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A RANDOMISED, DOUBLE-BLIND COMPARISON OF THE EFFICACY AND SAFETY OF CITALOPRAM COMPARED TO MIANSERIN IN ELDERLY, DEPRESSED PATIENTS WITH OR WITHOUT MILD TO MODERATE DEMENTIA

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ABSTRACT

Depression is the most common psychiatric disorder among the elderly and in old age may interact with emotional and cognitive functioning. Depression in old age has been shown to be associated with degenerative changes in the brain. It is, therefore, important that in this patient population antidepressants with a favourable tolerability profile, such as the selective serotonin reuptake inhibitors (SSRIs), are examined for both antidepressant efficacy and effect on cognitive function and emotional impairment. This randomised, double-blind study compared the efficacy and tolerability of citalopram and mianserin in 336 elderly, depressed patients with or without dementia. Patients received either citalopram 20–40 mg/day or mianserin 30–60 mg/day for 12 weeks. The treatments were equivalent with respect to change in Montgomery–Åsberg Depression Rating Scale (MADRS) total score; patients in both treatment groups responded well. Patients with dementia showed a smaller decrease in total MADRS score than patients without dementia. Both treatments were well tolerated with a relatively low incidence of adverse events. Fatigue and somnolence were more frequent with mianserin, while insomnia was more frequent with citalopram. Overall, this study showed that the two treatments were equivalent in efficacy, and that citalopram is an effective, well-tolerated and non-sedative treatment for elderly depressed patients with or without dementia. Copyright © 2000 John Wiley & Sons, Ltd.

KEY WORDS—citalopram; mianserin; elderly; depression; dementia

Depression is the most common psychiatric disorder among the elderly. Depressive symptoms affect 15% of elderly people living in the community (Blazer, 1989). In residential care, the prevalence may be as high as 25–30% (Reynolds *et al*., 1993). Physical health problems and related psycho-social disabilities are strongly associated with depressive disorders in the elderly (Roberts *et al*., 1997; Williamson and Schulz, 1995).

Depression in late life has been shown to be associated with white matter degenerative changes in the brain (for review see Baldwin, 1993; Krishnan and Gadde, 1996). These findings have suggested a 'vascular depression hypothesis' (Alexopoulos *et al*., 1997a) and similar criteria have been proposed by Steffens and Krishnan (1998). Kramer-Ginsberg *et al*. (1999) found an association between signal hyperintensities on magnetic resonance brain scans and cognitive disturbances, while Alexopoulos *et al*. (1997b) showed that patients fulfilling criteria for vascular depression also had significantly more cognitive disturbances.

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In addition, the dementia disorders are often associated with depression. There is a high comorbidity of depression and dementia in the elderly (Jones and Reifler, 1994; Alexopoulos *et al*., 1993). Dementia is dominated by cognitive impairment, but also includes symptoms of emotional disturbance. One disorder may predispose the patient to the development of the other condition, and the two disorders may be superimposed (Alexopoulos, 1991).

In identifying an adequate treatment for elderly depressed patients, it is therefore important to evaluate both the antidepressant efficacy of a drug and its effects on dementia disorder and associated emotional symptoms. Such a treatment should not induce cognitive impairment and should be well-tolerated and safe to use in elderly patients with compromised health or who are taking concurrent medical therapies.

Selective serotonin reuptake inhibitors (SSRIs) are commonly used for the treatment of major depression and provide effective relief of depressive symptoms without the anticholinergic side effects reported with tricyclic antidepressants (TCAs). This reduction in the frequency of anticholinergic side effects compared to TCAs, means that there is a reduced risk of disturbing cognitive functions in frail elderly patients (Nyth *et al*., 1992) and of cardiovascular toxicity in overdose (Leonard, 1988). In addition, the SSRIs lack sedative properties which makes them useful for long-term treatment, particularly for elderly patients (Knegtering *et al*., 1994).

