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A Double-Blind Comparison of Sertraline and Imipramine in Outpatients with Major Depression: Acute (8 Weeks) and Continuation (16 Weeks) Treatment

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In a double-blind multicentre trial in patients with major depression, the efficacy and the tolerability of sertraline were compared to those of imipramine, during an 8-week acute treatment phase followed by a 16-week continuation treatment phase in treatment responders. A total of 104 patients who met DSM-III-R criteria for major depression, HAM-D 17-item $\geqslant 18$ and Raskin Depression score > Covi Anxiety score, were randomized to receive either sertraline or imipramine. The initial daily dosage of 50 mg of sertraline or imipramine was rapidly titrated upwards in increments of 50 mg/day at weekly intervals, tolerability permitting, to a maximum of 200 mg/day by the fourth week. Eighty-eight patients completed at least 3 weeks of treatment and were included in the efficacy evaluable population. Both treatment groups demonstrated similar improvements on depression and anxiety rating scales during acute treatment, however, sertraline demonstrated significantly more improvement relative to imipramine on the HAM-D and Covi Anxiety scales after 1 week of treatment. Sertraline was more effective (HAM-D 17-item, CGI-S, SCL-56 Total score, SCL-56 Depression score, Covi Anxiety score) than imipramine in reducing depressive symptoms at the end of 24 weeks of treatment. There were significant improvements in all rating scales at week 24 relative to week 8 in the sertraline group but not in the imipramine group. The SCL-56 Total score, SCL-56 Depression score, Raskin Depression score and Covi Anxiety score at week 24 relative to week 8 showed significantly greater improvement in the sertraline group compared to the imipramine group. Imipramine was associated with a significantly higher incidence of dry mouth, sweating, constipation, palpitations, and a significantly higher heart rate and blood pressure. Sertraline was associated with a significantly higher incidence of diarrhoea/loose stools and insomnia. This study demonstrated a faster onset of therapeutic effect for sertraline relative to imipramine, reflecting the initiation of sertraline in a therapeutic dose of 50 mg/day and the need for gradual titration of imipramine to a therapeutic dose, at the beginning of treatment. Although efficacy was similar in both treatment groups at the end of the 8 weeks of acute therapy, sertraline-treated patients continued to manifest gradual improvements in depressive and anxiety symptoms during the 16 weeks of continuation therapy such that sertraline-treated patients were significantly more improved at the end of 24 weeks of therapy. © 1997 by John Wiley & Sons, Ltd.

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INTRODUCTION

Sertraline is a potent and selective serotonin reuptake inhibitor with little or no affinity for neurotransmitter receptors (Koe, 1990). Sertraline has been shown to be an effective antidepressant in an extensive clinical trial programme. Studies of the acute treatment of major depression have been carried out comparing sertraline with placebo (Olie *et al*., 1994; Fabre *et al*., 1995), and both placebo and amitriptyline, mianserin or dothiepin as a reference comparator (Reimherr *et al*., 1990; Lydiard, 1994; Doogan and Langdon, 1994; Malt, 1995). In the treatment of pure dysthymia sertraline has been compared with imipramine (Thase *et al*., 1996), and placebo (Guelfi and Wiseman, 1995; Thase *et al*., 1996). The efficacy of sertraline in seasonal affective disorder (Blashko, 1995), and premenstrual dysphoric disorder (Yonkers *et al*., 1996) has also been demonstrated in placebo-controlled trials. The long-term efficacy of sertraline has also been established in studies which compared the ability of sertraline and placebo to prevent relapse in the medium term and to reduce the risk of the recurrence of new episodes of depression in the long term (Montgomery *et al*., 1991). Sertraline has also demonstrated efficacy in anxiety associated with major depression (Lapierre, 1991; Moon *et al*., 1993) and in the treatment of depression in the elderly (Cohn *et al*., 1990; Coffey and Richter, 1994; Newhouse and Richter, 1994).

Imipramine is a tricyclic antidepressant (TCA) which blocks the reuptake of norepinephrine as its predominant mode of action but also has weaker effects on the reuptake of serotonin. The TCAs also have activity in a wide range of neurotransmitter systems unnecessary for antidepressant activity and as a consequence cause many unwanted side-effects. The clinical application of these agents has been limited by difficulties in achieving adequate dosing, and by undesirable side-effects which may hinder compliance (Johnson, 1981), cause premature discontinuation of treatment (Montgomery *et al*., 1994) and may render the TCAs an expensive treatment option as the major component of the treatment cost of depression is the cost of treatment failure (Lane and McDonald, 1994). In addition, the TCAs are also highly toxic if taken in overdose.

The proper treatment of depression requires not just the relief of the acute symptoms but also a period of continuation treatment following acute treatment. After initial resolution of the acute depressive symptoms it appears that patients remain vulnerable to a return of their depression and if antidepressant treatment is discontinued too soon relapse of the symptoms is likely. The continuation phase of therapy to prevent relapse (i.e. re-emergence of the index episode of depression), typically extends 4–6 months after resolution of symptoms (Montgomery and Montgomery, 1992). In the study of Montgomery *et al*. (1991) patients with a major depressive episode received open-label sertraline for 8 weeks. Two hundred and ninety-five of these patients, who were stabilized on treatment, were randomly allocated to received either sertraline or placebo in the proportion of 2 : 1, sertraline:placebo in a double-blind fashion. The return of depressive symptoms in the following 4 months after apparent response to the index episode, defined as becoming and remaining moderately ill or worse on the Clinical Global Impression Scale was 18·5 per cent in sertraline-treated patients and 44·5 per cent in placebo-treated patients ($p < 0{\cdot}001$). Although sertraline and other SSRIs have been compared to TCAs in short-term acute clinical efficacy studies of 6–8 weeks duration and have shown comparable efficacy (Murdoch and McTavish, 1992), there have been few comparisons of sertraline or other SSRIs and TCAs in long-term studies. In a six-month placebo-controlled study in depressed patients in Norwegian primary care sertraline demonstrated superior efficacy to the tetracyclic antidepressant mianserin. In a 3-month study in elderly outpatients with major depression sertraline demonstrated superior efficacy to nortriptyline (Coffey and Richter, 1994). Of the TCAs, imipramine has the most evidence of long-term efficacy (Kupfer *et al*., 1992).

The present study compares the efficacy and safety of sertraline and imipramine in outpatients with major depression. Although patients were to receive active treatment for 6 months the study was conceptualized in two parts; an initial 8-week acute treatment phase followed by a 16-week continuation phase.

