

ORIGINAL ARTICLE

A comparative, randomised, double-blind study of trazodone prolonged-release and paroxetine in the treatment of patients with major depressive disorder

S. Kasper^a, L. Olivieri^b, G. Di Loreto^b and P. Dionisio^b

^a Department of General Psychiatry, Medical University, Vienna, Austria

^b Angelini ACRAF SpA, Medical Department, Rome, Italy

Address for correspondence: Dr. Luisa Olivieri, Angelini ACRAF SpA, Medical Department, Ple della Stazione snc, 00040 S Pomezia, Rome, Italy. Tel.: +39 06 91045347; Fax: +39 06 9194333; email: l.olivieri@angelini.it

Key words: Major depressive disorder – Paroxetine – Randomised controlled trial – Remission – Trazodone

ABSTRACT

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

Research design and methods: A total of 108 patients aged 20–68 years were enrolled in this multicentre, double-blind, double-dummy, randomised, paroxetine-controlled study. Each patient received 3 days single-blind placebo treatment followed by 6 weeks double-blind treatment with either trazodone prolonged release 150–450 mg/day ($n = 55$) or paroxetine 20–40 mg/day ($n = 53$).

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

Results: Trazodone and paroxetine were equally effective at reducing symptoms of

depression and promoting remission. Onset of efficacy was slightly faster for patients treated with paroxetine. Overall, there were no significant differences between the groups at endpoint in efficacy measures, and in percentage of responders (> 85%) or patients in remission (> 65%). Sleep disorders (HAM-D subset) were significantly less evident for patients in the trazodone group at the end of the study ($p < 0.05$). Adverse drug reactions were reported by 35% of trazodone-treated patients (mainly of the nervous system) and 26% of paroxetine-treated patients (mainly gastrointestinal), although none was considered to be serious.

Conclusions: This study showed that after a 6-week period trazodone and paroxetine are not different in reducing the symptoms of depression and, in many patients, in producing the remission of the illness. The known divergence in tolerability profile of the two medications, related to their differing pharmacological properties, was also confirmed. Trazodone may be of advantage in depressed patients with sleep difficulties.

* The results of the study were in part presented at the 24th CINP Congress, Paris, June 2004

Introduction

Major depression is a common, often chronic or recurrent disorder, which is associated with significant disability and comorbidity, imposing personal suffering on individuals and their families¹. Major depression alone is estimated to be the fourth most important cause of worldwide loss in disability-adjusted life years²; it is estimated that by the year 2020 depression will be second only to ischaemic heart disease worldwide as a source of disability and economic burden³.

Trazodone, the first Serotonin-2 Antagonist/Reuptake Inhibitor (SARI)⁴, to be developed for the treatment of depression, is a potent and selective postsynaptic serotonin 5-HT_{2A} antagonist and moderately potent inhibitor of serotonin reuptake^{4,5}. It shows high affinity for 5-HT_{2A} receptors and a moderate affinity for 5-HT_{1A} receptors⁶. Main characteristics of trazodone are a good safety profile and prompt relief of symptoms, frequently in the first week of treatment, particularly in the control of anxiety and sleep disturbances related to depression^{7,8}.

Clinical trials have shown trazodone to be at least as effective as classical tricyclic antidepressants, such as imipramine and amitriptyline^{9,10}, and Serotonin Selective Reuptake Inhibitors (SSRIs), such as fluoxetine, fluvoxamine and sertraline^{11–13}, with a tolerability profile better than that of classical tricyclic antidepressants and comparable to SSRIs. However, there is no reported direct comparison in Caucasian patients between trazodone and the SSRI paroxetine, which currently represents a standard reference treatment for depression. In contrast to trazodone, paroxetine is a selective and potent inhibitor of presynaptic serotonin reuptake, with a low affinity for 5-HT₂ receptors¹⁴.

The objective of this trial was to study the efficacy and tolerability of the trazodone prolonged release formulation in the treatment of patients with major depressive disorder, and to compare it with paroxetine.