Citalopram is the most selective SSRI available (Hyttel *et al*., 1995). It has been evaluated in over 20 000 patients in clinical studies and been prescribed to almost 10 million patients, and has been shown to be an efficacious and well-tolerated treatment for depression (Montgomery and Johnson, 1995; Baldwin and Johnson, 1995; Muldoon, 1996). Adverse effects are mostly mild to moderate in severity, and include nausea, dry mouth, increased sweating, somnolence, tremor, diarrhoea and ejaculation failure (Muldoon, 1996). It has fewer anticholinergic side effects than the classical TCAs. Only nausea and ejaculation failure are more frequent with citalopram than with TCAs (Muldoon, 1996). Citalopram has good efficacy with few side effects in elderly patients (Nyth *et al*., 1992; Ragneskog *et al*., 1996; Gottfries, 1996). Compared with placebo, citalopram has been shown to improve emotional disturbances and other characteristic symptoms common in dementia disorders in elderly patients (Nyth and Gottfries, 1990; Nyth *et al*., 1992).

Mianserin is a second-generation piperazinoazepine used to treat depression in the elderly, and chosen as the comparator for this study. It has been used as a reference treatment in several other studies at recommended dose levels of 20–60 mg (Moon and Jesinger, 1991; Muijen *et al*., 1988). Mianserin enhances central noradrenergic turnover, presumably by blocking presynaptic noradrenergic receptor sites. Mianserin appears to have no cardiotoxic or anticholinergic effects and is well tolerated even in overdose (Burgess *et al*., 1978; Kopera, 1978; Burrows *et al*., 1979). Severe adverse events are rare and include blood dyscrasia, hypomania and hypotonia. However, it does possess sedative properties, which may be associated with an increased incidence of falls in the elderly (Blake *et al*., 1988). In addition, mianserin has been reported to cause delirium (Fisch and Alexandrowitz, 1988; Koponen *et al*., 1990; Bonne *et al*., 1995).

Two previous double-blind studies in young depressed patients have shown comparable efficacy of citalopram and mianserin (Ahlfors *et al*., 1988; de Wilde *et al*., 1985). The primary aim of this study was to compare the efficacy and tolerability of citalopram (20–40 mg) and mianserin (30–60 mg) over 12 weeks of treatment in elderly depressed patients with or without dementia. The Montgomery–Åsberg Depression Rating Scale (MADRS; Montgomery and Åsberg, 1979) was used as the primary efficacy scale. A number of secondary scales were also used.

METHODS

Patients

Male and female patients aged 65 years or older being treated as in- or outpatients in psychiatric hospitals, psychiatric specialist or general practices, or geriatric units were eligible for inclusion into this study. Patients were to have a diagnosis of major depression (DSM-III-R 296.2 or 296.3) and/or dysthymic disorder (DSM-III-R 300.4), a MADRS total score of $\geqslant 20$, and a Mini-Mental-State-Examination (MMSE) total score of $\geqslant 16$ (American Psychiatric Association, 1987; Folstein *et al*., 1975). For patients with a MMSE score of 16–24, the DSM-III-R diagnosis forms for dementia were completed.

Patients were excluded from the study if they had schizophrenia or a related psychotic disorder, a neurological disease other than vascular or primary degenerative dementia, a focal cortical deficit or chronic drug or alcohol abuse. Patients with severe somatic disorders, such as cardiac, renal, hepatic or endocrinological disorders or blood laboratory abnormalities, which, in the opinion of the investigator, interfered with participation in the study, were also excluded. Patients were not to have received other antidepressants (including moclobemide) during the previous 4–7 days; irreversible monoamine oxidase (MAO)-inhibitors (A or B), lithium and/or carbamazepine during the previous 2 weeks; or fluoxetine during the previous 5 weeks. Patients were also excluded if they had received electroconvulsive therapy within the previous 8 weeks, oral or parenteral neuroleptics during the previous week, depot neuroleptics during the previous 4 weeks, an investigational drug during the previous 3 months, or were known to be intolerant to or have had a non-response to the study drugs. Patients at risk for suicide in the investigator's opinion and patients treated with oral anticoagulants were also excluded.