METHODS

The study was conducted in 10 centres across Canada (Service de Psychiatrie Ste-Foy; Institute Allan Memorial, Montreal; Vancouver General Hospital; Lakeshore General Hospital, Pointe

Claire; U.B.C. Health Sciences Centre Hospital, Vancouver; University Hospital, Saskatoon; Hospital Louis-H La Fontaine, Quebec; Wellesley Hospital, Toronto; Victoria Hospital, London; Montreal General Hospital). The first patient entered the study in January 1989 and the last patient completed the study in October 1990. Male and female outpatients, 18 to 65 years of age, who met DSM-III-R criteria for single episode or recurrent major depressive disorder were enrolled in this double-blind, randomized, parallel group trial. Patients were excluded from entry into the study if, female of childbearing potential and not using an adequate form of contraception, receiving anticholinergic or anticonvulsant medication, significant physical illness or illness likely to be exacerbated by the anticholinergic properties of imipramine, substance abuse within the last 6 months, and electroconvulsive therapy or inpatient psychiatric care in the last 2 months. Initially, patients received a single-blind placebo washout 4–14 days. Patients with a minimum total score of 18 on the first 17 items of the Hamilton Depression scale (HAM-D) and a score on the Raskin Depression scale greater than on the Covi Anxiety scale at the end of the placebo washout period were randomly assigned to study treatment with either sertraline or imipramine. Study treatment was given on a double-blind basis for 24 weeks. The sertraline and imipramine dosage was set at 50 mg/day for the first week with rapid upward titration in increments of 50 mg/day at weekly intervals, tolerability permitting, to a maximum of 200 mg/day by the fourth week. The titration schedule was well suited to finding the optimal dose of imipramine. At the time this study was conceived in 1987, the usually effective dose of sertraline was unknown, and the study was designed to find the maximum tolerated efficacious dose of sertraline in the range of 50 to 200 mg/day rather than the optimal dose. It is now known that the starting dose of 50 mg/day of sertraline is the usually effective dose of sertraline in depression (Preskorn and Lane, 1995).

ASSESSMENT

Patients were assessed every week for the first 4 weeks, bi-weekly during the following 4 weeks and monthly for the remaining 16-week period. The HAM-D scale (17-item total score and 24-item total score) (Hamilton, 1960), Clinical Global Impression-Severity of illness (CGI-S measured on a scale of 1–7, changing from normal, not at all ill to among the most severely ill) (Guy, 1976), the Hopkins Symptom Checklist (SCL-56-total score) (Derogatis *et al*., 1974), Raskin Depression score (three items, each measured on a scale of 1–5, changing from better to worse) (Lipman, 1982), and Covi Anxiety score (three items, each measured on a scale of 1–5, changing from better to worse) (Lipman, 1982) were used to monitor patients' response to treatment.

Patients were monitored for side-effects at each visit and blood pressure, heart rate, and temperature were also assessed. Routine laboratory tests and EKG were performed at baseline and at the final visit. Additional laboratory tests were performed at week 8. Blood was taken for plasma level determination of sertraline and imipramine (including its demethylated metabolite desipramine) at week 4, 8 and 24.

Data analysis methods

The study was designed to detect a 4-point difference in the HAM-D 17-item total scores between the treatments assuming a standard deviation of 5·5. A total of 85 evaluable patients was estimated to provide the study with 90 per cent power (type II error $\beta = 0{\cdot}10$), assuming type I error of $\alpha = 0{\cdot}05$.

The following patient data sets were defined for the efficacy and safety analysis. Patients were included in the efficacy evaluable group if they had completed at least 21 days of active treatment. All patients who received at least one dose of the study medication were included in the safety analysis.

Last visit analyses (in which patients discontinuing prior to the last study visit had their last observation carried forward to subsequent observation time points) were performed for acute treatment (i.e. baseline to week 8), acute and continuation treatment (i.e. baseline to week 24) and for continuation treatment (i.e. week 8 to week 24).

A multicentre two-way ANOVA with treatment, centre and their interaction in the model was conducted on all efficacy variables in efficacy evaluable patients at baseline and last visit. The changes and percentage changes from baseline to last visit were analysed for centre-by-treatment interactions and a significance level of greater than 0·1 was the limit to represent no centre-by-treatment interaction.

Table 1. Demographics, diagnosis and baseline condition

	Number (%) of patients*		
	Treatment group		
	Sertraline	Imipramine	Total
Gender			
Male	25 (46)	19 (38)	44 (42)
Female	29 (54)	31 (62)	60 (58)
DSM II R classification			
Major depression, single episode	21 (39)	22 (44)	43 (41)
Major depression, recurrent episode	33 (61)	28 (56)	61 (59)
On previous psychotropic treatment†	42 (81)	41 (82)	83 (81)
Flurazepan	12 (22)	7 (14)	19 (18)
Amitriptyline	8 (15)	10 (20)	18 (17)
Lorazepam	9 (17)	6 (12)	15 (14)
Alprazolam	8 (15)	5 (10)	13 (13)
Desipramine	5 (9)	6 (12)	11 (11)
Imipramine	4 (7)	7 (14)	11 (11)
Trimipramine	5 (9)	6 (12)	11 (11)
		Mean (SD)	
	Sertraline	Imipramine	Total
Age (years)	41 (11)	40 (11)	41 (11)
Weight (kg)	72 (16)	71 (16)	71 (16)
Age at onset of first symptoms (year)	33	33	33
Duration of depressive history (year)	6·3	6·0	6·2

*Reported in 104 randomized patients.
†No data available for two patients in the sertraline group.

All efficacy variables were analysed using parametric statistical tests with the exception of HAM-D responder rates. All tests of hypotheses were carried out with a two-sided significance level of 0·05. Comparisons of efficacy between treatment groups at each time point and last visit were done using the one-way ANOVA procedures while within group comparisons of change from baseline were computed by means of a Student paired *t*-test.

Non-parametric testing procedures were also used for the HAM-D depression item No. 1 and the CGI-Severity Score (Mann–Whitney *U* test for between treatment comparisons and Wilcoxon matched-pair signed-test for within group comparisons), and HAM-D responder rates (chi square with Yates correction for continuity for between treatment comparisons).

RESULTS

Demographics and baseline characteristics are summarized by treatment group in Table 1. There were no significant differences between treatment groups in their baseline demographics or in their baseline severity of depressive or anxiety symptoms (Table 2). There were more males and less females in the sertraline group, more patients in the sertraline group had received prior therapy with benzodiazepines and more patients in the imipramine group had received prior antidepressant treatment. Table 3 details patient disposition by treatment group: of the 104 patients who entered the active treatment period, 85 per cent ($n = 88$) completed at least 3 weeks of active treatment and were included in the efficacy evaluable group. Slightly more than half of the patients completed the full 24 weeks of study treatment. The number of patients who discontinued the study for various reasons was comparable between the treatment groups (Table 3).

