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ORIGINAL ARTICLE

A comparative, randomized, double-blind study of trazodone prolonged-release and sertraline in the treatment of major depressive disorder

C. Munizza [a], L. Olivieri [b], G. Di Loreto [b] and P. Dionisio [b]

[a] *Fourth Local Health Unit, Mental Health Department, Turin, Italy*

[b] *Angelini ACRAF SpA, Medical Department, Rome, Italy*

Address for correspondence: **Dr. Luisa Olivieri, Angelini Farmaceutici ACRAF SpA, Medical Department, P.le della Stazione s.n.c. – 00040 Pomezia, Rome, Italy. Tel.: +39 06 91045347; Fax: +39 06 9194333; email: l.olivieri@angelini.it**

Key words: **Major depressive disorder – Randomized controlled trial – Remission – Sertraline – Trazodone**

ABSTRACT

Objectives: To evaluate the efficacy and safety of trazodone prolonged-release compared with sertraline in the treatment of patients with major depression.

Research design and methods: A total of 122 patients aged 19–64 years were enrolled in this multicenter, double-blind, double-dummy, randomized, comparator-controlled study. Patients received 7 days of single-blind placebo treatment followed by 6 weeks of double-blind treatment with trazodone prolonged-release 150–450 mg/day ($n = 62$) or sertraline 50–100 mg/day ($n = 60$).

Outcome measures: Efficacy was evaluated by mean changes from baseline in the Hamilton Depression Rating scale (HAM-D), Montgomery Asberg Depression Rating Scale, Hamilton Anxiety Rating scale, and the Clinical Global Impression-Global Improvement/Severity scores; and by the rates of patients responding to treatment and considered to be in remission. Time to onset of efficacy and safety were assessed.

Results: Trazodone and sertraline were equally effective in reducing depressive symptoms and promoting remission, and had similar onset times. In the Intent-to-Treat population, there were no significant differences in favor of trazodone at study endpoint in all efficacy measures, while a statistically significant difference was detected in the Per-Protocol population on HAM-D and in the percentage of responders. Analysis of HAM-D factors (anxiety/somatization, cognitive disturbance, retardation, and sleep disturbance) indicated that sleep disturbances were significantly less evident for patients taking trazodone at study endpoint. Adverse drug reactions, mostly of mild intensity, were reported in 42% of trazodone-treated patients (mainly of the nervous system) and 43% of sertraline-treated patients (mainly gastrointestinal). One event was considered to be serious: a patient treated with trazodone 450 mg/day showed moderate anxiety/tremor/insomnia and was hospitalized. Treatment was discontinued; the patient made a full recovery.

Conclusions: This study showed that after 6 weeks, trazodone and sertraline were not different in reducing symptoms of depression and in producing disease remission. Tolerability profiles reflected the differing pharmacological properties of these antidepressants. Trazodone may be a therapeutic option in the treatment of patients with major depression showing prevalent sleep disturbances.

Introduction

Major depression is a common psychiatric disorder with high morbidity, mortality, psychosocial, and economic burden[1,2]; its estimated lifetime risk is 4–18%[3]. While effective treatments have been available for many years, most of the older antidepressants are associated with serious or unpleasant side effects because of their pharmacological actions on multiple neurotransmitter receptors that are unrelated to antidepressant action[4]. Such side effects may lead to non-compliance with treatment, premature discontinuation, limitation of long-term maintenance therapy and, ultimately, to relapse[5,6]. Additional research in the treatment of depression has been characterized by molecular targeting of specific neurotransmitters and their receptors[7]. The resulting newer antidepressants offer more acceptable side effect profiles and improved quality of life than that of the earlier classes of medications, with equal efficacy[8,9]. Because each patient presents with an individual problem, it is important that clinicians understand the similarities and differences between the increasing numbers of antidepressants in order to tailor the treatment to the specific needs of the patient.

Trazodone is the first Serotonin-2 Antagonist/Reuptake Inhibitor (SARI) to be developed for the treatment of depression[10]. Differing pharmacologically from other currently available antidepressants, it is a potent and selective postsynaptic 5-HT_{2A} antagonist and moderately potent serotonin reuptake inhibitor, with high affinity for 5-HT_{2A} receptors and moderate affinity of 5-HT_{1A} receptors[10–12].

Following oral administration, trazodone is completely absorbed from the gastrointestinal tract. A single dose of prolonged-release trazodone 150 mg in fasting condition has a C_{max} of about 1235 ng/mL at 3.6 h after administration, an $AUC_{0-\infty}$ of 15 071 ng/mL/h and a half-life of about 11 h. Twice daily administration was chosen to maintain adequate drug blood levels in patients with depression. In comparison, a single oral dose of immediate-release trazodone 50 mg has a C_{max} of about 770 ng/mL at 1.3 h after administration, an $AUC_{0-\infty}$ of 5268 ng/mL/h and a half-life of about 9 h (data on file, ACRAF, 2000). Pharmacokinetic assessments at steady state showed that once-daily administration of prolonged-release trazodone 150 mg is bioequivalent to immediate-release trazodone 50 mg taken three times a day in terms of extent of absorption (data on file, ACRAF, 2000). Trazodone is well tolerated and its effects, particularly in controlling anxiety and sleep disturbances, may be seen within the first week of treatment[13,14]. Trazodone has been shown to be at least as effective as classical tricyclic antidepressants, such as imipramine[15] and amitriptyline[16], and Serotonin Selective Reuptake Inhibitors (SSRIs), like fluoxetine[17], fluvoxamine[18], paroxetine[19], and sertraline[20], and have a tolerability profile superior to classical tricyclic antidepressants and comparable to SSRIs.