Patients and methods

Study design

Trazodone and paroxetine were compared in an international multicentre, double-blind, randomised, parallel group clinical trial. The double-dummy technique was used to mask the twice daily dosing of trazodone versus the once daily administration of paroxetine. The study was performed in 7 centres in Austria, Czech Republic, Hungary, Poland and Slovak Republic. The enrolment period was of 14 months.

Patient selection

Outpatients aged 18–65 years with diagnosis of major depressive disorder according to DSM-IV criteria¹⁵

were selected to be enrolled in the study. Inclusion criteria were the following: an 18–24 score on the 17-item Hamilton Depression Rating scale (HAM-D)¹⁶ 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)¹⁷ at baseline; symptoms of depression present for at least 1 month before the run-in phase of the study; patients not receiving treatment for the current phase of illness.

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

Patients were also excluded if they used psychopharmacologic or non-psychopharmacologic drugs with psychotic effects or electroconvulsive therapy, with the exception of patients stabilised on benzodiazepines. During the single-blind period and the first 2 weeks of the double-blind treatment only, patients were allowed to take, on an 'as needed basis', up to 3 times a week, either zolpidem up to 10 mg or chloral hydrate up to 1000 mg.

Study procedures

Each patient was evaluated at screening (Visit 1, day -3), baseline (Visit 2, day 1), and after 7 days (Visit 3), 21 days (Visit 4) and 42 days (Visit 5) of treatment.

The study comprised two phases, a run-in single-blind phase and a double-blind phase. During the 3-day run-in phase after screening, patients were treated with placebo twice daily, in order to exclude placebo responder patients from the double-blind phase of the study.

Eligible patients were randomly assigned to receive 6-weeks of treatment with either trazodone prolonged release 150 mg twice daily or paroxetine immediate-release 20 mg once daily. A one week 150 mg/day dose-titration was scheduled for trazodone-treated patients.

The double-blind conditions were maintained by administering to each patient two daily indistinguishable capsules provided in different packages (one for the morning, and one for the evening administrations).

While titrating the dose, patients randomised in the trazodone group received one capsule containing placebo in the morning, and one capsule containing the active drug in the evening. After the 1-week dose titration, these patients continued to be treated with

one capsule **twice daily**, but always containing the active drug. Patients in the paroxetine group took one capsule containing the active drug in the morning, and one capsule containing placebo in the evening.

After 3 weeks of treatment, non-responder patients (Clinical Global Impression, Global Improvement score > 3) were treated with an increased dosage of trazodone (450 mg/day) or paroxetine (40 mg/day).

Starting doses were those recommended by the manufacturers; dose increases for patients considered to be non-responders were selected from previous experience for paroxetine¹⁸, or was that recommended for hospitalised patients for trazodone.

Medical and psychiatric history, and a urine drug screen for substances of abuse were assessed at screening; a urine pregnancy test was carried out for women of child-bearing potential at Visits 1 and 4. Physical examination, ECG and laboratory measurements were carried out at screening and at Visit 5. Vital signs, body weights and adverse events (MedDRA classification) were recorded at each visit.

At Visit 1, patients were assessed with the 17-item HAM-D scale only. At Visits 2–5, patients were assessed with the 17-item HAM-D, MADRS and CGI scale (Clinical Global Impression)¹⁹.

Patients were asked to return at each visit the used medication packages. Compliance to treatments was checked by counting the returned bottles and unused capsules.

Adverse events were those spontaneously reported by patients and/or those reported following active questioning of patients at each visit.

Outcome measures

The efficacy outcome measures were the CGI-Severity (CGI-S) and the CGI-Global Improvement (CGI-GI) scales and the mean changes from baseline in the 17-item HAM-D and MADRS scores.

Success of treatment was defined in terms of rate of responder patients and patients with remission: responder patients were those with a 50% improvement on the HAM-D and/or MADRS in comparison to baseline; patients with remission were those with a HAM-D score ≤ 7 ^{20,21}.

