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CITALOPRAM MAY REDUCE SYMPATHOADRENAL HYPERACTIVITY IN ELDERLY DEPRESSED PATIENTS: AN OPEN MULTICENTER STUDY IN BELGIUM AND LUXEMBOURG

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SUMMARY

Introduction: *Through effects of catecholamines upon the heart, blood vessels and platelets, sympathoadrenal hyperactivity contributes to the development of cardiovascular diseases in elderly depressed patients.*

To assess the cardiovascular effect of Citalopram in elderly depressed patients, data from an open multicenter study in Belgium and Luxembourg, in which a total of 811 patients were evaluated, was retrospectively analysed. Although the aim of the study was to assess the efficacy and safety of Citalopram, blood pressure and heart rate were also monitored.

Subject and methods: *Patients included in the study were referred either by psychiatrists, geriatricians or general practitioners. Clinical assessment included ratings on the Hamilton Rating Depression Scale, the Clinical Global Impression Scale, the UKU Side effect rating scale and the assessment of side effects spontaneously reported.*

Results: *With few side effects, Citalopram significantly improves the clinical condition of elderly patients suffering from depressive symptoms.*

A series of repeated multivariate analyses of covariance were performed on heart rate and blood pressure controlling for the effect of age. Interestingly, a sustained decrease of these parameters was shown during the whole study period reaching significance for systolic blood pressure ($p<0.05$). These effects were observed both in responding as well as non-responding patients, and were somewhat more marked in responders for heart rate ($p=0.058$).

Conclusion: *The slight but significant decrease in systolic blood pressure and heart rate suggests that citalopram may reduce sympathoadrenal hyperactivity and the related increased cardiovascular morbidity and mortality associated with depression.*

Key words: *elderly – depression - Citalopram*

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INTRODUCTION

Depression is known to be one of the most frequent mental disorders in the elderly responsible for important individual suffering and significant social cost (Tecco 1998). Surveys have shown that between 1 to 2% of elderly people living in the community suffer from major depression (Blazer 1989) and 10 to 15% of people 65 years of age or older manifest clear symptoms of depression (Wattis 1990). Although the reason for this high prevalence of depressive symptoms in the elderly remains unclear, there are indications that depression is related to functional changes in the central noradrenergic and serotoninergic systems (Barchas 1977) and that noradrenaline and serotonin activity is reduced in normal aging (Palmer 1993).

Elderly depressed patients are at risk of cardiovascular morbidity and mortality. Risk factors other than those associated with old age have been documented in recent studies. Advances in biological psychiatry suggest that sympathoadrenal hyperactivity contributes to the increased vulnerability of depressed patients to cardiovascular diseases.

Citalopram is a selective serotonin reuptake inhibitor showing little or no effect on other amines (Hyttel 1982). Oral citalopram has proved to be efficacious in the treatment of depression in a series of double-blind placebo controlled and active reference comparative trials (Bech 1992, Keller 2000). A pooled analysis of placebo-controlled clinical trials demonstrated that citalopram effectiveness is comparable across gender, age, race or severity of disease (Willetts 1999). Controlled studies have also demonstrated that citalopram has a potent antidepressive efficacy in elderly depressed patients with a particularly favourable side-effects profile (Koskinen 1998, Nyth 1990, Gottfries 1992, Nyth 1992).

The purpose of this study was to further explore citalopram efficacy, tolerance and the relationship between efficacy and cardiovascular parameters influenced by sympathoadrenal activity in a very large naturalistic sample of elderly depressed patients.

SUBJECTS AND METHODS

Patients

Male and female patients aged at least 65 could be included in the study provided they suffered from depressive symptoms requiring treatment, or were inadequately treated with their current antidepressant medication. In order to study a representative

"naturalistic" sample of depressed patients, case selection by applying diagnostic criteria was deliberately avoided.

Patients were included in the study if their HDRS 17-items (Hamilton 1960) score was higher than 15 (psychiatrist sample) or if their score on the Clinical Global Impressions of Severity scale (Guy 1976) was higher than 1 (GP sample). Psychiatrists prospectively defined at baseline the DSM-IV mood disorder diagnosis.

Exclusion criteria included patients with epilepsy, alcohol or drug abuse during the past 12 months, pregnancy, mood incongruent psychoses, epilepsy, severe somatic disease (hepatic and/or renal impairment, severe cardiopathology, organic brain damage) known hypersensitivity to citalopram or prior treatment with MAOI or other antidepressants respectively 2 and 1 weeks before study inclusion.