Sertraline, a potent and selective inhibitor of neuronal serotonin reuptake with minimal affinity for other serotonin receptors[8], including 5-HT_2, currently represents a standard reference treatment for patients with depression. A double-blind trial has previously demonstrated that trazodone and sertraline are of comparable efficacy, safety and usefulness in treating patients with depression or depressive state in Japan[20]. The objective of this 6-week trial was to compare the efficacy and tolerability of the trazodone prolonged-release versus sertraline in the treatment of outpatients with major depressive disorder.

Patients and methods

Study design

This was a 6-week multicenter, double-blind, randomized, parallel-group trial comparing trazodone and sertraline. The study design incorporated the double-dummy technique to mask the twice daily dosing of trazodone and once daily administration of sertraline. The study was performed from September 2002 to July 2005 in 11 centers in Hungary, Italy, Poland, Portugal, Spain, and Slovak Republic.

Patient selection

Outpatients aged 18–65 years with a DSM-IV[21] diagnosis of major depressive disorder were enrolled in the study. They were required to have a score of 18–24 on the 17-item Hamilton Depression Rating scale (HAM-D)[22] with a no greater than 20% decrease in HAM-D score between screening and baseline; a score lower than 30 on the Montgomery Asberg Depression Rating Scale (MADRS)[23] at baseline; symptoms of depression for at least 1 month before the run-in phase of the study; and not to be receiving treatment for the current phase of illness.

Excluded from the study were patients with melancholia or psychosis, a high risk of suicide or any primary psychiatric disorder other than major depression, a positive history for major depression refractory to medical treatments, alcohol or psychoactive substance abuse or dependence, seizure disorders, a history or presence of bipolar disorder, or any psychotic or mental disorder due to a general medical condition, or with any other clinically significant medical condition (hepatic or renal disease, myocardial infarction, pregnancy/lactation).

Patients were also excluded if they used psychopharmacologic or non-psychopharmacologic drugs with

psychotic effects or electroconvulsive therapy, with the exception of patients stabilized on benzodiazepines. During the single-blind run-in period and the first 2 weeks of the double-blind treatment only, patients were allowed to take either zolpidem up to 10 mg or chloral hydrate up to 1000 mg as required up to three times a week. Well established psychotherapy was also permitted.

Study procedures

The study comprised a single-blind placebo treatment run-in phase and a double-blind active treatment phase. Patients were evaluated at screening (visit 0, Day –7), baseline (visit 1, Day 1), and on Days 7, 21, and 42 of treatment (visits 2, 3, and 4, respectively).

To exclude responders to placebo entering the double-blind phase of the study, patients were treated with placebo twice daily during the 7-day run-in phase after screening. Eligible patients were randomly allocated to receive either 6 weeks of treatment with trazodone prolonged-release 150 mg twice daily or sertraline immediate-release 50 mg once daily. A centralized randomization list generated with a SPSS/8 for Windows NT version 4 program was used.

Trazodone was titrated over 1 week to the recommended dose. Study medication remained blinded by administering to patients two identical capsules each day provided in two different containers (one for the morning dose, the other for the evening dose). For the first 7 days, patients in the trazodone group received one placebo capsule in the morning and one capsule containing 150 mg trazodone in the evening. After 1 week of dose titration, these patients continued to take one capsule twice daily but both capsules contained the active drug (300 mg daily). Patients in the sertraline group took one sertraline 50 mg capsule in the morning and one placebo capsule in the evening from Day 1.

Patients considered to be non-responders after 3 weeks of treatment (Clinical Global Impression-Global Improvement score > 3)[24] were treated with an increased dosage of trazodone (450 mg/daily) or sertraline (100 mg/daily). In nine (trazodone four; sertraline five) of these cases, this was an independent decision by the clinician based on the patients' psychiatric condition and not on a CGI-GI score > 3 as required by the protocol.

Medical and psychiatric history was taken at screening, and a urine drug screen for substances of abuse, thyroid stimulating hormone levels and a urine pregnancy test for women of child bearing age were also assessed at this time. Physical examination, electrocardiograms (ECGs) and laboratory measurements were carried out at screening and on Day 42. Vital signs, body weights, concomitant medications and adverse events (MedDRA classification) were recorded at each visit.

Patients were assessed on the 17-item HAM-D scale at all visits. In addition, they were evaluated using the MADRS, Hamilton Anxiety Rating scale (HAM-A)[25] and Clinical Global Impression scale (CGI)[24] on Days 1, 7, 21, and 42 (or at premature study discontinuation).

All unused study medication was returned at each visit, and compliance to study medication was assessed from unused containers and capsules.

At each visit, all adverse events, both spontaneously reported by patients and following active questioning, were recorded. At the final visit (Day 42), patients' overall clinical tolerability of the study treatment was rated on a 5-point scale (very poor to very good).

Outcome measures

Efficacy outcome measures were the mean changes from baseline in the 17-item HAM-D, HAM-A and MADRS scores and CGI-Severity of Illness (CGI-S) and CGI-Global Improvement (CGI-GI), at Day 42. Analysis of HAM-D factors (anxiety/somatization, cognitive disturbance, retardation and sleep disturbance) was also performed.

Treatment efficacy was assessed from the rates of responding patients and patients in remission. Responder patients were defined as those patients with a 50% improvement on the HAM-D and/or MADRS and/or a CGI-GI score of 1 or 2 (very much improved or much improved) in comparison to baseline. A patient was deemed a 'sustained responder' if the observed response persisted until the last visit. Patients in remission were those with a HAM-D score of ≤ 7[26].