The placebo washout period lasted for an average of 8 days (range 4–15 days) After randomization, the mean daily dose increased from an initial 50 mg/day to 170 mg/day by the end of the fourth week in both treatment groups. Over the next 4 weeks the dose was adjusted downwards if side-effects emerged. At the end of the eighth week

Table 2. Efficacy results at last visit

Variable	Sertraline ($n = 43$)		Imipramine ($n = 45$)		Between group significance for change in scores ($p =$)
	Mean baseline score	Change from baseline to last visit	Mean baseline score	Change from baseline to last visit	
HAM-D 17 item total score	23·2	−16·5 (71%)	23·3	−13·5 (62%)	0·04
CGI-S	4·8	−3·0 (63%)	4·6	−2·4 (52%)	0·04
SCL-56 total score	118	−33·5 (28%)	114	−20 (17%)	0·01
SCL-56 depression score	25	−9·1 (34%)	25	−7·3 (22%)	0·04
Raskin depression score	10	−5·6 (54%)	10·2	−4·6 (46%)	n.s.
Covi anxiety score	6·4	34%	6·5	22%	0·03

Table 3. Disposition of patients

	Number (%) of patients		
	Treatment group		
	Sertraline	Imipramine	Total
Randomized*	54 (100)	50 (100)	104 (100)
Completed 3 weeks†	43 (80)	45 (90)	88 (95)
Completed 8 weeks	38 (70)	38 (76)	76 (73)
Completed 24 weeks	26 (48)	27 (54)	53 (51)
Discontinued	28 (52)	23 (46)	51 (49)
Lack of efficacy	5 (9)	6 (12)	11 (11)
Adverse events	9 (17)	6 (12)	15 (14)
Maximum efficacy	2 (4)	2 (4)	4 (4)
Other reasons, unrelated to study treatment	12 (22)	9 (18)	21 (20)
Protocol violations‡	11 (20)	5 (10)	16 (15)
Study treatment <3weeks	6 (11)	3 (6)	9 (9)
Other protocol violations	5 (9)	2 (4)	7 (7)

*Patients included in the safety analysis.
†Patients included in the primary efficacy analysis.
‡Patients excluded from efficacy analysis.

the mean daily dose was 174 mg for sertraline and 168 mg for imipramine. The mean daily dose at last visit was 163 mg for both groups with 39 per cent and 42 per cent of the sertraline and imipramine patients, respectively, treated at the maximum daily dose of 200 mg.

Compliance, evaluated by returned tablet count, was high with mean compliance levels of 94 per cent or above in both treatment groups. This was supported by the analyses of plasma levels of sertraline and imipramine/desmethylimipramine at weeks 4, 8 and 24 which indicated similar high levels of compliance in both treatment groups. Drug plasma levels were not detected in one sertraline-treated patient and two imipramine-treated patients at 8 weeks and in one sertraline patient at 24 weeks. In patients with detectable plasma levels the mean plasma level at week 8 in sertraline-treated patients ($n = 33$) was 70 ng/ml and in imipramine-treated patients ($n = 33$) was 159 ng/ml. The majority of patients in the imipramine group were titrated to a dose of 200 mg/day and the mean level in these patients was 198 ng/ml. At week 24 the mean plasma level in patients receiving sertraline ($n = 22$) was 53 ng/ml and in imipramine-treated patients ($n = 21$) was 147 ng/ml, with patients who received imipramine 200 mg/day with a mean plasma level of 201 ng/ml. The duration of therapy was identical in both treatment groups in patients included in the safety analysis with a mean of 117 days but differed slightly in the efficacy analysis, sertraline-treated patients having a mean duration of 140 days compared to 128 days in imipramine-treated patients.

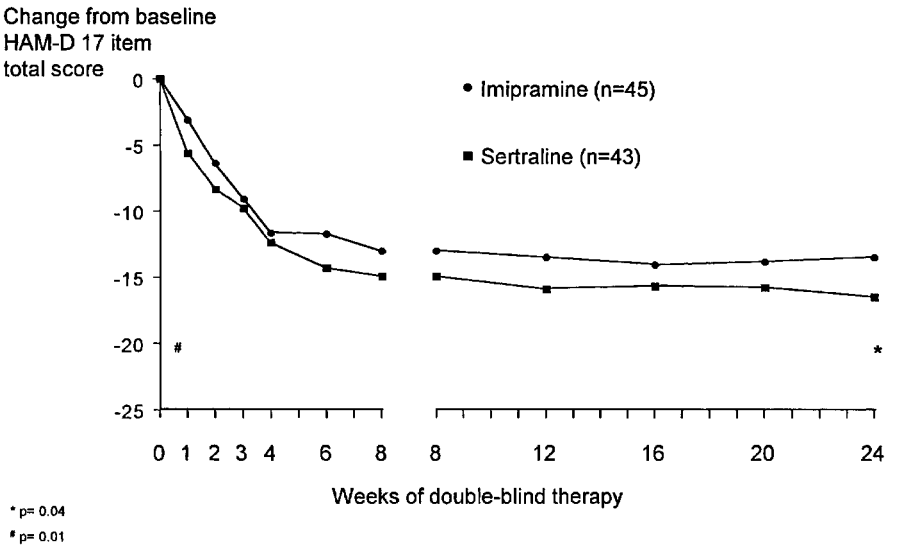

Figure 1. Mean change from baseline HAM-D 17-item score by visit (efficacy evaluable patients). For patients who discontinued therapy prior to 24 weeks, the last observation was carried forward to subsequent observation time points

Efficacy

The primary statistical comparison of treatments was carried out in the efficacy evaluable patient population (88 patients in total who completed at least 3 weeks of treatment) using the last available observation for each patient (Table 2, Figure 1).

All efficacy variables in the sertraline and imipramine groups demonstrated significant improvement (i.e. amelioration of symptoms of depression and accompanying symptoms of anxiety) relative to baseline at the last visit. All efficacy variables in Table 2 with the exception of the Raskin Depression scale, showed a significantly greater improvement in the sertraline-treatment group at last visit compared to the imipramine-treatment group. The numerical superiority of the Raskin Depression scale in favour of sertraline at last visit did not achieve statistical significance. However, in those patients completing 24 weeks of double-blind treatment, the improvement in the Raskin Depression score was significantly greater in the sertraline group compared to the imipramine group ($p = 0{\cdot}02$).