The onset time of efficacy was the visit on which a 50% improvement in HAM-D and/or MADRS was observed. A patient was considered a sustained responder when the observed response persisted until the last assessment.

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 randomised patients who had the baseline assessment 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 randomised patients who met the eligibility criteria, completed all visits, and who 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.

Numbers of responders, numbers of patients with remission, CGI-GI and changes from baseline in CGI-S were compared using the Cochran–Mantel–Haenszel test. The mean changes from baseline in HAM-D and MADRS were compared across the two treatment groups using an analysis of covariance. Time to onset of efficacy was analysed using the Kaplan–Meier test.

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

Ethics

The study was carried out in accordance with the latest revision of the Declaration of Helsinki, Good Clinical Practice and local regulatory requirements, and was approved by the local Ethics Committees. Written informed consent was obtained from each patient. Patients were free to withdraw from the study at any time for any reason, without effect on their medical care. No patient was offered financial inducement to participate in the study.

Results

Patient characteristics

One hundred and eight Caucasian patients (trazodone, 55; paroxetine, 53) out of 110 enrolled into the single-blind phase of the study were randomised to treatment in the double-blind phase. A total of 103 patients (trazodone, 50; paroxetine, 53) completed the study.

At baseline, the two treatment groups were balanced for age, sex and weight; no differences in vital signs, ECG or physical examinations between the groups were found. Demographics of the two groups, including psychiatric history are shown in Table 1. The psychiatric condition of patients in the trazodone group appeared to be more severe compared to those in the paroxetine group: significantly more patients in the trazodone group reported previous episodes of depression and

Table 1. Demographic characteristics at baseline

	Trazodone (n = 55)	Paroxetine (n = 53)
Male/female	23/32	17/36
Age (years), mean ± SD	43.5 ± 12.23	44.3 ± 11.28
Weight (kg), mean ± SD	72.4 ± 15.07	72.1 ± 13.22
Duration from first to current episode (years), mean ± SD	8.5 ± 7.48	9.6 ± 9.76
Duration of disease (months), mean ± SD	2.9 ± 4.94	2.1 ± 1.81
Previous episodes of depression, n (%)	50/55 (90.9)*	38/53 (71.7)
Previous hospitalisation due to depression, n (%)	14/50 (28.0)	9/38 (23.7)
Suicide attempts, n (%)	5/55 (9.1)	1/53 (1.9)
Other psychiatric illness/symptoms, n (%)	0/55 (0)	1/53 (1.9)

**p* < 0.05

numerically more patients had been hospitalised. Moreover, the current depressive symptoms had lasted longer, and more patients had attempted suicide in the trazodone group. However, HAM-D, MADRS and CGI-S were comparable between the groups at baseline.

Seven patients (5 trazodone and 2 paroxetine) were treated with benzodiazepines before study inclusion and continued with this treatment during the study (stable benzo-users). Moreover, one patient in each treatment group was treated with zolpidem in accordance with the protocol criteria, while 3 patients in each group (not included in the PP analysis) received this medication for a longer period than that indicated in the study protocol.

Discontinuations

Five patients (trazodone group) discontinued the study during the double-blind phase; three patients for adverse events (dry mouth/vertigo after 2 days of treatment, headache after 9 days, and oedema of legs/hands after 21 days), one patient for lack of efficacy, and one withdrew consent.

Study medication

The mean daily dose of trazodone was 305 mg/day and of paroxetine was 22 mg/day. Treatment doses were increased on Day 21 in 16 (29.1%) non-responder patients taking trazodone (to 450 mg/day) and 8 (15.1%) taking paroxetine (to 40 mg/day).

Efficacy

Results hereinafter presented refer to the ITT population, unless otherwise stated.

Trazodone and paroxetine were not different when evaluated by HAM-D and MADRS (Table 2, Figures 1 and 2). Results of CGI-GI and CGI-S are shown in Figures 3 and 4. Statistically significant differences in favour of paroxetine were detected at Day 21 (*p* < 0.05) on the HAM-D, CGI-S and CGI-GI, and disappeared at the end of the study.