The onset time of efficacy was the visit on which a 50% improvement in HAM-D and/or MADRS was observed.

Statistical analysis

Statistical tests were interpreted at a 5% significance level (two-tailed). Efficacy analysis was performed on the Intent-To-Treat population (ITT) and the per-Protocol Population (PP). ITT was defined as all randomized patients who had the baseline assessment and at least one dose of study medication and at least one post-baseline efficacy assessment; missing values were replaced by the Last Observation Carried Forward (LOCF). PP analysis was defined as all randomized patients who met the eligibility criteria, and who completed all assessment procedures or dropped out

due to lack of efficacy/adverse drug reaction and had 80% or more compliance to the assigned treatment. Patients who withdrew for lack of efficacy or drug-related adverse events were included in the PP analysis as treatment failures.

The mean changes from baseline in HAM-D, MADRS and HAM-A were compared across the two treatment groups using an analysis of variance (ANOVA) or covariance (ANCOVA). CGI-GI and changes from baseline in CGI-S were compared using the Cochran–Mantel–Haenszel test. Numbers of responders and patients in remission were analyzed using the chi-square or Fisher's Exact test. A Kaplan–Meier analysis was used to assess the time to onset of efficacy.

Chi-square or Fisher's Exact test was used to compare the rate of discontinuations and incidence of adverse events between groups. Changes from baseline in vital signs and body weights were examined using an analysis of variance. The overall clinical rating of tolerability was compared by the Cochran–Mantel–Haenszel test.

Ethics

The study was performed in accordance with the latest revision of the Declaration of Helsinki, and the European Community Committee for Proprietary Medicinal Products guidelines of Good Clinical Practice for Trials on Medicinal Products (CPMP/ICH/135/1995); and was approved by the local Ethics Committees. Written informed consent was obtained from each of the participants, who could withdraw at any time from the study without compromising their subsequent medical care. No financial inducement was offered to patients.

Results

Patient characteristics

Of the 126 patients who entered the study, 122 were randomized to treatment (trazodone, 62; sertraline 60) in the double-blind phase. Four patients were not randomized due to spontaneous withdrawal (one patient), occurrence of exclusion criteria (two patients) and occurrence of placebo response (one patient). A total of 109 patients (trazodone, 57; sertraline, 52) completed the 6-week study.

Demography of the two groups is shown in Table 1, which includes psychiatric history. At baseline, the two treatment groups were balanced for gender, age and body weight, and there were no differences of clinical significance in vital signs, ECGs and physical examinations. The psychiatric condition of patients in the sertraline group appeared to be slightly more severe than those in the trazodone group, as patients reported numerically more hospitalizations and had suffered depressive symptoms for longer. This may be offset because patients in the trazodone group had suffered the present episode of depression for longer and previously taken more psychiatric medications. Furthermore, HAM-D, MADRS and HAM-A mean scores, and CGI-S were comparable between the groups at baseline.

A total of 20 patients (trazodone, 11; sertraline nine) were stabilized on benzodiazepines at study inclusion and continued on this treatment during the study. During the single-blind run-in period, seven patients

Table 1. *Demographic characteristics at baseline*

	Trazodone (n = 62)	Sertraline (n = 60)
Gender: male/female	25/37	18/42
Age (years), mean ± SD	45.0 ± 11.50	46.9 ± 10.55
Weight (kg), mean ± SD	72.0 ± 11.5	71.0 ± 15.9*
Duration of the present depression episode (months), mean ± SD	3.1 ± 4.79	2.4 ± 3.27
Duration from first to current episode (years), mean ± SD	8.2 ± 6.18	10.8 ± 10.11
Patients with previous episodes of depression, n (%)	45 (72.6)	43 (71.7)
Previous episodes of depression with hospitalization, n (%)	6 (9.6)	10 (16.7)
Previous episodes of depression without hospitalization, n (%)	45 (72.7)	40 (66.7)
Patients with history of suicidal attempts, n (%)	3 (4.8)	3 (5.0)
Other previous psychiatric illness, n (%)	1 (1.6)	0 (0)
Patients previously treated with psychiatric medications, n (%)	36 (58.1)	36 (60.0)
Previous psychiatric medications, n	166	127

*n = 59

SD = standard deviation

Patients in the sertraline group reported numerically more hospitalizations and had suffered depressive symptoms for longer; patients in the trazodone group had suffered the present episode of depression for longer and previously taken more psychiatric medications

(trazodone two; sertraline five) required zolpidem, but only three of them (trazodone one; sertraline three) continued this treatment in the first 2 weeks of the double-blind period.

Discontinuations

During the double-blind phase, eight patients (trazodone, two; sertraline, six) discontinued the study for adverse events, including dizziness, anxiety, insomnia and tremor (trazodone group) and gastrointestinal upset, headache, insomnia, palpitation, agitation, vertigo, hypertension, allergic bronchitis, dizziness and tremor (sertraline group); one trazodone-treated patient for lack of efficacy, and two patients in each group withdrew consent.

Study medication

Considering the whole treatment period, the mean daily dose of trazodone was 297 mg/day and of sertraline was 59 mg/day. Dosages were increased on Day 21 for 15 non-responder patients in the trazodone group (to 450 mg/day) and 15 in the sertraline group (100 mg/day).

Efficacy

Unless otherwise stated, results for the ITT population are presented here. There were no statistically significant differences between the trazodone and sertraline groups after 6 weeks of treatment when evaluated by the HAM-D, MADRS and HAM-A (Table 2, Figures 1–3). In the PP population, the trazodone group showed a significantly better HAM-D mean score on Days 21 and 42 ($p < 0.05$).