The results for the HAM-D total score (17 items) by treatment group are shown in Table 2. The change from baseline in the HAM-D total score showed significantly more improvement in the sertraline group compared to the imipramine group at the end of week 1, week 24 and at last visit. In sertraline-treated patients all efficacy variables showed significant changes from baseline by the end of the first week of treatment. In imipramine treated patients only the CGI-S, HAM-D 17 item and the Raskin Depression score showed significant change from baseline. In addition, at the end of the first week the improvements in HAM-D total score and Covi Anxiety score were significantly greater in sertraline-treated compared to imipramine-treated patients. Although the HAM-D item 1 showed significant change from baseline in both groups at the end of week 1, at the end of week 2 the improvement was significantly greater in the sertraline treatment group.

There were no significant differences between treatment groups at week 8 (Figures 1–4). However, after this time assessment measures remained fairly static in imipramine-treated patients but continued to improve in sertraline-treated patients (Table 4; Figures 1–4). In sertraline-treated patients there were significant within group changes on all efficacy variables tested from week 8 to week 24 in sertraline-treated patients (Table 4). In contrast, there were no significant changes in efficacy parameters in the imipramine group in the last 4 months of the study (Table 4). For four of the efficacy variables, the SCL-56 Total score, SCL-56 Depression score, Raskin Depression score and the

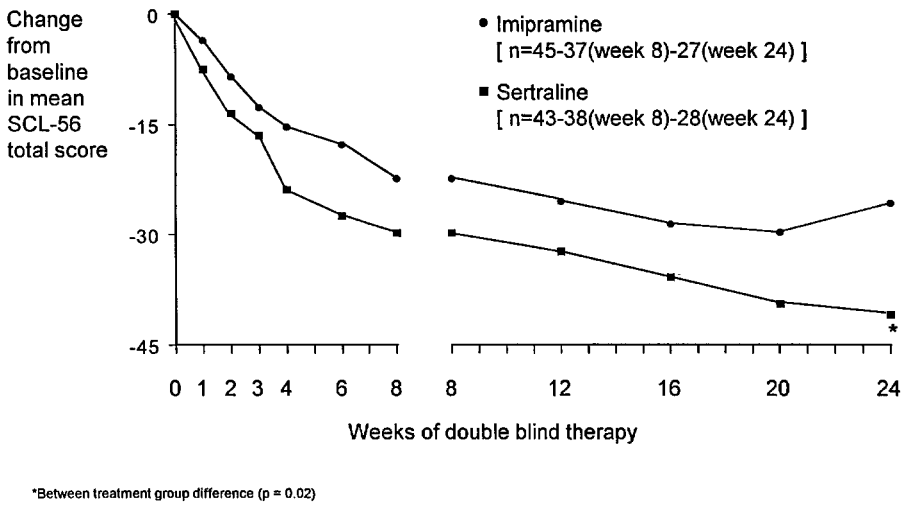

Figure 2. Change from baseline in mean SCL-56 Total score by treatment group and visit (efficacy evaluable patients)

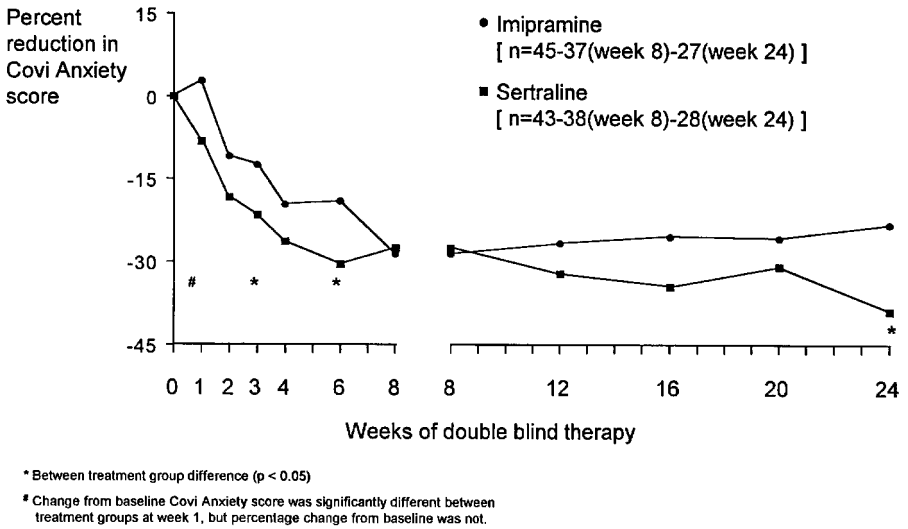

Figure 3. Percentage reduction from baseline in Covi Anxiety score by treatment group and visit (efficacy evaluable patients)

Covi Anxiety score there was significantly greater improvement in sertraline-treated patients relative to imipramine-treated patients (Table 4). There was no increase in the percentage of patients in the imipramine group achieving a reduction in HAM-D total score of $\geqslant 50$ per cent from week 8 (71 per cent) to week 24 (71 per cent), whilst in the sertraline group there was an increase in patients who met this criterion from week 8 (74 per cent) to week 24 (81 per cent). This increase was not statistically significant.

The SCL-56 Anxiety score was not significantly improved over baseline until the third week of treatment in the sertraline group, after which the SCL-56 Anxiety score remained significantly improved ($p < 0{\cdot}001$). For the imipramine group, significant improvement was observed after 8 weeks, and improvement was maintained for the rest of the study ($p < 0{\cdot}01$). The SCL-56 Anxiety score was significantly more improved at week 4 for sertraline-relative to imipramine-treated patients. The Covi Anxiety score was