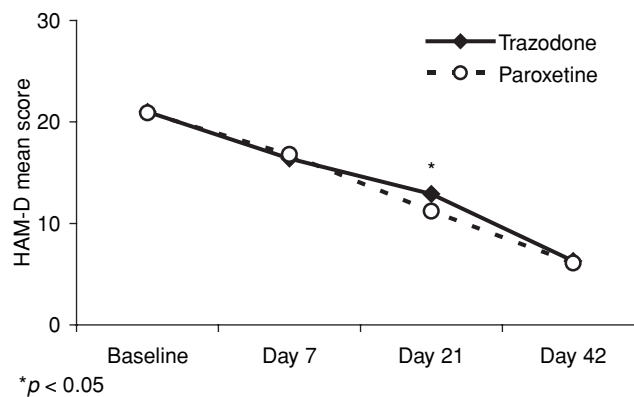


Figure 1. Time-course of the HAM-D scale (trazodone n = 55; paroxetine n = 53)

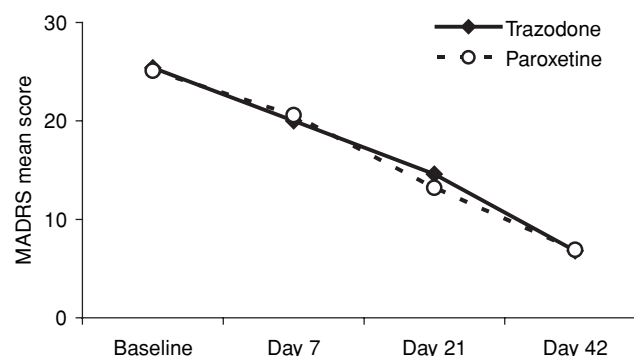


Figure 2. Time-course of the MADRS scale (trazodone n = 55; paroxetine n = 53)

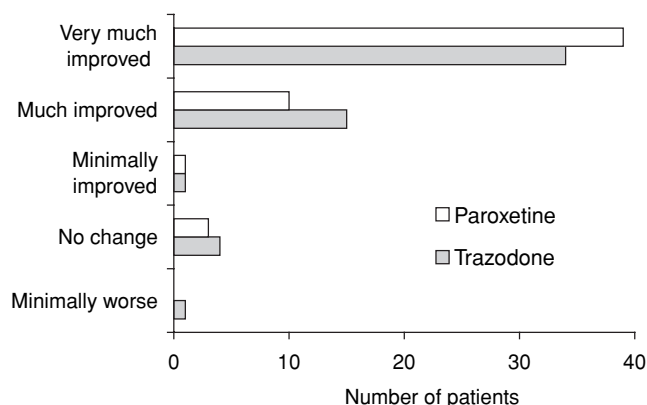


Figure 3. CGI-Global Improvement at Day 42 (trazodone n = 55; paroxetine n = 53)

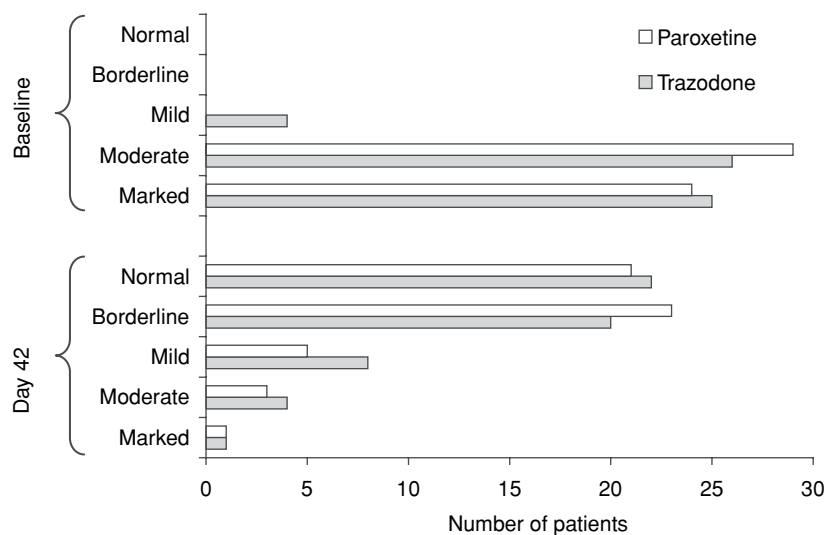


Figure 4. CGI-Severity of Illness (trazodone n = 55; paroxetine n = 53)