The statistically significant difference in favor of trazodone detected on Day 7 on the HAM-A (mean difference between treatments –1.6; 95% CI, –2.8, –0.3; $p < 0.05$) was not observed on Day 21 or at the end of the study. HAM-D factor analyses indicated that at the end of the study there was a statistically significant difference in favor of trazodone in sleep disturbance ($p < 0.05$) in both the ITT and PP populations.

Table 2. *HAM-D and MADRS scores*

	HAM-D		MADRS	
	Trazodone (n = 62)	Sertraline (n = 59)	Trazodone (n = 60)	Sertraline (n = 59)
Baseline				
Mean ± SE	21.7 ± 0.22	21.9 ± 0.22	25.3 ± 0.57	25.6 ± 0.55
Day 42				
Mean ± SE	8.6 ± 0.93	9.5 ± 0.82	9.0 ± 0.99	10.5 ± 1.04
Change ± SE*	–12.9 ± 1.15	–11.5 ± 1.08	–16.5 ± 1.67	–15.0 ± 1.51

*Least squares mean change from baseline
HAM-D = Hamilton Depression Scale; MADRS = Montgomery Asberg Depression Rating Scale; a reduction in score on the HAM-D and on the MADRS represents an improvement

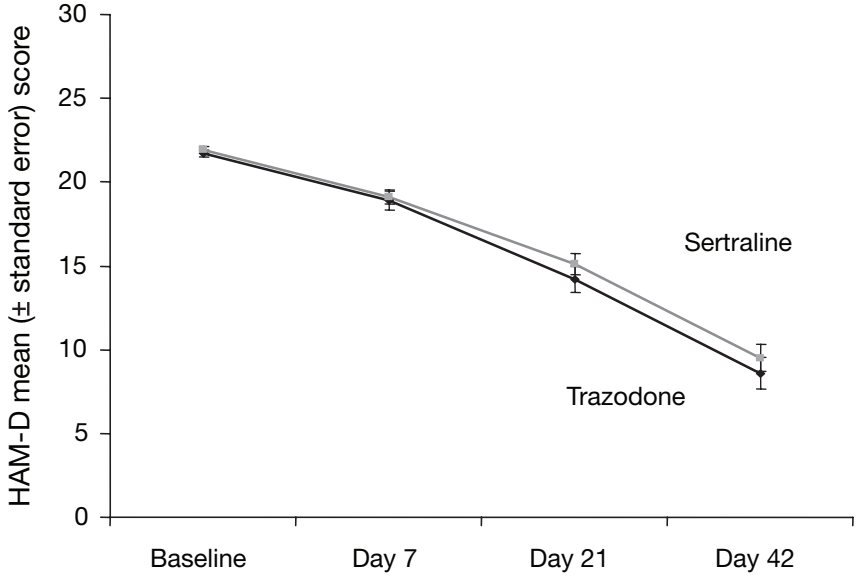

Figure 1. *Hamilton Depression Scale (HAM-D) from baseline to Day 42 (end of study) (trazodone,* n = 62*; sertraline,* n = 59*)*

Figure 2. *Montgomery Asberg Depression Rating Scale (MADRS) from baseline to Day 42 (end of study) (trazodone,* n = *60; sertraline,* n = *59)*

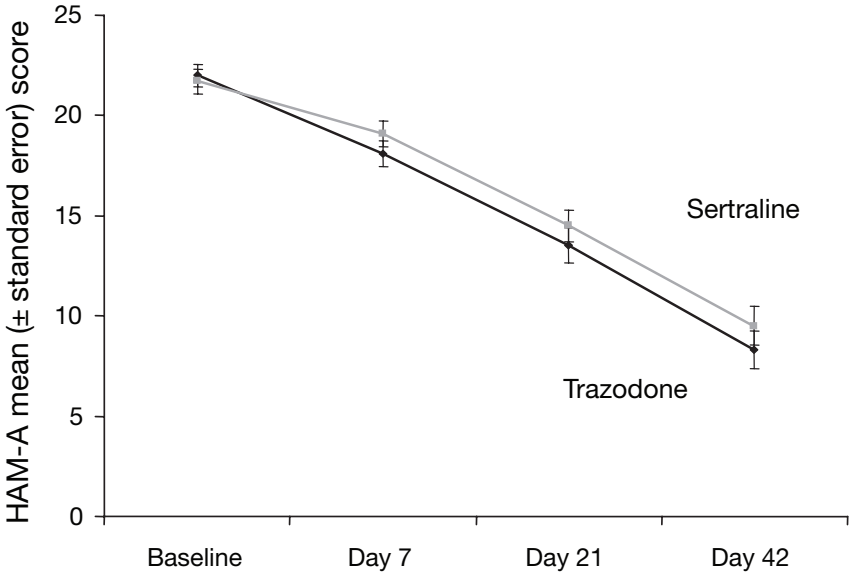

Figure 3. *Hamilton Anxiety Scale (HAM-A) from baseline to Day 42 (end of study) (trazodone,* n = *60; sertraline,* n = *59)*

Evaluation of CGI-GI and CGI-S showed that there were no statistically significant differences between the groups (Figures 4 and 5). At baseline, the large majority of patients (trazodone 60/60, 100%; sertraline 58/59, 98.3%) were considered to be moderately or markedly ill and no patient was considered to be normal or borderline. By the end of the study, over 80% in either group were considered to be normal or borderline or mildly ill (trazodone 52/60, 86.6%; sertraline 49/59, 83.1%).