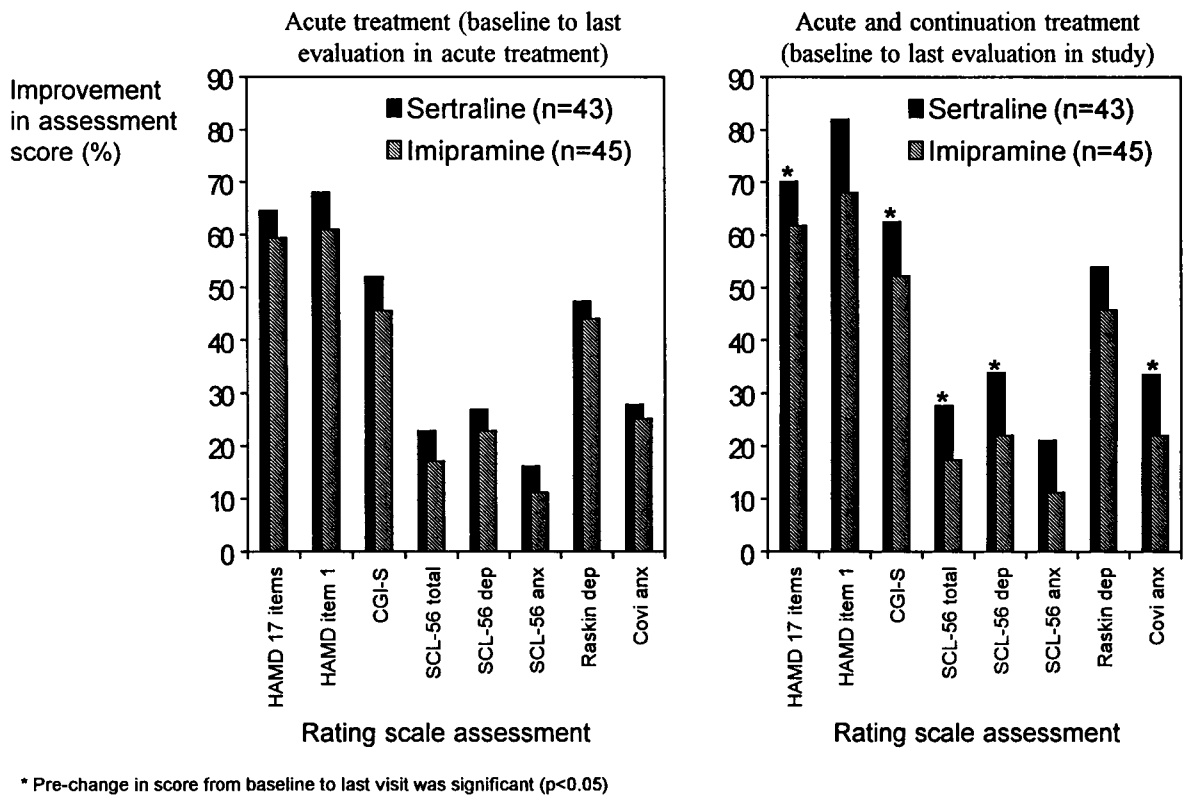

Figure 4. Percentage change in efficacy assessments during acute treatment and in acute and continuation treatment in efficacy evaluable patients. (Patients discontinuing prior to the last visit in acute or continuation treatment had the last observation carried forward to subsequent observation time points)

significantly improved over baseline in the sertraline group after 1 week and in the imipramine group after 2 weeks. The sertraline-treated patients showed a significantly greater change from baseline in the Covi Anxiety score at week 1, week 8 and week 24, compared to the imipramine group. The mean change in the Covi Anxiety score from week 8 to subsequent visits indicated continuing improvement in the sertraline group, whilst no such improvement occurred in the imipramine group, and at week 24 the mean change from week 8 was significantly greater in the sertraline group compared to the imipramine group (Table 4).

Table 4. Continuation efficacy results between week 8 and week 24

Variable	Sertraline		Imipramine		Between group significance ($p =$)
	Change from week 8 to week 24	Within group significance ($p =$)	Change from week 8 to week 24	Within group significance ($p =$)	
HAM-D 17 item	−3·6	0·005	−0·6	n.s.	n.s.
HAM-D item 1	−0·7	0·002	−0·3	n.s.	n.s.
CGI-S	−0·9	0·003	−0·3	n.s.	n.s.
SCL-56 Total score	−11·2	<0·001	−1·3	n.s.	0·006
SCL-56 Depression score	−3·1	<0·001	−0·3	n.s.	0·004
SCL-56 Anxiety score	−1·1	0·01	−0·2	n.s.	n.s.
Raskin Depression score	−1·4	0·007	−0·1	n.s.	0·04
Covi Anxiety score	−0·8	Not tested	0·4	Not tested	0·03

Safety

Over the entire course of the study 15 patients, nine (17 per cent) in the sertraline and six (12 per cent) in the imipramine group, discontinued therapy due to adverse effects, six patients, (five receiving sertraline and one receiving imipramine) discontinued treatment due to adverse events in the first 3 weeks of double-blind therapy. Of patients withdrawing prematurely for adverse events six sertraline patients had gastrointestinal complaints (nausea, diarrhoea, dyspepsia), one patients had whole body pruritus, one had perceived weight gain and one had elevated liver enzymes (AST, ALT, alkaline phosphatase). Two imipramine patients discontinued therapy due to cardiovascular effects (tachycardia), one due to cold sweating, numbness, painful ejaculation, blurred vision, dizziness, sedation and dry mouth, one due to somnolence and difficulty concentrating, one due to flu-like symptoms which may have been a hypersensitivity reaction, and one due to elevated liver enzymes (AST, ALT).

The most frequently reported adverse events are shown in Table 5. The anticholinergic side-effects (dry mouth, 66 per cent; sweating, 48 per cent; constipation, 34 per cent, and palpitations, 14 per cent) and dizziness, (26 per cent) had a significantly greater incidence in the imipramine group. The incidence of diarrhoea/loose stools (24 per cent) and insomnia (24 per cent) was significantly greater in the sertraline group.

Table 5. Incidence of adverse events with incidence >10 per cent in either group

Adverse event	Number (%) of patients	
	Sertraline	Imipramine
Patients exposed to study drug	54	50
Dry mouth	13 (24)	33 (66)*
Sweating	10 (19)	24 (48)*
Constipation	6 (11)	17 (34)*
Nausea	16 (30)	12 (24)
Sexual dysfunction	14 (26)	10 (20)
Dizziness	5 (9)	13 (26)*
Insomnia	13 (24)*	6 (12)
Diarrhoea/loose stools	13 (24)*	2 (4)
Drowsiness	11 (20)	7 (14)
Headache	9 (17)	8 (16)
Tremors/shakes	9 (17)	7 (14)
Fatigue/malaise	9 (17)	4 (8)
Palpitations	0 (0)	7 (14)*
Hot flushes	5 (9)	6 (12)
Light-headedness	1 (2)	6 (12)

*Between group comparison significant ($p < 0{\cdot}05$)

The average heart rate decreased from baseline to last assessment by 3/min in the sertraline group and increased by 10/min in the imipramine group (the difference between the two groups was significant at $p < 0{\cdot}0001$). The mean diastolic blood pressure slightly decreased in the sertraline group (by less than 1 mmHg) and increased by 4 mmHg in the imipramine group ($p < 0{\cdot}05$). The systolic blood pressure showed similar differences, though not statistically significant, between the two treatments. Three sertraline and eight imipramine-treated patients had treatment-emergent abnormal ECG recordings following initiation of study treatment.

In addition to the two patients (one from each treatment group) who were discontinued from the study due to elevated liver enzymes, one sertraline patient showed increased AST and ALT concentrations, and one imipramine patient exhibited increased urine red blood cell count (these patients remained in the study). No other clinically significant laboratory abnormalities were reported.