Table 2. HAM-D and MADRS scores (trazodone n = 55; paroxetine n = 53)

	HAM-D		MADRS	
	Trazodone	Paroxetine	Trazodone	Paroxetine
Baseline				
Mean ± SE	21.0 ± 0.21	20.9 ± 0.21	25.4 ± 0.51	25.1 ± 0.43
Day 42				
Mean ± SE	6.3 ± 0.74	6.1 ± 0.68	6.8 ± 0.84	6.9 ± 0.86
Change ± SE*	-14.6 ± 0.66	-15.0 ± 0.68	-18.3 ± 0.80	-18.4 ± 0.82

*Least squares mean change from baseline
HAM-D = Hamilton Depression Scale
MADRS = Montgomery Asberg Depression Rating Scale

At the end of treatment, over 85% of patients responded to treatment with either trazodone or paroxetine, without any statistical difference between the groups (Table 3). Sustained responses to treatment were observed in all patients, except for 2 trazodone-treated patients, in which the response on Day 7 was not confirmed on Day 21 but reappeared on Day 42. No statistical difference between groups was found.

At the end of treatment, more than two-thirds of patients showed disease remission (Table 4), with no statistically significant differences between the groups.

Few statistical differences between treatments in the HAM-D subsets (anxiety/somatisation, cognitive disturbance, retardation and sleep disturbance) were observed. On Day 21, the mean reductions in anxiety/somatisation and retardation were greater for paroxetine-treated patients than for those taking trazodone ($p < 0.05$). At the end of the study, the mean sleep score was significantly better in the trazodone than in the paroxetine group (PP population: $p < 0.05$).

Ten out of 16 (trazodone) and 2 out of 8 (paroxetine) patients requiring a dose increase on Day 21, showed remission at endpoint.

Table 3. Rate of patients responding to treatment

	Trazodone (n = 55)		Paroxetine (n = 53)	
	n (%)	95% CI	n (%)	95% CI
HAM-D				
Day 7	7 (12.7)	3.9–21.5	6 (11.3)	2.8–19.9
Day 21	17 (30.9)	18.7–43.1	24 (45.3)	31.9–58.7
Day 42	48 (87.3)	78.5–96.1	48 (90.6)	82.7–98.4
MADRS				
Day 7	7 (12.7)	3.9–21.5	6 (11.3)	2.8–19.9
Day 21	24 (43.6)	30.5–56.7	27 (50.9)	37.5–64.4
Day 42	49 (89.1)	80.9–97.3	46 (86.8)	77.7–95.9

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

Table 4. Rate of patients with remission

	Trazodone (n = 55)		Paroxetine (n = 53)	
	n (%)	95% CI	n (%)	95% CI
HAM-D				
Day 7	5 (9.1)	1.5–16.7	4 (7.6)	0.4–14.7
Day 21	10 (18.2)	8.0–28.4	13 (24.5)	12.9–36.1
Day 42	38 (69.1)	56.9–81.3	36 (67.9)	55.4–80.5

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

Table 5. Adverse drug reactions (ADRs) and number of patients with ADRs

	Total	Trazodone (n = 55)	Paroxetine (n = 53)
Nausea	7	1	6
Insomnia	6	3	3
Dry mouth	4	0	4
Headache	4	4	0
Tremor	4	2	2
Dizziness	3	2	1
Hypersomnia	3	3	0
Somnolence	2	1	1
Vertigo	1	1	0
Asthenia	1	0	1
Diarrhoea	1	0	1
Hypotension	1	0	1
Panic attack	1	0	1
Sedation	1	1	0
Sleep disorders	1	1	0
Sleepiness	1	1	0
Sweating	1	0	1
Total ADRs	42	20	22
Total patients with ADRs	33/108 (30.6%)	19/55 (35%)	14/53 (26%)