Study Design

The study was an open multicentre trial in Belgium and in Luxembourg, with a total of 811 patients recruited. Recruitment on an in- and outpatients basis was performed at psychiatric or geriatric departments and at private practices. There was no community advertising for patient recruitment and patients were all primary or secondary referrals to participating GPs or psychiatrists.

The total study and treatment period with citalopram was 8 weeks. After a minimum of two weeks of treatment, the daily dose of citalopram could be increased from 10 mg to a maximum of 40 mg if, in the investigators opinion, patient response was unsatisfactory and side-effects did not preclude dose escalation.

Clinical assessments were performed at baseline (before start of treatment) and, for the psychiatrist sample, at the ends of weeks 2, 4, 6, and 8 of treatment. Efficacy parameters consisted of the 17-items HDRS and the CGI-S. In the GP sample, assessments were limited to CGI-S on weeks 1, 2, 4 and 8. Benzodiazepine and low potency neuroleptics such as alimemazine and thioridazine were the permitted anxiolytics/ hypnotics medication given as needed during the trial.

Clinical Evaluation

The efficacy of citalopram was assessed using the 17 items HDRS (Hamilton Depression Ratting Scale) the Clinical Global Impression Scale and the HDRS Subscales (anxiety and somatic, cognitive disturbance, retardation and sleep disturbance).

The safety was assessed with the UKU side effects list, the UKU Global Impression and the withdrawal data.

UKU side effects list reported 38 possible side effects including neurovegetative side effects and side effects classified as «others», with scores ranging from zero to 3 (absent, mild, moderate, severe).

The UKU Global Impression was an assessment of the interference of the existing side effects on the daily functions of the patient. This is evaluated by a score ranging from 0 to 3 (absent, mid, moderate, severe) given by the investigator as well as by the patient.

Safety was also assessed using the percentage of withdrawals due to side effects and the relationship of these side effects to the study medication as well as the duration of treatment preceding the withdrawals.

Signs and symptoms reported by the patient or observed by the investigator were categorised into four subgroups (namely, psychic, neurological, neurovegetative and others).

Psychiatrists also used the UKU Side effect rating scale (Lingjaerde 1987) to assess, both by the patient and by the investigator, their consequences on the patient daily functioning with a score ranging from 0 to 3 (absent, mild, moderate and severe).

Statistical Analysis

The relationship between variables was evaluated with Pearson's product-moment correlation. To test the independence of classification system, we used Chi Squire statistics. Between-group comparisons involving continuous data were made using Student's t-tests. Paired difference t-tests were performed to assess change in continuous variables within the treatment group. Multiple relationships and association between variables were evaluated using repeated measures analysis of variance/covariance extracting effect due to treatment, group membership and interaction among these factors. A discriminant analysis was performed in order to characterise patients responding to treatment. Kaplan-Meier survival analyses were used to assess whether group membership could differentiate course of treatment response rate. Hypothesis tests were two-sided and carried out at the 5% significance level.

Tolerability analyses were performed on the intent to treat (ITT) population whereas analyses regarding efficacy were restricted to patients having completed at least 14 days of treatment using the last observation carried forward (LOCF) method. Symptoms were considered as side effects if 1) they were not present at week 0 before first drug administration or 2) were rated as more severe compared to week 0. To appraise side effects severity, week 0 scores were subtracted from symptoms severity recorded during the study.

RESULTS

Patient characteristics

A total of 811 patients (71.6% females) aged 73.3+/-6.9, 677 of whom recruited by GPs, were included in the study and constitutes the ITT population. Mean CGI score at study entry was 3.57+/-0.97 and the sample comprises 44.8% of moderately depressed patients (CGI 2-3), 39.7% of obviously depressed patients (CGI 4) and

15.5% of patients with severe depression (CGI 5-6). In the psychiatric sample, DSM-IV diagnoses were as follows: 99 Major Depressive Disorder (41 Recurrent, 36 Single Episode, 18 Not Otherwise Specified and 4 Bipolar I Disorder), 20 Depressive Disorder Not Otherwise Specified, 12 Dysthymic Disorder and 3 Adjustment disorder with depressed mood. Mean HDRS score was 25.2+/-5.6 with a range from 15 to 40.

Among the ITT population, 87.4% completed the 2 month study period, and among non-completers, 37 (42%) withdrawn for side effects, 19 (21.6%) for non-observance, 5 (5.7%) for clinical aggravation despite treatment, 16 (18.2%) were not willing to continue the treatment because they felt recovered and finally 11 (12.5%) withdrawn for other reasons.

689 patients were treated at least 14 days and comprised the efficacy sample. Mean citalopram daily dosage during the entire study period was 10.4+/-2.2 mg and 76.3% ITT sample took 10 mg during the all study period.