DISCUSSION

This randomized, double-blind study assessed and compared the safety and efficacy of 24 weeks of treatment with sertraline versus imipramine in 104 outpatients who met the DSM-III-R criteria for single episode or recurrent major depressive disorder.

Safety analyses show similar incidences of total number of adverse events for the two treatments. Imipramine was associated with a higher incidence of anticholinergic effects, i.e. dry mouth, sweating, constipation and palpitation (tachycardia). Sertraline was associated with a higher incidence of diarrhoea/loose stools and insomnia. The incidence of some of the adverse events in both groups, but particularly in the sertraline group, is higher than those reported in other studies. Likely reasons include the rapid upward titration and the high total daily dose of sertraline used in this study. Five of the nine patients in the sertraline-treatment group who discontinued the study due to adverse experiences did so in the first 3 weeks of double-blind treatment (compared to just one of six in the imipramine group). These early discontinuations were primarily for gastrointestinal side-effects.

The rapid upward titration dosing schedule employed in this study is not in line with current

sertraline dosing recommendations. At the time the study was designed in 1987 the usually effective dose of sertraline in depression was unknown. This study along with others (Reimherr *et al*., 1990; Cohn *et al*., 1990), performed early in the clinical development of sertraline, employed a rapid upward titration dosage regimen. The dosage was increased by design rather than clinical assessment of need in 50 mg/day increments at weekly intervals from 50 mg/day to 200 mg/day for all patients unless limiting side-effects occurred. Thus rapid upward titration design artificially led to many patients receiving the higher dose levels of 150 mg and 200 mg/day by the third and fourth week, respectively, of active treatment and experiencing more side-effects (especially gastrointestinal), regardless of whether they needed such high doses to experience an antidepressant response. The fact that patients receiving sertraline demonstrated a faster onset of therapeutic effect on the HAM-D and Covi Anxiety scales relative to imipramine after 1 week of double-blind therapy when patients had only received 50 mg/day of either treatment suggests that a longer trial at this dose was warranted in the sertraline group. At the end of the first week sertraline-treated patients relative to imipramine-treated patients were showing significantly greater HAM-D 17 item and Covi Anxiety score reductions (Figures 1 and 2). Similarly, significantly greater efficacy was also seen on the HAM-D item 1 at the end of week 2. This is perhaps unsurprising when it is considered that 50 mg/day is the usually effective antidepressant dose of sertraline in depression (Preskorn and Lane, 1995). However, the side-effect profile of imipramine prevents starting treatment at effective antidepressant doses. It is recommended that depressed patients remain on the starting does of sertraline, 50 mg/day, for at least 2–4 weeks before escalation of the dose is considered (Preskorn and Lane, 1995).

As a class SSRIs do not require dose titration, in contrast to the TCAs (Schatzberg, 1991). Dose titration is necessary with TCAs due to the fact that nuisance and sometimes more serious adverse effects prevent starting treatment with these drugs at effective antidepressant doses. In contrast, all SSRIs can be started at effective antidepressant dose. This difference led to an initial overestimation of the usually effective dose of all SSRIs during their clinical trial development programmes. In forced titration (i.e. ascending dose) studies the relatively benign side-effect profile of SSRIs meant that rapid titration of the dose was possible before an adequate trial of efficacy of the lower dose could be assessed. As the optimal therapeutic response to each dose of antidepressant only develops over the course of several weeks, the dose of SSRIs achieved in ascending dose studies were higher for all of these drugs than was necessary for clinical effect. Large fixed-dose studies, where various fixed-dose levels from across the clinically relevant dose range are compared to each other and placebo, were required to establish the dose–efficacy response relationship. Large fixed-dose studies in patients with major depression (Fabre *et al*., 1995), and with panic disorder (DuBoff *et al*., 1995) and obsessive compulsive disorder (Greist *et al*., 1995) have established 50 mg/day to be an effective dose relative to placebo, and higher doses (of 100 mg/day and 200 mg/day) to be no more effective. However, in these studies there was a dose-response relationship for the number of patients reporting adverse events and for discontinuations due to side-effects.

In other clinical studies of sertraline and imipramine in depression involving a more flexible dosing regimen i.e. dosage was escalated based on a clinical assessment of both efficacy and tolerability, have shown very significant differences in favour of sertraline in the number of patients discontinuing for adverse events. In a 12-week double-blind placebo-controlled trial in the treatment of 'pure' dysthymia sertraline and imipramine were equally efficacious but significantly more imipramine-treated patients (18·4 per cent) prematurely discontinued treatment for adverse events compared to the sertraline group (6·0 per cent) (Thase *et al*., 1996). In this study the incidences of dry mouth, constipation, dizziness, abnormal vision and postural hypotension were significantly higher for imipramine, whereas the incidences of diarrhoea and insomnia were significantly higher for sertraline.

In the present study sertraline was more effective (on the HAM-D 17 item, CGI-S, SCL-56 Total score, SCL-56 Depression score, Covi Anxiety score) than imipramine in reducing depressive symptoms at the end of 6 months of treatment (Table 2, Figures 1 and 4). In acute clinical efficacy studies of 6–8 weeks sertraline has demonstrated equivalent efficacy to other antidepressants (Murdoch and McTavish, 1992), although in a 6-week study in general practice patients with major depression, sertraline demonstrated significantly greater efficacy relative to placebo in contrast to dothiepin (Doogan and Langdon,

1994). However, in a 6-month placebo-controlled study in depressed patients in Norwegian primary care sertraline demonstrated superior efficacy to mianserin (Malt, 1994). Improvement in efficacy parameters was no different between sertraline and mianserin after 8 weeks of treatment and if the study had been terminated at this point the conclusion would have been that these antidepressants had comparable efficacy. A consistent finding of all studies of 6 months or more with sertraline, whether open (Floris *et al*., 1995), placebo-controlled (Montgomery *et al*., 1991; Malt, 1994) or active comparator-controlled (Malt, 1994; Van Moffaert *et al*., 1995), is the continuing reduction in depressive symptoms in the sertraline group over the entire course of the study. Similar findings have not always been demonstrated for active comparators, for example, in the study of Malt (1994), the efficacy of mianserin appeared to plateau during the latter half of the study. A similar pattern of efficacy response is seen in the sertraline and imipramine groups in the present study (Figures 1–4). There was a significant improvement in the HAM-D 17 item total score, HAM-D item 1, CGI-S, SCL-56 Total score, SCL-56 Anxiety score and Raskin Depression score at week 24 relative to week 8 in the sertraline group but not in the imipramine group (Table 4). In fact, the SCL-56 Total score, SCL-56 Depression score, Raskin Depression score and Covi Anxiety score at week 24 relative to week 8 showed significantly greater improvement in the sertraline group compared to the imipramine group (Table 4).