Safety

No deaths or serious adverse events were reported during the study. Overall, 33 patients (19 in the trazodone group and 14 in the paroxetine group) reported 42 non-serious adverse drug reactions (Table 5). These most frequently involved the nervous system for patients in the trazodone group (17 out of a total of 20) and the gastrointestinal system for those in the paroxetine group (11 out of a total of 22). One patient taking paroxetine who had a panic attack of moderate severity, required benzodiazepine treatment but no modification in the study medication.

After treatments, no clinically significant changes in vital signs, body weights, ECGs, and physical examination when compared to baseline were found. A mild increase in the level of aspartate aminotransferase in one paroxetine-treated patient was reported as a treatment-related adverse event at the end of the study.

Discussion

This study demonstrated that there is no difference in the efficacy of trazodone and paroxetine for the treatment of patients with major depression of mild to moderate severity. Previous studies, comparing other SSRIs such as fluoxetine¹¹, fluvoxamine¹² and sertraline¹³ with trazodone found comparable antidepressive properties for the SSRIs and this SARI.

Trazodone, but not paroxetine, was administered according to a dose titration schedule in order to reduce the severity of adverse drug reactions typically observed

when the starting dose coincides with the therapeutic one. The double-dummy technique allowed the study to remain blinded.

At study endpoint, no statistically significant differences between trazodone and paroxetine were found in any of the efficacy measurements. Although the small sample size does not allow any definite conclusions, the efficacy of trazodone is strengthened as patients treated with this medication appeared to have greater psychiatric morbidity at baseline, which was significant in terms of previous episodes of depression.

In each group, over 85% of patients responded to treatment and more than two thirds of patients showed remission of the disease. The high percentages of responders observed in this study, although reported previously in other studies^{10,22-24}, are probably in part due to an additive placebo effect, which includes the beneficial effects of increased patient-clinician interaction. The lack of a placebo-controlled arm does not allow this effect to be quantified exactly.

Remission of the disease, or a return to premorbid levels of functioning, is considered to be the goal in the treatment of major depressive disorder²¹. These results indicate that patients not only responded well but achieved good rates of remission. However, as the treatment duration was only 6 weeks, longer periods of treatment are necessary to confirm the long-lasting effect over time. Similar rates of response and remission have been previously observed at 6 weeks and 12 weeks in a double blind study comparing two paroxetine formulations²⁰.

Onset of efficacy was slightly faster for paroxetine-treated patients than for those taking trazodone. Patients

taking paroxetine showed significantly greater improvement after a 3-week treatment period, although the difference had disappeared by 6 weeks. Interestingly, an earlier onset of antidepressant activity has been previously reported for paroxetine compared with fluoxetine after 3 weeks of treatment (but not after 6 weeks) when onset was measured by a 50% reduction from baseline in HAM-D and MADRS scores²⁵, although generally paroxetine showed equivalence to other SSRIs¹⁴.

As a result of the time of onset of efficacy, fewer patients required a dose increase after 3 weeks of paroxetine treatment than after trazodone therapy. In contrast, more non-responders after 3 weeks of treatment with trazodone showed remission at the end of the study compared to those treated with paroxetine following an increase in dose of antidepressant (2/8 paroxetine, 10/16 trazodone). This suggests that some patients benefit from the higher trazodone dose and achieve remission, while dose increases in paroxetine may not achieve this effect. Dose increases of trazodone to 450 mg daily should therefore be considered in non-responders, although an adequate period of dose titration is recommended to reduce the occurrence of side effects.

During the study, few patients in both treatment groups were stable benzo-users or received concomitant therapy to treat insomnia. However, at the end of the study the only difference between treatments was for sleep disturbances which were significantly less evident in patients treated with trazodone than with paroxetine (PP population).