At the end of treatment, over 70% of patients responded to trazodone and over 60% responded to sertraline; in the ITT population, there were no statistical differences between the groups (Table 3), while in the PP population the rate of patients responding to trazodone was significantly higher (80% vs. 62.1%, $p < 0.05$).

Seventeen patients in the trazodone group and 12 patients in the sertraline group showed a sustained response. In two sertraline-treated patients, the response observed at Day 21 was not confirmed at Day 42, and in one patient, the effect observed on Day 7 was not confirmed on Day 21 but reappeared on Day 42.

At the end of the study, 60% of patients in the trazodone group and 49% in the sertraline group showed disease remission; there were no statistical

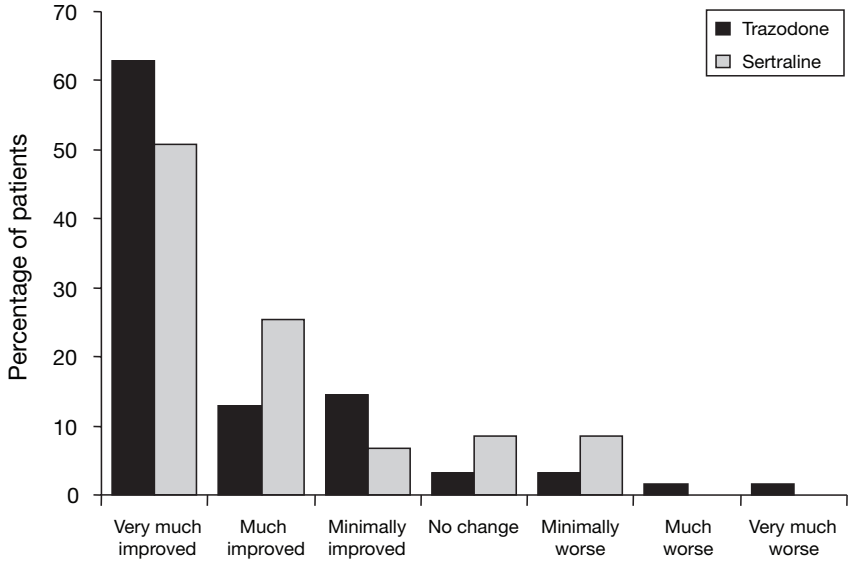

Figure 4. *Clinical Global Impression-Global Improvement (CGI-GI) at Day 42 (trazodone,* n = *62; sertraline,* n = *59)*

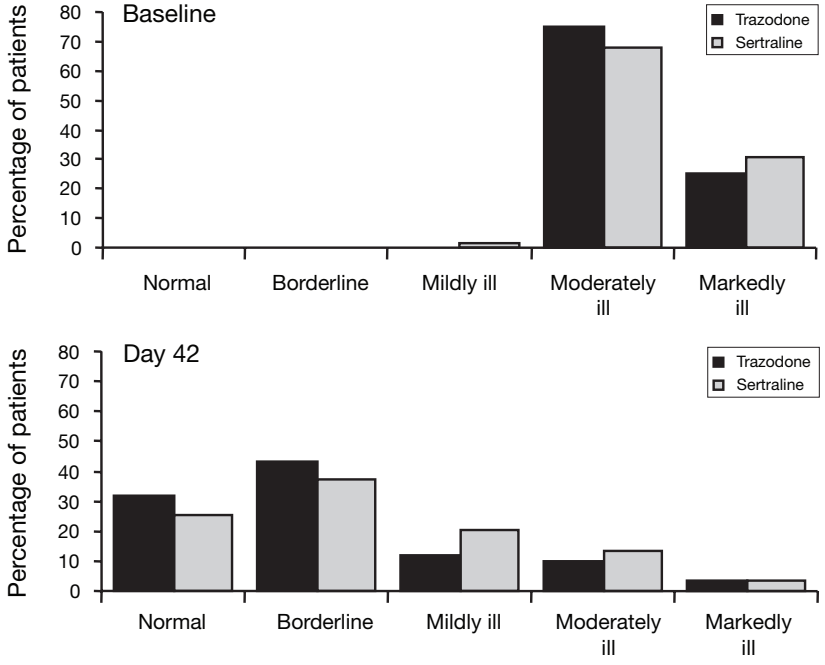

Figure 5. *Clinical Global Impression-Severity of illness (CGI-S) at baseline and at Day 42 (end of study) (trazodone,* n = *60; sertraline,* n = *59)*

Table 3. *Number (%) of patients responding to treatment (responder rates)*

	Trazodone (n = 62)*		Sertraline (n = 59)	
	n (%)	95% CI	n (%)	95% CI
HAM-D				
Day 7	3 (4.8)	–0.5, 10.2	1 (1.7)	–1.6, 5.0
Day 21	17 (27.4)	16.3, 38.5	14 (23.7)	12.9, 34.6
Day 42	46 (74.2)	63.3, 85.1	37 (62.7)	50.4, 75.1
MADRS				
Day 7	3 (5.0)	–0.5, 10.5	–	–
Day 21	22 (36.7)	24.5, 48.9	15 (25.4)	14.3, 36.5
Day 42	47 (78.3)	67.9, 88.8	39 (66.1)	54.0, 78.2

*n = 60 MADRS
HAM-D = Hamilton Depression Scale; MADRS = Montgomery Asberg Depression Rating Scale; Response: 50% decrease

differences between the groups (Table 4). Four of the 15 patients in each treatment group requiring a dose increase on Day 21 showed remission at endpoint.

There were no significant differences between the groups in efficacy onset time.