In this study sertraline was more effective than imipramine in ameliorating the symptoms of anxiety accompanying major depression (Table 2, Figure 3). In addition, sertraline showed a significantly greater anxiolytic effect at week 1 on the Covi Anxiety scale ($p = 0{\cdot}03$) and at week 4 on SCL-56 Anxiety score ($p = 0{\cdot}03$). This faster onset of therapeutic effect relative to imipramine in anxiety symptoms accompanying depression has also been demonstrated for paroxetine (Dunbar *et al*., 1995). Sertraline has demonstrated equal efficacy with clomipramine in the treatment of anxiety symptoms accompanying depression (Moon *et al*., 1994). Clomipramine, alone amongst the TCAs, is a potent serotonin reuptake inhibitor. Potent serotonin reuptake inhibition would appear to predict good anxiolytic effects. In a meta-analysis of 27 published and presented placebo-controlled studies in panic disorder, the SSRIs were shown to be significantly superior to both imipramine and alprazolam (Boyer, 1995). However, the anxiolytic potential of the SSRIs may vary amongst the group. Sertraline 50 mg/day, the lowest recommended daily dose, has been demonstrated to be an efficacious dose in fixed dose studies in depression, obsessive-compulsive disorder and panic disorder (Fabre *et al*., 1995; Greist *et al*., 1995; DuBoff *et al*., 1995). In contrast the minimum effective dose of paroxetine in depression, 20 mg/day (Dunner and Dunbar, 1992), has been shown to be ineffective in fixed-dose studies in obsessive-compulsive disorder (Wheadon *et al*., 1994) and panic disorder (Dunbar *et al*. 1995).

The high rate of sexual dysfunction in both the sertraline and imipramine groups needs to be addressed. The sexual dysfunction reported was primarily male ejaculatory delay or absence (Table 5) and the slightly higher incidence of sexual dysfunction in the sertraline group is attributable to the relatively higher number of male patients in the sertraline group (Table 1). The incidence of sexual dysfunction is dose related for sertraline (Preskorn and Lane, 1995) which is yet another reason to avoid the rapid upward titration to unnecessarily high doses of sertraline. Other rapid upward titration studies (Reimherr *et al*., 1990) employing high doses of sertraline (145 mg/day) demonstrated higher levels of side-effects in general, particularly nausea (36 per cent) and diarrhoea (24 per cent), but also a high incidence of male sexual dysfunction (21 per cent). Other controlled studies of sertraline in acute therapy (Doogan and Langdon, 1994; Bennie *et al*., 1995) and active comparator studies of sertraline in continuation therapy (Van Moffaert *et al*., 1995), where 50 mg was the usual daily dose, have reported a much lower incidence of sexual dysfunction.

The cardiovascular side-effect profile observed in this study confirms previous experience (Lane *et al*., 1994). Heart rate and blood pressure in the imipramine group were significantly higher and treatment-emergent ECG abnormalities were reported more often in the imipramine group compared with the sertraline group.

This study demonstrates that sertraline and imipramine demonstrate similar efficacy at the end of 8 weeks of acute treatment for a major depressive episode. The study illustrates the need to give the usually effective dose of sertraline, 50 mg/day, an adequate trial before escalating the dose, as unnecessarily rapid titration of the dose at weekly intervals in this study adversely affected the tolerability profile of sertraline causing an excess of

early discontinuations from treatment due, primarily, to gastrointestinal side-effects. In addition, when sertraline and imipramine are compared over the more clinically relevant treatment period of 6 months sertraline demonstrates superior efficacy to imipramine.

Adequate pharmacological therapy for a depressive episode requires the continuation of treatment beyond the stage of acute remission of symptoms to prevent relapse (i.e. re-emergence of symptoms of the index depressive episode). However, this study, in agreement with other studies of sertraline in continuation therapy, demonstrates that patients are not merely maintained by continuation therapy with sertraline but continue to manifest gradual improvement in depressive and anxiety symptoms throughout the full duration of continuation therapy.

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REFERENCES

Bennie, E. H., Mullin, J. M. and Martindale, J. J. (1995). A double-blind multicenter trial comparing sertraline and fluoxetine in outpatients with major depression. *Journal of Clinical Psychiatry*, **56**, 229–237.

Blashko, C. A. (1995). A double-blind, placebo-controlled study of sertraline in the treatment of outpatients with seasonal affective disorder. *European Neuropsychopharmacology*, **5** (Suppl. 3), 258.

Boyer, W. (1995). Serotonin uptake inhibitors are superior to imipramine and alprazolam in alleviating panic attacks: a meta analysis. *International Clinical Psychopharmacology*, **10**, 45–50.

Coffey, D. J. and Richter, E. M. (1994). A double-blind comparison of sertraline and nortriptyline in the treatment of depressed geriatric outpatients. *European Neuropsychopharmacology*, **4**, 333–334.

Cohn, C. K., Shrivastava, R., Mendels, J., Cohn, H. B., Fabre, L. F., Claghorn, J. L., Dessian, E. C., Itil, T. M. and Lautin, A. (1990). Double-blind, multicenter comparison of sertraline and amitriptyline in elderly depressed patients. *Journal of Clinical Psychiatry*, **51(B)**, 28–33.

Derogatis, L. R., Lipman, R. S., Rickels, K., *et al.* (1974). The Hopkins Symptoms Checklist (HSCL): a self-report symptom inventory. *Behavioral Science*, **19**, 1–15.

Doogan, D. P. and Langdon, C. J. (1994). A double-blind placebo controlled comparison of sertraline and dothiepin in the treatment of major depression in general practice. *International Clinical Psychopharmacology*, **9**, 95–100.

DuBoff, E. A., England, D., Ferguson, J. M., Londborg, P. D., Rosenthal, M. H., Smith, W., Weise, C. and Wolkow, R. M. (1995). Double-blind comparison of three fixed doses of sertraline and placebo in patients with panic disorder. *European Neuropsychopharmacology*, **5**(3), 287.

Dunbar, G., Steiner, M., Oakes, R., Gergel, I., Burnham, D. and Wheadon, D. E. (1995). A fixed dose study of paroxetine (10 mg, 20 mg, 40 mg) and placebo in the treatment of panic disorder. *European Neuropsychopharmacology*, **5**(3), 361.

Dunner, D. L. and Dunbar, G. C. (1992). Optimal dose regimen for paroxetine. *Journal of Clinical Psychiatry*, **53** (Suppl 2), 21–26.

Fabre, L. F., Abuzzahab, F. S., Amin, M., Claghorn, J. L., Mendels, J., Petrie, W. M., Dube, S. and Small, J. G. (1995). Sertraline safety and efficacy in major depression: a double-blind fixed dose comparison with placebo. *Biological Psychiatry*, **38**, 592–602.

