality of life perception, effective human and financial costs and their repercussions should be developped.

These parameters, according to the literature, should influence the course of treatments but, so far, do not seem to have been systematically explored.

RESUME

Etude ouverte, multicentrique, évaluant l'efficacité et la tolérance de la fluoxétine à la dose de 20 mg, chez des patients ambulatoires souffrant de dépression majeure

Cette étude ouverte fut réalisée en Belgique, auprès de 544 patients ambulatoires, souffrant de Dépression Majeure suivant les critères diagnostiques du DSM III R, et traités par fluoxétine 20 mg, durant 6 semaines consécutives.

Une diminution statistiquement significative du score total de l'échelle d'Hamilton fut observée, visite après visite.

La même évolution fut confirmée, lorsqu'on considère chaque item individuel et en particulier les tendances suicidaires, troubles du sommeil et anxiété.

Les effets secondaires, régulièrement recherchés, présentaient un taux d'incidence moindre que celui mentionné dans d'autres études. Quelques problèmes liés à la méthodologie de recherche sont évoqués.

SAMENVATTING

Open, multicentrische studie ter beoordeling van de doeltreffendheid en tolerantie van fluoxetine 20 mg bij ambulante patienten met depressie in de engere zin

Deze openstudie werd uitgevoerd in België bij 544 ambulante patiënten met depressie in engere zin volgens de diagnostische criteria van DSM III R, die gedurende 6 opeenvolgende weken werden behandeld met fluoxetine 20 mg. Bij elk bezoek werd een statistisch significante daling van de totale score op de Hamilton schaal (HRS-D) vastgesteld.

Dezelfde evolutie werd bevestigd bij de beoordeling van elke parameter afzonderlijk, vooral wat betreft zelfmoordneigingen, slaapstoornissen en angst.

Er werden regelmatig bijwerkingen vastgesteld, maar de incidentie ervan was lager dan in andere studies. Er wordt gewezen op een aantal problemen in verband met de onderzoeksmethode.

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REFERENCES

AMERICAN PSYCHIATRIC ASSOCIATION : Diagnostic and Statistical Manual for Mental Disorders, third Edition, Revised. Washington DC, (1987).

BEASLEY C.M. : Fluoxetine versus trazodone : efficacy and activating-sedating effects. *J. Clin. Psychiatry 52 : 7*, (1991).

BEASLEY C.M. Jr., DORNSEIF B.E., BOSOMWORTH J.C., SAYLER M.E., RAMPEY A.H. Jr., HEILIGENSTEIN J.H., THOMPSON V.L., MURPHY D.J., MASICA D.N. : Fluoxetine and suicide : a meta-analysis of controlled trials of treatment for depression. *Br. Med. J. 303 :* 685-692, (1991).

BREMNER J.D. : Fluoxetine in depressed patients : a comparison with imipramine. *J. Clin. Psychiatry 45 :* 411-419, (1984).

COOPER G.L. : The Safety of Fluoxetine - An update. *Br. Psychiatry, 153 (suppl. 3)* 77-86 (1988).

DECLARATION OF HELSINKI : *Recommendations Guiding Physicians in Biomedical Research involving Human Subjects.* Adopted by the 18th World Medical Assembly, Helsinki, Finland. June 1964, amended by the 29th World Medical Assembly, Tokio, Japan, October 1975, the 35th World Medical Assembly, Venise, Italy, October 1983, and the 41st World Medical Assembly, Hong Kong, September 1989.

FABRE L.F., PUTMAN III H.P. : A fixed-dose clinical trial of fluoxetine in out patients with major depression. *J. Clin. Psychiatry 48 :* 406-408, (1987).

FEIGHNER J.P. : A comparative trial of fluoxetine and amitriptyline in patients with major depressive disorder. *J. Clin. Psychiatry 46 :* 369-372, (1985).

FRANK E., KUPPER D.J., PEREL J.M., CORNES C., JANETT D.B., MELLINGER A.G., THASE M.E., McEACHRAN A.B., GROCHOCINSKI V.J. : Three years outcomes for maintenance therapies in recurrent depression. *Arch. Gen. Psychiatry, 47 :* 1093-1099, (1990).

GUY W. : ECDEU Assessment Manual for Psychopharmacology, 3rd edition. National Institute of Mental Health, Rockville, (1976).

HAMILTON M. : A rating scale for depression. *J. Neurol Neurosurg. Psychiatry 23 :* 985-988, (1960).

LOEB C. ET AL. : Fluoxetine versus imipramine. *Int. Clin. Psychopath, 4 (suppl. 1)* : 75-79, (1989).

MONTGOMERY S.A., GREEN M., BALDWIN D., MONTGOMERY D. : Prophylactic treatment of depression : A public health issue. *Neuropsychobiology 22 :* 214-219, (1989).

POTTER W.Z., RUDORFER M.V., MANJI H. : The pharmacological treatment of depression. *N. Engl. J. Med., 325 :* 633-642, (1991).

RICKELS K. : Fluoxetine in major depression : a controlled study. : *Curr. Ther. Res. 39 :* 559-563, (1986).

ROPERT R. : Fluoxetine versus clomipramine in major depressive disorders. Multicentre study. *Int. Clin. Psychopath., 4 (suppl. 1) :* 89-95, (1989).

VAN RIEZEN H., SEGAL M. : Comparative evaluation of rating scales for clinical psychopharmacology. The Hamilton psychiatric rating scale for depression (HPRSD) - Section VI - 127-128. Elsevier, (1988).

Dr P. MESTERS,
Eli Lilly Benelux s.a.,
Rue de l'Etuve 52
1000 Bruxelles