In depressed patients, paroxetine has been previously associated with an increase in the number of awakenings²⁶, while trazodone has been shown to positively affect all sleep patterns inducing significant improvements in objective and subjective sleep and awakening quality²⁷. Early relief of insomnia in a patient with depression may increase compliance with treatment and daytime performance and overall functioning, and complete relief of insomnia may improve prognosis²⁸. To counteract the effects of SSRIs on sleep architecture, patients are frequently co-prescribed low dose trazodone at the beginning of SSRI treatment²⁸. However, as adjunctive hypnotic-sedative therapy for insomnia may reduce treatment compliance, an antidepressant that alleviates both depression and insomnia may be more useful than one that requires concomitant sedative therapy²⁸.

The highest frequency of adverse effects generally develops in the first few weeks of trazodone treatment and is likely to diminish over time²⁹; similarly, a number of adverse drug reactions, particularly nausea, appear to decrease in incidence after a few weeks of paroxetine treatment¹⁴. In this study, approximately 50% of adverse drug reactions occurred within the first week

of treatment in both groups, and no change in tolerance was observed with dose increase. Events were generally of mild or moderate intensity; none were considered to be serious but 3 patients were withdrawn from trazodone treatment due to adverse events. While there was no difference in the overall occurrence of adverse drug reactions, the profile of events for each group corresponded to the pharmacological properties of the two antidepressants; trazodone more often produced effects related to the nervous system, whereas paroxetine more often induced gastrointestinal events. Similar to this study, the most common undesirable events occurring during trazodone treatment reported in a review of 58 studies and 1621 patients were drowsiness (5.6% patients) and tiredness (3.1% patients)³⁰, while that occurring during paroxetine treatment is reported to be nausea, in clinical trials (22% of patients) and in post-marketing surveillance (14% of patients)^{14,31}.

The study supports the crucial role of serotonin in the pathophysiology of depression because patients were treated effectively in the majority of cases. The results of this study show a comparable antidepressant effect of trazodone and paroxetine, and confirm that trazodone may have some advantages for patients with major depression who have difficulties with sleeping.

Acknowledgements

This study was funded by ACRAF SpA. We would like to acknowledge the study investigators: Professor A Czernikiewicz, Medical University of Bialystok, Poland; Professor J Landowski, Medical University of Gdansk, Poland; Professor A Grzywa, Medical Academy of Lublin, Poland; Professor J Novotná, Ambulatory of Psychiatry, Brno, Czech Republic; Professor P Molčan, Psychiatric Hospital SPAM, Bratislava, Slovak Republic; Professor L Tringer, Medical University of Budapest, Hungary.

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. Mulrow CD, Williams Jr JW, Trivedi M, et al. Treatment of depression – newer pharmacotherapies. *Psychopharmacol Bull* 1998;34:409-579
3. Michaud CM, Murray CJL, Bloom BR. Burden of disease: implications for future research. *J Am Med Assoc* 2001;285: 535-9
4. Stahl SM. *Essential psychopharmacology. Neuroscientific basis and practical applications*. Cambridge: Cambridge University Press; 2000
5. Stahl SM. Basic psychopharmacology of antidepressants. Part 1. Antidepressants have seven distinct mechanisms of action. *J Clin Psychiatry* 1998;59(Suppl 4):5-14