DESIGN

This randomised, double-blind study was conducted at 34 European centres: Austria (1), Belgium (14), Estonia (3), Norway (9), Sweden (3) and Switzerland (4). Evaluator-rating sessions were held before the start of the study and at 6-month intervals during the study to reduce inter-rater variability. A steering committee, consisting of the principal investigators from each country, regularly met to discuss the progress and safety aspects of the study.

Patients were randomly assigned to 12 weeks of oral treatment with either citalopram or mianserin. The dose was fixed at one tablet per day (either citalopram 20 mg/day or mianserin 30 mg/day) for the first 4 weeks (fixed-dose phase). During weeks 5–12 (flexible-dose phase) the dose could be increased to two tablets per day (citalopram 40 mg/day or mianserin 60 mg/day), according to the investigator's judgement. These dose ranges were based on the recommended dosages for elderly patients in the participating countries and on previous studies that compared the two drugs at similar dose ranges (de Wilde *et al*., 1985; Ahlfors *et al*., 1988). To ensure blinding, the citalopram and mianserin tablets were identical in appearance and were taken once daily, preferably in the evening.

Prior treatment with benzodiazepines and/or hypnotics could be continued, but no other psychotropics were allowed. There was no restriction on treatment for somatic disorders, but the use of sumatriptan and oral anticoagulants was not permitted.

All patients gave written informed consent to participate in the study and were free to withdraw at any time.

Evaluation of efficacy

The primary efficacy variable was the MADRS total score and this was assessed at baseline and Weeks 4, 6, 9 and 12. The MADRS was chosen because it is designed to be sensitive to change (Montgomery and Åsberg, 1979), and has been widely used in depression studies in elderly (e.g. Kyle *et al*., 1998). There were a number of secondary efficacy variables which included the Clinical Global Impressions (CGI) severity of illness and global improvement scales (assessed at baseline and Weeks 2, 4, 6, 9 and 12), Gottfries-Bråne-Steen (GBS) subscale 3 ('emotional functions') and subscale 4 ('symptoms common in dementia disorders') (Gottfries *et al*., 1982), and MMSE (both assessed at baseline and Weeks 6 and 12). In addition, a modified Well-being Questionnaire (Bradley and Lewis, 1990) was completed at baseline and Week 12.

A comparison of the effect of treatment on the MADRS total score for patients with or without dementia was also performed. At the request of the Norwegian ethical committee, no patients with dementia were recruited in Norway.

Treatment compliance was assessed by a tablet count at each visit.

Efficacy and intent-to-treat population

The primary efficacy (EFF) population comprised all patients who fulfilled the inclusion criteria, had completed $\geqslant 4$ weeks of study treatment, had a compliance level of at least 50%, had taken no prohibited medication during the first 4 weeks of treatment, and had at least one MADRS assessment after baseline. If prohibited medication was taken after 4 weeks, the subsequent assessments were excluded from the EFF data set. Assessments made more than 1 day after last drug intake were also excluded from the EFF data set.

The intent-to-treat (ITT) population included all patients who had received at least one dose of study medication and who had at least one MADRS assessment after baseline.

Safety evaluation

On entry into the study, the medical history of each patient was recorded. On Day 1, a physical examination (including body weight), blood pressure and pulse rate, electrocardiogram (ECG) and laboratory analyses (haematology and clinical chemistry) were performed. At subsequent visits, body weight, blood pressure and pulse rate were checked.

All randomised patients who had received at least one dose of study drug were included in safety analyses. Adverse events were coded to WHO classification and compared by survival analyses. The withdrawal pattern was analysed by exact permutation tests. Adverse events were monitored throughout the study and recorded by the investigator, with a description of the event, its intensity and its relationship to the study drug.

Double-blind medication was made available to the patients for an additional 12 treatment weeks. Patients who continued treatment beyond 12 weeks were given an additional physical examination, vital signs measurement and evaluation of adverse events at the end of the total treatment period of 24 weeks or at discontinuation.