Concomitant treatment

78.4 %of the ITT sample were taking one or more concomitant somatic medications and 68.7% were on psychotropic drugs (mostly on benzodiazepine – 58.2% - and on neuroleptics - 6.7%). Prescribed concomitant somatic medication were mainly cardiovascular (46.3%) and gastrointestinal (20.9%) drugs as well as vitamins (14.9%).

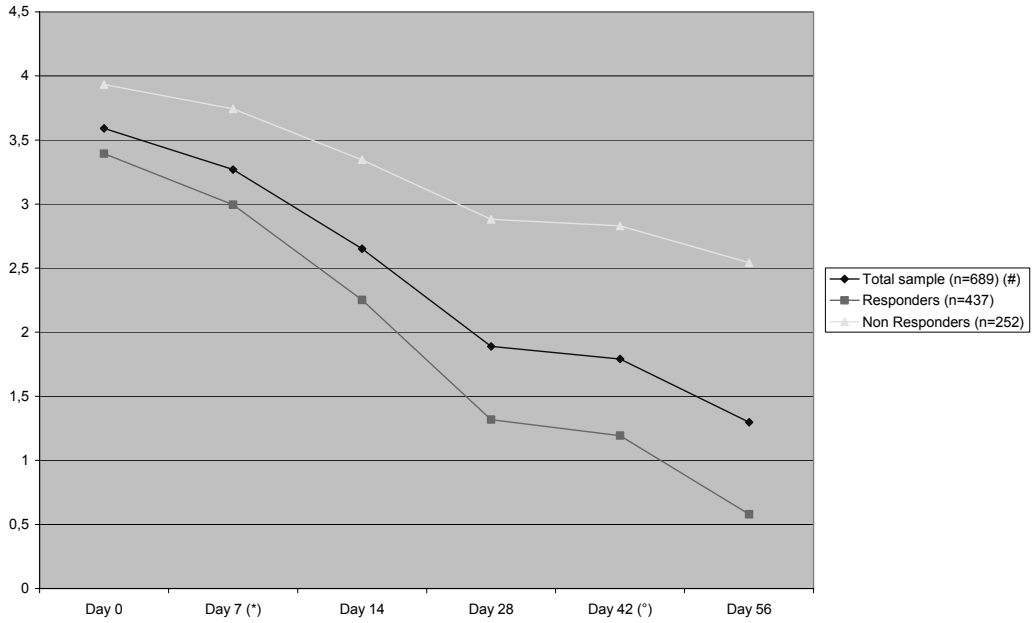

Figure 1. Reduction of CIG over time

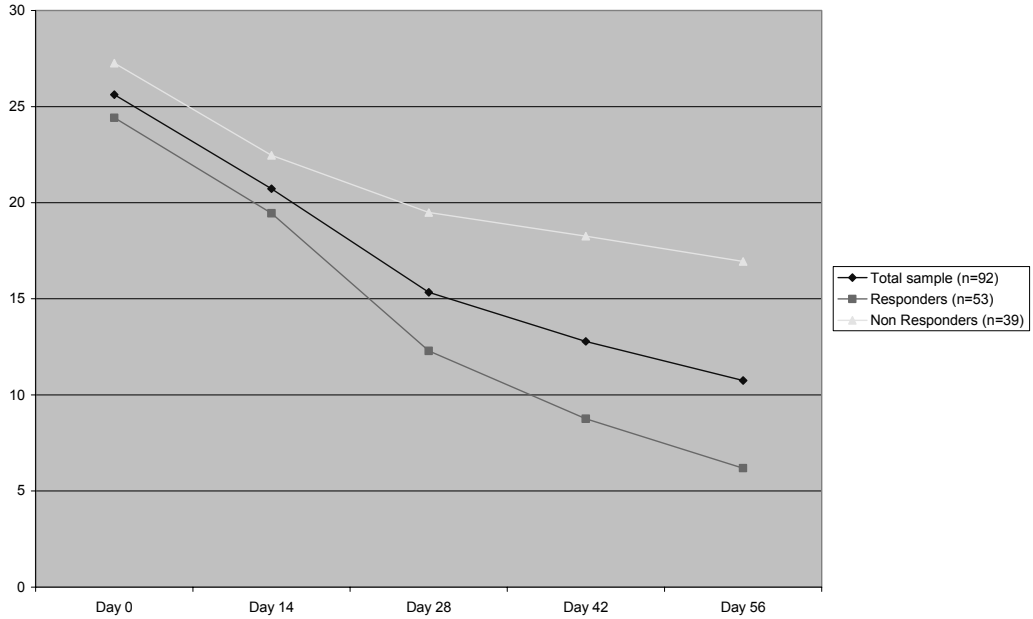

Figure 2. Reduction of HDRS over time

Efficacy assessment

Among the efficacy sample, 639 patients were recruited by GPs and 117 by psychiatrists. A highly significant ($p<0.0001$) improvement was observed in both samples as reflected by the sustained decrease of CGI and HDRS scores during the whole study period. For CGI, significant differences ($p<0.0001$) from baseline scores appears as early as 1 week of treatment (Figure 1 & 2). Patients were dichotomised according to their treatment response as revealed by their CGI scores, patients maintaining a score less than 2 being considered as responders (n=437). As shown in Table 1 responding patients were younger, less severely ill (as assessed by CGI and HDRS), and were more frequently diagnosed as having a single major depressive episode. Non responders had a higher mean citalopram dosage, were taking more concomitant psychotropic drugs and reported more side effects (mostly psychiatric and neurovegetative symptoms).

The severity of adverse events was not rated differently in the two groups. A discriminant analysis performed between responding and non responding patients revealed that, among the 17 HDRS items scores obtained at study entry, three significantly differentiate the two groups: depressive mood, late insomnia and work & activities, non-responders scoring higher on these three items. The discrimant analysis correctly classified 69.8% of the sample.

Table 1. Demographics of patients

	Non Responder (n=273)	Responder (n=483)	Statistical Significance
Demographics			
Age	74.05+/-7.2	72.84+/-6.9	<0.05
Gender (% males)	26	29.3	NS
Weight	68.47 +/- 12.6	69.25 +/- 12.5	NS
Cardiovascular status			