Safety

There were no deaths reported during the study. One patient treated with trazodone 450 mg/day reported one episode of moderate anxiety with concomitant moderate insomnia and tremor, requiring hospitalization. Trazodone was reduced to 300 mg/day and after 6 days discontinued. The symptoms were treated with lorazepam 2.5 mg/day and the patient made a full recovery.

A total of 52 patients (26 patients in each group) reported 114 adverse drug reactions (45.6% trazodone vs. 54.4% sertraline) (Table 5). Most were observed during the first week of treatment (48% trazodone vs. 58% sertraline). One-hundred and eleven of the 114 adverse events were non-serious; 71 were of mild intensity, 34 were of moderate and six were of severe intensity; severity was evenly distributed across the groups. The events most frequently involved the nervous system for patients in the trazodone group, and the gastrointestinal system for patients in the sertraline group.

After 6 weeks of treatment, no clinically significant changes in vital signs, body weights, ECGs and physical examination compared to baseline were found. Twelve laboratory tests (five hematology or blood biochemistry, seven urinalysis) in seven patients (trazodone three, sertraline four) were outside normal ranges on Day 42. Most were reported to be similar at screening, with the exception of mild increases in urinary leukocytes (trazodone, one patient) and in urinary erythrocytes (sertraline, one patient), and a positive urinary glucose (trazodone, one patient who also had a mild increase in glucose at screening and Day 42).

Table 4. *Number (%) of patients with remission (remission rates)*

	Trazodone (n = 62)		Sertraline (n = 59)	
	n (%)	95% CI	n (%)	95% CI
HAM-D				
Day 7	1 (1.6)	–1.5, 4.8	–	–
Day 21	7 (11.3)	3.4, 19.2	2 (3.4)	–1.2, 8.0
Day 42	37 (59.7)	47.5, 71.9	29 (49.2)	36.4, 61.9

HAM-D = Hamilton Depression Scale; Remission: HAM-D ≤ 7

Table 5. *Adverse drug reactions (ADRs) in > 1 patient and number of patients with ADRs*

	Total	Trazodone	Sertraline
Dizziness	20	12	8
Nausea	15	6	9
Somnolence	8	5	3
Headache	6	1	5
Insomnia	6	3	3
Diarrhea	5	2	3
Dry mouth	5	3	2
Vomiting	5	3	2
Tremor	4	3	1
Fatigue	3	1	2
Stomach ache	3	0	3
Anorexia	2	0	2
Anxiety	2	2	0
Mental concentration difficulty	2	2	0
Palpitation	2	1	1
Sedation	2	2	0
Sleepiness	2	2	0
Total ADRs (> 1 in any group)	92	48	44
Total ADRs (≥ 1 in any group)	114	52	62
Total patients with ADRs, n (%)	52/122 (42.6%)	26/62 (41.9%)	26/60 (43.3%)

Clinical tolerability was evaluated as good or very good in 58 (93.6%) of the trazodone-treated patients and 52 (86.6%) of the sertraline-treated patients; with no statistically significant differences between the groups.

Discussion

This multicenter, randomized, double-blind, parallel-group study demonstrated that at 6 weeks there is no difference in the efficacy of the SARI, trazodone, and the SSRI, sertraline, in treating patients with major depression of mild to moderate severity, even if some advantages of trazodone over sertraline in the PP population were observed. This is in agreement with previous studies that compared the antidepressive efficacy of trazodone and SSRIs, including sertraline[17–20].

The study design incorporated a single-blind placebo run-in phase to eliminate patients responding to placebo from entering the double-blind phase. During this phase, one patient only showed response to placebo. To reduce the severity and possible occurrence of adverse events, trazodone was titrated to the therapeutic dose. After 3 weeks of treatment, 15 patients in both treatment groups required dosage augmentation. No reduction in the daily dosage was foreseen in the study protocol or was needed during the trial.

A double-dummy technique enabled the study to remain blinded, and minimize bias in assessments. Doses were those recommended by the manufacturers, and the trazodone dose increase for patients considered to be non-responders was that recommended in hospitalized patients.

In the ITT population, there were no statistically significant differences between the trazodone- and sertraline-treated groups in any of the efficacy measurements at 6 weeks. Responder rates to the two treatments were not different, with over 70% of patients responding to treatment with trazodone and over 60% of patients to sertraline at study endpoint. However, trazodone showed some advantages over sertraline when used in well-selected patients, as demonstrated by the statistically significant results reported in the PP population, namely in the HAM-D mean score and rate of responder patients.

These results indicate a better therapeutic response to trazodone than to sertraline when the experimental procedures are rigorously followed, (e.g. when the treatment period is of adequate duration or when there are no major protocol to violations). On the other hand, the ITT analysis more strictly reflects usual clinical practice.

Previous studies have reported high responder rates in trazodone-treated patients[16,17,27], and similar responder rates in 6- and 8-week studies in sertraline-treated patients[9,28,29]. Whereas in other trials the high percentages of responders may have been partly due to an additive placebo effect, this seems less likely in this study because the placebo run-in phase removed placebo-responders. Nevertheless, the lack of a placebo-control group means that the proportion of responses due to the effect of the medication only remains unclear.

As with many therapies, the overall aim of treatment is to achieve disease remission and to return to a premorbid level of functioning[30]. Results of this study confirm that patients on either trazodone or sertraline achieve good rates of remission at 6 weeks. Findings are comparable to those in other SSRI-comparator studies[20,28], although treatment over longer time periods are necessary to confirm sustained efficacy that is a prerequisite for long-term maintenance therapy.