STATISTICAL METHODS

The statistical analysis focused on demonstrating equivalence in efficacy and a possible difference in tolerability between the two treatment groups. The choice of analysis set and statistical method was pre-specified in the study protocol and the statistical analysis plan.

Two different populations were analysed: For primary efficacy analysis the EFF population was chosen. The use of the EFF population when testing for equivalence is recommended by the ICH E9 guidelines (ICH, 1998). For secondary analysis, the ITT population was chosen. Primary and secondary efficacy variables were evaluated in both of these populations.

Based on the assumption that the end point MADRS scores are normally distributed with a standard deviation of 10 points, it was estimated that, at a 5% level of significance, 135 patients were required in each treatment group to ensure at least 90% power of identifying a true equivalence in efficacy (two one-sided tests procedure; Schuirmann, 1987).

Efficacy analyses

The primary efficacy analysis was a test for equivalence between the two treatments in the EFF population. A difference of four points in MADRS total score was defined as clinically relevant (Montgomery, 1994). An analysis of covariance on change from baseline to last valid MADRS total score was performed. Equivalence was defined by the 90% confidence interval (CI) for the mean difference between treatment groups lying fully within the interval -4 to $+4$.

CGI severity of illness and global improvement were analysed by survival analyses. Equivalence testing and exact permutation tests were used for the GBS scale. The WHO Well-being scale was analysed using equivalence testing and Student's *t*-test. As the subgroup of demented patients was too small to allow for separate statistical analyses, no results are presented for the MMSE and the GBS scale, as these scales are not adequate for the mixed cohort of predominantly non-demented patients.

Safety analyses

Statistical analyses of the safety population were made for any treatment-emergent adverse event and for each treatment-emergent adverse event occurring in more than 5% of patients.

RESULTS

Patients

Thirty-four centres in six countries recruited patients into the study. A total of 345 patients entered the study. Nine patients (four on citalopram, five on mianserin) from two centres were excluded from all analyses because of very poor protocol compliance. Therefore, the safety population was 163 patients in the citalopram group and 173 in the mianserin group. Sixteen patients who did not have at least one MADRS assessment after baseline were excluded from the ITT population, which consisted of 157 patients in the citalopram group and 163 in the mianserin group. Thirty-one patients from the ITT population were excluded

Table 1. Demographic data for the ITT population

	Citalopram ($N = 157$)	Mianserin ($N = 163$)
Sex (no. of patients [%])		
Female	123 [78]	132 [81]
Male	34 [22]	31 [19]
Age (years)		
Mean (SD)	74.5 (6.94)	75.8 (6.88)
Range	65–93	64–95
Dementia (no. of patients [%])		
Yes	26 [17]	27 [17]
No	131 [83]	136 [83]
Weight (kg)		
Mean (SD)	66.3 (12.44)	64.1 (11.79)
Range	34.0–105.0	34.0–100.0
Setting (no. of patients [%])		
Inpatient	64 [41]	71 [44]
Outpatient	93 [59]	92 [56]
Diagnosis (no. of patients [%])		
Dysthymia only	29 [18]	34 [21]
Dysthymia + first episode MD	11 [7]	11 [7]
Dysthymia + recurrent MD	17 [11]	13 [8]
No dysthymia + first episode MD	37 [24]	43 [26]
No dysthymia + recurrent MD	63 [40]	62 [38]
Age of onset (no. of patients [%])		
$\geqslant 60$ years	105 [67]	117 [72]
<60 years	52 [33]	43 [26]
Missing data	0	3 [2]
Family history of depression (no. of patients [%])		
Yes	27 [17]	22 [13]
No	130 [83]	141 [87]

MD = major depression.

from the EFF population because they had less than 4 weeks of treatment (17 patients), or had taken other psychoactive drugs during the first 4 weeks of treatment (13 patients), or both (one patient). The EFF population consisted of 140 patients in the citalopram group and 149 patients in the mianserin group.