6. Owen MJ, Morgan WN, Plott SJ, Nemeroff CB. Neurotransmitter receptor and transporter binding profile of antidepressants and their metabolites. *J Pharmacol Exp Ther* 1997;283:1305-22
7. Feighner JP. Trazodone, a triazolopyridine derivative, in primary depressive disorder. *J Clin Psychiatry* 1980;41:250-5
8. Fabre LF, Feighner JP. Long-term therapy for depression with trazodone. *J Clin Psychiatry* 1983;44:17-21
9. Patten SB. The comparative efficacy of trazodone and imipramine in the treatment of depression. *Can Med Assoc J* 1992;146:1177-82
10. Goldberg HL, Finnerty RJ. Trazodone in the treatment of neurotic depression. *J Clin Psychiatry* 1980;41:430-4
11. Beasley Jr CM, Dornseif BE, Pultz JA, Bosomworth JC, Saylor ME. Fluoxetine versus trazodone: efficacy and activating-sedating effects. *J Clin Psychiatry* 1991;52:294-99
12. 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
13. Tsutsui SA, et al. A clinical evaluation of sertraline hydrochloride, a selective serotonin reuptake inhibitor, in the treatment of depression and depressive state. *Jpn Neuropsychopharmacol* 1997;19:549-68
14. Gunasekara NS, Noble S, Benfield P. Paroxetine. An update of its pharmacology and therapeutic use in depression and a review of its use in other disorders. *Drugs* 1998;55:85-120
15. American Psychiatric Association. DSM-IV diagnostic and statistical manual of mental disorders, 4th ed. [International version with ICD-10 codes, 1995]. Washington (DC): American Psychiatric Association; 1994
16. Hamilton M. Development of a rating scale the primary depressive illness. *Br J Soc Clin Psychol* 1967;6:278-96
17. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry* 1997;174:332-89
18. Benkert O, Szegedi A, Kohlen R. Mirtazapine compared with paroxetine in major depression. *J Clin Psychiatry* 2000;61:656-63
19. Guy W. ECDEU Assessment manual for psychopharmacology [revised]. Rockville (MD): US Department of Health, Education and Welfare; 1976. p. 217-222
20. Golden RN, Nemeroff CB, McSorley P, Pitts CD, Dube EM. Efficacy and tolerability of controlled-release and immediate-release paroxetine in the treatment of depression. *J Clin Psychiatry* 2002;63:577-84
21. Ballenger JC. Clinical guidelines for establishing remission in patients with depression and anxiety. *J Clin Psychiatry* 1999;60:29-34
22. Perry PJ, Garvey MJ, Kelly MW, Cook BL, Dunner FJ, Winokur G. A comparative trial of fluoxetine versus trazodone in outpatients with major depression. *J Clin Psychiatry* 1989;50(8):290-4
23. Szegedi A, Wetzel H, Angersbach D, et al. A double-blind study comparing paroxetine and maprotiline in depressed outpatients. *Pharmacopsychiatry* 1997;30:97-105
24. Szegedi A, Wetzel H, Angersbach D, Philipp M, Benkert O. Response to treatment in minor and major depression: results of a double blind comparative study with paroxetine and maprotiline. *J Affect Disorders* 1997;45:167-78
25. 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
26. Staner L, Kerkhofs M, Detroux D, Leyman S, Linkowski P, Mendlewicz J. Acute, subchronic and withdrawal sleep EEG changes during treatment with paroxetine and amitriptyline: a double blind randomized trial in major depression. *Sleep* 1995;18:470-7
27. 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
28. Thase ME. Antidepressant treatment of the depressed patient with insomnia. *J Clin Psychiatry* 1999;60(Suppl 17):28-31
29. Saletu-Zyhlarz GM, Anderer P, Arnold O, Saletu B. 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
30. Pohlmeier H, De Gregorio M, Sieroslowski H. Clinical data on trazodone: a review of the literature. In: Gershon, Rickels, Silvestrini, editors. Trazodone – a new broad spectrum antidepressant [Proc 11th Congress CINP, July 9–14, 1978]. Amsterdam: Excerpta Medica; 1980. p. 8-26
31. Leyman S, Mattelaer PM, Van Steenberge I. Paroxetine: post-marketing experience on 4024 depressed patients in Belgium. *Eur J Clin Res* 1995;7:287-96

CrossRef links are available in the online published version of this paper:
<http://www.cmrojournal.com>
 Paper CMRO-3012_4, Accepted for publication: 27 May 2005
 Published Online: 17 June 2005
 doi:10.1185/030079905X53243