Onset of efficacy for alleviating depression (as measured using HAM-D and MADRS) was comparable, with both groups receiving benefits within 1 week of starting treatment. In a previous 6-week study in 218 patients with depression or depressive state, the percentage of patients with early onset efficacy (defined as moderate or marked improvement within the first week of treatment) was 46.9% and 40.4% in the trazodone and sertraline groups, respectively[20]. Interestingly, the SSRI, paroxetine, has been found to have a slightly faster onset of antidepressive activity compared with trazodone[19] and fluoxetine[31] after 3 weeks but was equally effective at 6 weeks. In comparison to fluoxetine, it appears that sertraline may also have an earlier time-to-response effect[32], while trazodone has shown a similar onset time[17].

Onset of anxiolytic activity (as measured using HAM-A) was faster for patients taking trazodone than for those on sertraline during the first week of treatment, although the difference was not apparent at 3 weeks. This early response may partly be attributed to the sedative effects of trazodone. Indeed, the rate of first occurrence of sedation is reported to peak during week 1 of trazodone treatment then decline, although new treatment-emergent sedation meant that the proportion of patients remained relatively stable[17]. Three patients only required concomitant treatment with zolpidem during the first 2 weeks of the double-blind period.

This study showed a positive effect of trazodone on the sleep disturbance factor of depression ($p < 0.05$ in both the ITT and PP populations), as observed in the sub-analysis performed on the HAM-D scale. Although this result may be related to the multiple analysis approach, which may throw up a significant result, the trazodone effect on sleep patterns of depressed patients, including significant improvements in

objective and subjective sleep and awakening quality, was formerly well recognized[33]. These effects, strictly related to its pharmacological characteristics, suggest that trazodone should be considered a treatment option for depressed patients with insomnia. The trazodone evening administration most probably enhances its sleep-inducing effect. Indeed, early relief of insomnia in a patient with depression may increase treatment compliance, daytime performance and overall functioning, while complete relief of insomnia may improve prognosis[30]. Insomnia is reported to be one of the most frequently reported adverse events in patients treated with SSRIs[8,17,32,34]. For example, data from a pooled analysis of 1902 sertraline-treated patients showed that 14% of patients reported insomnia[35]. Moreover, trazodone has been observed to produce a significant improvement in insomnia compared with sertraline[20]. Patients are frequently co-prescribed low dose trazodone at the beginning of SSRI treatment to prevent the negative effects of these antidepressants on sleep architecture[30]. However, as polytherapy can reduce treatment compliance, it may be more prudent to use an antidepressant that alleviates both depression and insomnia than one that requires concomitant sedative therapy[30].

Adverse events are generally most frequent during the first few weeks of trazodone treatment and decrease with continued use[36]. A similar decrease in number of adverse events and overall adverse effect burden (i.e., daily sum of subjective severity scores of all adverse effects) over time has been reported with sertraline treatment[8]. In this study, most adverse drug reactions were observed during the first week of treatment (48% trazodone vs. 58% sertraline), with the large majority being of mild or moderate intensity. One trazodone-treated patient reported an episode of moderate anxiety with concomitant moderate insomnia and tremor following a dose increase to 450 mg/day. This event was classified as serious as the patient required hospitalization. Numerically more patients taking sertraline discontinued the study for adverse events (trazodone, 3.2%; sertraline, 10%). Overall, there was no difference in the occurrence of adverse events and the clinical tolerability of both antidepressants was considered to be good/very good.

The tolerability profiles of the two groups reflected the differing pharmacological properties of the treatments; trazodone was most frequently associated with effects related to the nervous system whereas sertraline more often caused gastrointestinal events. As observed in this study, the most common adverse events occurring in a review of 1621 trazodone-treated patients from 58 studies were drowsiness (5.6% patients), tiredness (3.1% patients), gastrointestinal disorders (3%) and dizziness (2.6%)[37], while those occurring during sertraline treatment were nausea (21%), headache (18%), dry mouth (16%), diarrhea/loose stools (14.5%), insomnia (14%), and dizziness (13%)[35].

Given that this study confirms that there is no difference in overall efficacy and tolerability of trazodone in the treatment of patients with major depressive disorder compared with sertraline, clinicians should turn to the detail of efficacy factor analyses and side effect profiles for each medication when tailoring antidepressant treatment to a patient's specific needs. As previously reported in the literature[13,14,19] , this trial suggests that trazodone may be a therapeutic option in the treatment of depressed patients showing prevalent sleep disturbances.

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References

1. Keller MB, Lavori PW, Mueller TI, et al. Time to recovery, chronicity, and levels of psychopathology in major depression: a 5-year prospective follow-up of 431 subjects. Arch Gen Psychiatry 1992;49:809-16
2. Michaud CM, Murray CJL, Bloom BR. Burden of disease: implications for future research. J Am Med Assoc 2001;285: 535-9
3. Angst J. Epidemiology of depression. Psychopharmacology 1992;106:S71-S74
4. Corruble E, Puech A. How to improve the risk–benefit ratio of antidepressants. Int Clin Psychopharmacol 1993;8:237-41
5. Maj M, Veltro F, Pirozzi R, et al. Pattern of recurrence of illness after recovery from an episode of major depression: a prospective study. Am J Psychiatry 1992;149:795-800
6. Kasper S. Rationale for long-term antidepressant therapy. Int Clin Psychopharmacol 1993;8:225-35
7. Preskorn SH. Comparison of the tolerability of nefazodone, imipramine, fluoxetine, sertraline, paroxetine, and venlafaxine. J Clin Psychiatry 1995;56(Suppl 6):12-21
8. Murdoch D, McTavish D. Sertraline: a review of its pharmacodynamic and pharmacokinetic properties and therapeutic potential in depression and obsessive–compulsive disorder. Drugs 1992;44:604-24