The two treatment groups were well-matched with regard to patient demographics and baseline characteristics (Table 1). The study population was predominantly female (80%) and had a mean age of 75 years. The majority of patients (69%), 105 patients (67%) in the citalopram group and 117 patients (72%) in the mianserin group, had experienced their first depressive episode after the age of 60. Slightly more than half the patients were out-patients (93 patients (59%) in the citalopram group and 92 patients (56%) in the mianserin group). Most patients had a diagnosis of first episode major depression (48 patients (31%) in the citalopram and 54 patients (33%) in the mianserin group) or recurrent episode of major depression (80 patients (51%) in the citalopram and 75 patients (46%) in the mianserin group) with or without dysthymia. A diagnosis of only dysthymia was given in 29 patients (18%) in the citalopram and 34 patients (21%) in the mianserin group. Seventeen percent of patients (26 patients (17%) and 27 patients (17%) in the citalopram and mianserin groups, respectively) had dementia.

From all patients in the safety population, 21 (13%) discontinued the study in the citalopram group. The reasons for discontinuation were adverse events (eight patients—5%), lack of efficacy (three patients—2%) or other reasons 10 patients—6%). Seventy-nine patients (48%) remained on the starting dose of 20 mg/day citalopram and 67 patients (41%) had a dose increase to 40 mg/day. The average daily dose during the flexible-dose phase was 28 mg. In the mianserin group, 30 patients (17%) discontinued the study. The reasons for discontinuation were adverse events (15 patients—9%), lack of efficacy (five patients—3%), or other reasons (10 patients—6%). Ninety-five patients (53%) remained on the starting dose of 30 mg/day mianserin, and 60 patients (35%) increased to 60 mg/day. The average daily dose during the flexible-dose phase was 40 mg.

EFFICACY

MADRS total score

The primary efficacy analysis of the reduction from baseline in MADRS total score in the EFF population showed equivalence between the two treatments, with the 90% CI being within the pre-set limits of 4 points (0.27, 3.61, at last valid assessment). Both treatment groups showed a good response over the 12-week study period, with a reduction at the Week 12 assessment of 16 points for citalopram and 18 points for mianserin (Fig. 1). The response rate (patients achieving final MADRS $\leqslant 12$) was 57% for citalopram and 65% for mianserin.

A reduction of at least 50% from baseline MADRS total score for the EFF population was recorded in 66.4% of citalopram-treated patients

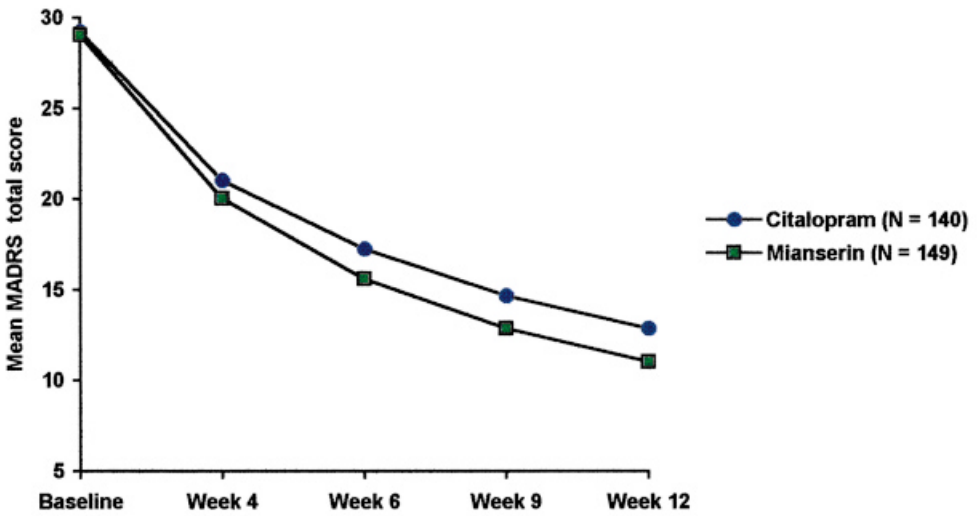

Fig. 1. Time course for mean MADRS total scores for citalopram and mianserin patients during the study period (EFF population)