Floris, M., DeNayer, A. R., Janssen, F., Van Houdenhove, B., Iancu, H. and Boxus, A. (1995). Acute and continuation therapy with sertraline in major depression: a large scale multicentre study. *European Neuropsychopharmacology*, **5**(3), 308–309.

Greist, J., Chouinard, G., DuBoff, E., Halaris, A., Kim, S. W., Koran, L., Lubowitz, M., Lydiard, B., Rasmussen, S., White, K. and Sikes, C. (1995). Double-blind parallel comparison of three dosages of sertraline and placebo in outpatients with obsessive–compulsive disorder. *Archives of General Psychiatry*, **52**, 289–295.

Guelfi, J. D. and Wiseman, R. L. (1995). Treatment of dysthymia with sertraline: a double-blind placebo-controlled trial in dysthymic patients without major depression. *European Neuropsychopharmacology*, **5**(3), 289.

Guy, W. (1976). *ECDEU Assessment Manual for Psychopharmacology*, revised edn. (DHEW Pub. No. (ADM) 76-338), NIMH, Rockville MD, pp. 217–222.

Hamilton, M. (1960). A rating scale for depression. *Journal of Neurology, Neurosurgery and Psychiatry*, **23**, 56–62.

Johnson, D. A. W. (1981). Depression: treatment compliance in general practice. *Acta Psychiatrica Scandinavica*, **63**, (Suppl. 290), 447–453.

Koe, B. K. (1990). Preclinical pharmacology of sertraline: a potent and specific inhibitor of serotonin reuptake. *Journal of Clinical Psychiatry*, **51** (12, Suppl. B), 13–17.

Kupfer, D. J., Frank, E., Perel, J. M., Cornes, C., Mallinger, A. G., Thase, M. E., McEachran, A. B. and Grochocinski, V. J. (1992). Five-year outcome for

maintenance therapies in recurrent depression. *Archives of General Psychiatry*, **49**, 769–773.

Lapierre, Y. D. (1991). Controlling acute episodes of depression. *International Clinical Psychopharmacology*, **6** (Suppl. 2), 23–25.

Lane, R. and McDonald, G. (1994) Reducing the economic burden of depression. *International Clinical Psychopharmacology*, **9**, 229–243.

Lane, R. M. and Sweeney, M. and Henry, J. A. (1994). Pharmacotherapy for the depressed patient with cerebrovascular and/or cerebrovascular illness. *British Journal of Clinical Practice*, **48**, 256–262.

Lipman, R. S. (1982). Differentiating anxiety and depression in anxiety disorders: use of rating scales. *Psychopharmacology Bulletin*, **18**, 69–77.

Lydiard, R. B. (1994). Sertraline vs. amitriptyline and quality-of-life: a double-blind, placebo-controlled study. *European Neuropsychopharmacology*, **10** (3, Part 2), 163S.

Malt, U. (1995). Practical aspects of long-term treatment. European Neuropsychopharmacology, **5**(3), 288–9.

Moon, C. A. L., Jago, W., Wood, K. and Doogan, D. P. (1994). A double-blind comparison of sertraline and clomipramine in the treatment of major depressive disorder and associated anxiety in general practice. *Journal of Psychopharmacology*, **8**(3), 171–176.

Montgomery, S. A., Doogan, D. P. and Burnside, R. (1991). The influence of different relapse criteria on the assessment of long term efficacy of sertraline. *International Clinical Psychopharmacology*, **6** (Suppl. 2), 37–46.

Montgomery, S. A., Henry, J., McDonald, G., Dinan, T., Lader, M., Hindmarch, I., Clare, A. and Nutt, D. (1994). Selective serotonin reuptake inhibitors: meta-analysis of discontinuation rates. *International Clinical Psychopharmacology*, **9**, 47–53.

Montgomery, S. A. and Montgomery, D. B. (1992). Prophylactic treatment in recurrent unipolar depression. In: *Long-Term Treatment of Depression*, Montgomery, S. A. and Rouillon, F. (Eds), Wiley, Chichester, pp. 53–79.

Murdoch, D. and McTavish, D. (1992). Sertraline: a review of its pharmacodynamic and pharmacokinetic properties and therapy potential in depression and obsessive-compulsive disorder. *Drugs*, **44**, 604–624.

Newhouse, P. A. and Richter, E. M. (1994). SSRIs in depressed elderly: a double-blind comparison of sertraline and fluoxetine in depressed geriatric outpatients. *European Neuropsychopharmacology*, **4**, 332–333.

Olie, J. P., Gunn, K. P. and Katz, E. (1997). A double-blind placebo–controlled multicentre study of sertraline in the acute and continuation treatment of major depression. *European Psychiatry*, **12** (in press).

Preskorn, S. H. and Lane, R. M. (1995). Sertraline 50 mg daily: the optimal dose in the treatment of depression. *International Clinical Psychopharmacology*, **10**, 129–141.

Reimherr, F. W., Chouinard, G., Cohn, C. K., Cole, J. O., Itil, T. M., LaPierre, Y. D., Masco, H. L. and Mendels, M. D. (1990). Antidepressant efficacy of sertraline: a double-blind, placebo- and amitriptyline-controlled, multicenter comparison study in outpatients with major depression. *Journal of Clinical Psychiatry*, **51**(12, B), 18–27.

Schatzberg, A. F. (1991). Dosing strategies for antidepressant agents. *Journal of Clinical Psychiatry*, **52** (Suppl.), 14–20.

Thase, M., Fava, M., Halbreich, U., Kocsis, J. H., Koran, L. and Davidson, J. (1996). A placebo controlled randomized clinical trial comparing sertraline and imipramine for the treatment of dysthymia. *Archives of General Psychiatry*, **53**, 777–784.

Van Moffaert, M., Bartholomew, F., Cosyns, P., Denayer, A. R. and Mertens, C. (1995). A controlled comparison of sertraline and fluoxetine in acute and continuation treatment of major depression. *Human Psychopharmacology*, **10**, 393–405.

Wheadon, D. E., Bushnell, W. D. and Steiner, M. (1994). A fixed dose comparison of 20, 40 or 60 mg paroxetine to placebo in the treatment of obsessive-compulsive disorder. Presented at the meeting of the American College of Neuropsychopharmacology (ACNP), San Juan, Puerto Rico, 12–16 December.

Yonkers, K. A., Halbreich, V., Freeman, E., Brown, C. and Pearlstein, T. (1996). Sertraline in the treatment of premenstrual dysphoric disorder. *Psychopharmacology Bulletin*, **32**(1), 41–46.