9. Lydiard RB, Stahl SM, Hertzman M, et al. A double-blind, placebo-controlled study comparing the effects of sertraline versus amitriptyline in the treatment of major depression. J Clin Psychiatry 1997;58:484-91
10. Stahl SM. Essential psychopharmacology. Neuroscientific basis and practical applications. Cambridge: Cambridge University Press; 2000
11. Owen MJ, Morgan WN, Plott SJ, et al. Neurotransmitter receptor and transporter binding profile of antidepressants and their metabolites. J Pharmacol Exp Ther 1997;283:1305-22
12. Stahl SM. Basic psychopharmacology of antidepressants. Part 1. Antidepressants have seven distinct mechanisms of action. J Clin Psychiatry 1998;59(Suppl 4):5-14
13. Feighner JP. Trazodone, a triazolopyridine derivative, in primary depressive disorder. J Clin Psychiatry 1980;41:250-5
14. Fabre LF, Feighner JP. Long-term therapy for depression with trazodone. J Clin Psychiatry 1983;44:17-21
15. Patten SB. The comparative efficacy of trazodone and imipramine in the treatment of depression. Can Med Assoc J 1992;146:1177-82
16. Goldberg HL, Finnerty RJ. Trazodone in the treatment of neurotic depression. J Clin Psychiatry 1980;41:430-4
17. Beasley Jr CM, Dornseif BE, Pultz JA, et al. Fluoxetine versus trazodone: efficacy and activating-sedating effects. J Clin Psychiatry 1991;52:294-9
18. Namiki M, Eiji M, Minemoto H, et al. A clinical phase III study of SME3110 (fluvoxetine maleate) in depressed patients at the Department of Internal Medicine. A double blind, comparative study with trazodone hydrochloride. J Clin Ther Med 1996;12:651-77
19. Kasper S, Olivieri L, Di Loreto G, et al. A comparative, randomised, double-blind study of trazodone prolonged-release and paroxetine in the treatment of patients with major depressive disorder. Curr Med Res Opin 2005;21:1139-46
20. Tsutsui SA, Okuse S, Sasaki D, et al. A clinical evaluation of sertraline hydrochloride, a selective serotonin reuptake inhibitor, in the treatment of depression and depressive state. Jpn J Neuropsychopharmacol 1997;19:549-68
21. American Psychiatric Association. DSM-IV diagnostic and statistical manual of mental disorders, 4th edition 1994. International version with ICD-10 codes. Washington (DC): American Psychiatric Association; 1995
22. Hamilton M. Development of a rating scale for primary depressive illness. Br J Soc Clin Psychol 1967;6:278-96
23. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change.Br J Psychiatry 1997;134: 332-89
24. Guy W. ECDEU assessment manual for psychopharmacology [revised]. Rockville, (MD): US Department of Health, Education and Welfare; 1976. p. 217-22
25. Hamilton M. The assessment of anxiety states by rating. Br J Med Psychol 1959;32:50-5
26. Ballenger JC. Clinical guidelines for establishing remission in patients with depression and anxiety. J Clin Psychiatry 1999;60:29-34
27. Perry PJ, Garvey MJ, Kelly MW, et al. A comparative trial of fluoxetine versus trazodone in outpatients with major depression. J Clin Psychiatry 1989;50:290-4
28. Mehtonen OP, Søgaard J, Roponen P, et al. Randomized, double-blind comparison of venlafaxine and sertraline in outpatients with major depressive disorder. J Clin Psychiatry 2000;61:95-100
29. Feiger A, Kiev A, Shrivastava RK, et al. Nefazodone versus sertraline in outpatients with major depression: focus on efficacy, tolerability, and effects on sexual function and satisfaction. J Clin Psychiatry 1996;57(Suppl 2):53-62
30. Thase ME. Antidepressant treatment of the depressed patient with insomnia. J Clin Psychiatry 1999;60(Suppl 17):28-31
31. De Wilde J, Spiers R, Mertens C. A double-blind, comparative study of paroxetine and fluoxetine in out-patients with depression. Br J Clin Res 1997;8:23-32
32. Newhouse PA, Krishnan KRR, Doraiswamy PM, et al. A double-blind comparison of sertraline and fluoxetine in depressed elderly outpatients. J Clin Psychiatry 2000;61:559-68
33. Saletu-Zyhlarz GM, Abu-Bakr MH, Gruber G, et al. Insomnia in depression: differences in objective and subjective sleep and awakening quality to normal controls and acute effects of trazodone. Prog Neuropsychopharmacol Biol Psychiatry 2002;26:249-60
34. Falk WE, Rosenbaum JF, Otto MW, et al. Fluoxetine versus trazodone in depressed geriatric patients. J Geriatr Psychiatry Neurol 1989;2:208-14
35. Doogan DP. Toleration and safety of sertraline: experience world-wide. Int Clin Psychopharmacol 1991;6(Suppl 2):47-56
36. Saletu-Zyhlarz GM, Anderer P, Arnold O, et al. Confirmation of the neurophysiologically predicted therapeutic effects of trazodone on its target symptoms depression, anxiety and insomnia by postmarketing clinical studies with a controlled-release formulation in depressed outpatients. Neuropsychobiology 2003;48:194-208
37. Pohlmeier H, De Gregorio M, Sieroslawski H. Clinical data on trazodone: a review of the literature. In: Gershon et al. (Eds), Trazodone – a new broad spectrum antidepressant. Proc 11th Congr CINP, July 9–14, 1978. Amsterdam: Excerpta Medica, 1980, pp.8-26

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