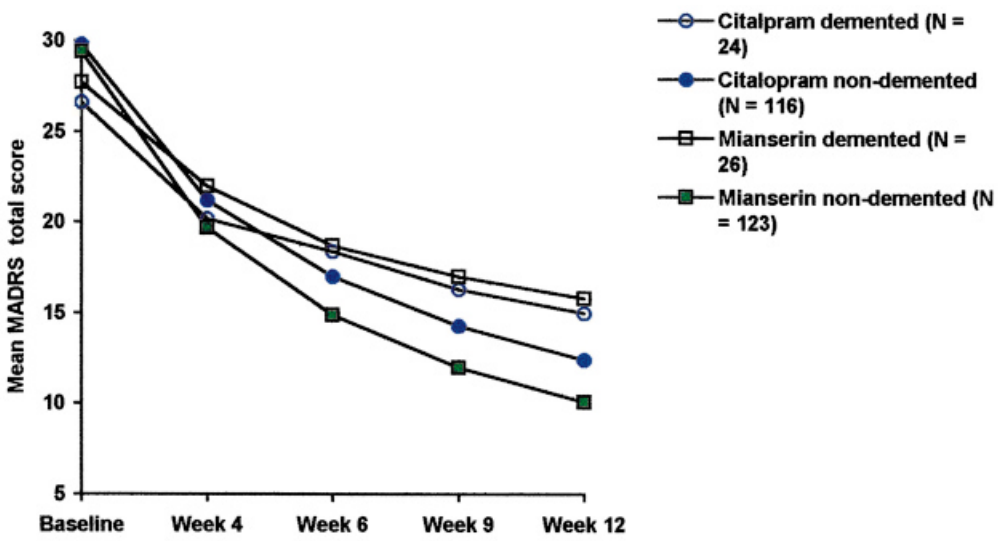

Fig. 2. Time course for mean MADRS total scores for citalopram and mianserin patients for the subgroups of demented and non-demented patients during the study period (EFF population)

and in 73.2% of mianserin-treated patients. There was no statistical difference between the two groups ($p = 0.25$).

Equivalence could not be demonstrated between the two treatments in the secondary analysis of MADRS total scores based on the ITT population, since the 90% CI slightly exceeded the pre-set limits of 4 points (1.17, 4.58 at last valid assessment).

In both treatment groups, the sub-group of patients with dementia responded less well to treatment than those without dementia (F-test, $p < 0.04$, Fig. 2). Analysis of the MADRS total score in the EFF population showed a greater decrease from baseline for patients without dementia (18 points) as compared to those with dementia (12 points), and there was no difference between treatment groups for this effect ($p > 0.7$). No further analyses were performed on the subgroup of patients with dementia due to the small patient numbers in this group.

Exploratory logistic regression analysis indicated that the subgroup of patients with a diagnosis of only dysthymia were more likely to show a response (MADRS $\leqslant 12$) than the other diagnoses groups ($p < 0.01$, EFF population).

CGI scale

A clinically relevant response was defined as an improvement of at least two points on the CGI severity of illness scale. A survival analysis to estimate the probability of response as a function of time showed a significant difference between the two treatments in favour of mianserin (probability of response was 0.8 for mianserin and 0.7 for citalopram; χ^2 test $p < 0.04$, EFF population).

A final score of $\leqslant 2$ was defined as a response on the CGI global improvement scale. The results again showed a significantly greater probability of response with mianserin compared with citalopram (0.9 versus 0.7, respectively; χ^2 square test $p < 0.01$, EFF population).

WHO Well-being scale

Mianserin-treated patients showed a greater improvement than citalopram-treated patients in the items measuring anxiety/depression on the WHO Well-being scale (F-test, $p < 0.04$). The two treatment groups were similar for items measuring positive well-being ($p > 0.1$).

SAFETY

In the citalopram group, there were 276 treatment-emergent adverse events which affected 118 patients. In the mianserin group, 289 adverse events affecting 131 patients were recorded during treatment. Thus, a similar number of treatment-emergent adverse events were reported for both treatment groups. Table 2 shows the treatment-emergent adverse events experienced by at least 5% of patients in either treatment group during the 12-week study period (four events for citalopram and eight events for mianserin). The incidence of fatigue and somnolence was significantly greater for mianserin than for citalopram ($p < 0.01$ and $p < 0.03$, respectively), whereas the incidence of insomnia was significantly greater for citalopram than mianserin ($p < 0.01$). There was no significant difference between treatment groups ($p = 0.94$) in the time to first event.

Fifteen patients in each treatment group discontinued treatment during the 12-week continuation phase. The reasons for this were: citalopram—one through adverse events, three through lack of efficacy, six through other reasons and five for unknown reasons; mianserin—one through adverse events, one through lack of efficacy, 12 through other reasons and one for unknown reasons.

Overall treatment compliance (defined by tablet count) was high in both treatment groups (99% for citalopram, 98% for mianserin).

Serious adverse events

There were five fatal and 12 non-fatal serious adverse events in each treatment group. For one of the fatalities, a relationship to treatment could not be ruled out. The patient was an 85-year-old female in poor health, with a history of atrial fibrillation, who died of ventricular arrhythmia 50 days after the start of treatment with citalopram. For all other fatalities, a relationship to treatment was considered 'unlikely' by the investigators.

A probable relationship to treatment was recorded for five non-fatal events; two in the citalopram group (one case of anxiety and one case of agitation which occurred after a non-permitted dose of citalopram 120 mg) and three in the mianserin group (a case of epileptic grand mal seizure in a 79-year-old male, a case of somnolence, bradyphrenia and urinary incontinence in a 77-year-old male, and a case of dyspepsia in a 67-year-old female).

Table 2. Most common treatment-emergent adverse events (occurring in >5% of patients in either treatment group) during the study period

Adverse event	Citalopram ($N = 163$) No. of patients (%)	Mianserin ($N = 173$) No. of patients (%)
Nausea	20 (12.3)	12 (6.9)
Insomnia*	18 (11.0)	7 (4.0)
Headache	12 (7.4)	12 (6.9)
Anxiety	11 (6.7)	8 (4.6)
Pain	6 (3.7)	9 (5.2)
Constipation	6 (3.7)	9 (5.2)
Back pain	6 (3.7)	10 (5.8)
Dizziness	4 (2.5)	10 (5.8)
Fatigue*	3 (1.8)	14 (8.1)
Somnolence**	2 (1.2)	10 (5.8)

*$p < 0.01$. **$p < 0.05$.

There were no clinically significant changes in vital signs, physical findings or other observations, including body weight measurement, during the course of the study.

DISCUSSION

The objective of this study was to compare the efficacy and tolerability of citalopram and mianserin in the treatment of elderly patients with or without dementia. Both drugs were administered for a period of 12 weeks, which is considered adequate for the evaluation of short-term efficacy of antidepressant drugs (Quitkin *et al*., 1984). As the efficacy of citalopram in placebo-controlled studies is well documented (Montgomery *et al*., 1992), a placebo control was not considered ethically appropriate.

The primary analysis of antidepressant efficacy, using the MADRS scale, indicates that the two treatments are equivalent. Both treatment groups showed a good response with a reduction from baseline in MADRS total score of 16–18 points over the 12 weeks of the study. At the end of the study, 61% of patients responded to treatment (where response was defined as a final MADRS total score of $\leqslant 12$), and 70% showed at least a 50% reduction from baseline in MADRS total score, with no difference between treatment groups. In the secondary analysis of the ITT population, a slight advantage for the mianserin group was evident. However, as the patients in the EFF population had received at least 4 weeks of treatment and no prohibited concomitant medication during those 4 weeks, the main conclusion of this study is based on the primary analysis in this population, which shows equivalent antidepressant efficacy for citalopram and mianserin.

The present large study generally confirms the indications from two previous double-blind studies in smaller groups of younger patients (Ahlfors *et al*., 1988; de Wilde *et al*., 1985).

The efficacy of other SSRIs has also been compared with mianserin. In double-blind comparisons of fluoxetine (20–80 mg) and mianserin (20–80 mg) over 6 weeks, the two drugs showed equivalent efficacy as measured on the Hamilton Depression Rating Scale in younger patients (Muijen *et al*., 1988) as well as in the elderly (La Pia *et al*., 1992). In a similar study, fluvoxamine (100–150 mg) was compared with mianserin (30–60 mg) in patients aged 18–60 years, over 8 weeks (Lavergne *et al*., 1996). Those patients receiving mianserin improved more on MADRS items 'concentration difficulties' and 'inability to feel' than patients receiving fluvoxamine. The two treatments were equivalent for the other MADRS items.

The results of the present study, therefore, agree with previous studies comparing citalopram and other SSRIs to mianserin in showing equivalence between the two treatments.

Unlike the results of previous studies in younger patients (Ahlfors *et al*., 1988; de Wilde *et al*., 1985), an analysis of CGI in the present study showed a slight advantage for mianserin. This was also seen in the results of the WHO Well-being scale for anxiety/depression in the elderly.

One of the secondary objectives of the present study was to compare the antidepressant efficacy of citalopram and mianserin in the subgroups of patients with and without dementia. The results showed that those patients with dementia (17% of the study population) responded less well to treatment than patients without dementia, as measured by the decrease from baseline in MADRS total score. Again, there was no difference between the treatment groups.

Depression in the elderly may be a heterogeneous disorder and, in spite of similar symptoms, have other pathogenic mechanisms than in younger ages. Much evidence shows an association of old age depression with brain degenerative alterations, especially white matter changes (Alexopoulos *et al*., 1993, 1997a; Baldwin, 1993; Kramer-Ginsberg *et al*., 1999; Krishnan and Gadde, 1996; Steffens and Krishnan, 1998). Such brain changes include a reduction in neurotransmitter functions which affect cholinergic, dopaminergic, noradrenergic, as well as serotonergic, systems (Gottfries, 1990). Our results show that a serotonergic and a noradrenergic therapeutic approach have comparable efficacy on the depressive symptomatology of elderly depressed patients.

O'Brien *et al*. (1998) showed that elderly patients with major depressive disorder *and* white matter lesions have poorer outcome than patients without. The present findings also suggest that depression states associated with degenerative changes in the brain are less responsive to treatment, as the patients with dementia have a poorer response to antidepressive treatment than the patients with no cognitive decline. This points to a need for more potent drug treatment in the demented patient group. More studies of subgroups of depression in the elderly are needed to confirm this result.

To summarise, both citalopram and mianserin were well-tolerated in this study. The incidence of adverse events was relatively low considering the advanced age of the patient population. In terms of frequency and time to onset of first event, the two treatments were equivalent. However, due to the lack of a placebo group, the present study can only show the difference between the two treatments. Nyth *et al*. (1992) reported no difference in side-effects between citalopram and placebo in a similar patient group. Citalopram was associated with a higher incidence of insomnia, whereas mianserin resulted in a greater incidence of fatigue and somnolence. This difference would be predicted from the drug profiles. Somnolence can be a particularly undesirable side effect in the elderly as it can result in increased numbers of falls or accidents and deterioration of cognitive function (Blake *et al*., 1988). It is also undesirable in a potentially long-term medication, where non-sedating properties are of most use. The frequency of serious adverse events was similar in the two treatment groups (10%).

In conclusion, the study showed that the two treatments were equivalent, and confirmed that citalopram is an effective and well-tolerated treatment for elderly depressed patients, with or without dementia.

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