Systolic Blood Pressure	141.21 +/- 167.6	139.81 +/- 158.4	NS
Diastolic Blood Pressure	82.24 +/- 8.4	81.32 +/- 8.4	NS
Heart Rate	78.3 +/- 9.1	77.1 +/- 8.6	NS
Clinical characteristics			
Depression severity			
Baseline CGI	3.92 +/- 0.9	3.38 +/- 0.9	<0.001
Baseline HDRS	26.96 +/- 5.3	24.2 +/- 5.5	<0.01
Depression characterisation			
Major Depressive Disorder	45.3	54.7	NS
Other Depressive Disorder	29	71	NS
Major Depression Single Episode	26.7	73.3	<0.05
Recurrent/Bipolar Major Depression	53.8	46.2	<0.05
Treatment			
Mean citalopram dosage (mg)	10.86 +/- 2.7	10.19 +/- 1.8	<0.01
Concomitant treatment (n) (°)	2.979 +/- 1.73	2.594 +/- 1.49	NS
Psychotropic drugs	1.062 +/- 0.69	0.783 +/- 0.66	<0.05
Non-Psychotropic drugs	1.917 +/- 1.61	1.812 +/- 1.42	NS
Tolerability (*)			
Total number of symptoms	0.641 +/- 1.45	0.267 +/- 0.69	<0.001
Severity according to patient (UKU)	0.094 +/- 0.37	0.031 +/- 0.49	NS
Severity according to clinician (UKU)	0.104 +/- 0.33	0.012 +/- 0.43	NS
Psychiatric symptoms			
Number	0.242 +/- 0.94	0.062 +/- 0.3	<0.01
UKU Severity	0.521 +/- 0.99	0.362 +/- 0.94	NS
Neurological symptoms			
Number	0.092 +/- 0.52	0.041 +/- 0.42	NS
UKU Severity	0.104 +/- 0.31	0.029 +/- 0.17	NS
Neurovegetative symptoms			
Number	0.286 +/- 0.61	0.153 +/- 0.41	<0.01
UKU Severity	0.5 +/- 1.01	0.348 +/- 0.76	NS
Other symptoms (n)	0.022 +/- 0.15	0.01 +/- 0.1	NS

(*) Tolerability is assessed 1) according to total number of reported symptoms from Week 1 to Week 8 minus the number of reported symptoms at study entry (visit 1) and 2) by mean severity scores (Week 1 to Week 8) minus visit 1 scores

(°) Number of drugs administered during the all study period

Figure 3 shows the course of the response rate during the study according to illness severity and it further illustrates the relationship between response and severity. Kaplan-Meier survival analyses indicates a significantly different survival function between the three groups (p<0.0001); post-hoc pairwise log rank tests for illness severity show significant differences between the less severely ill patients and the two other groups (both p<0.0001) while the latter were not discriminated on this basis.

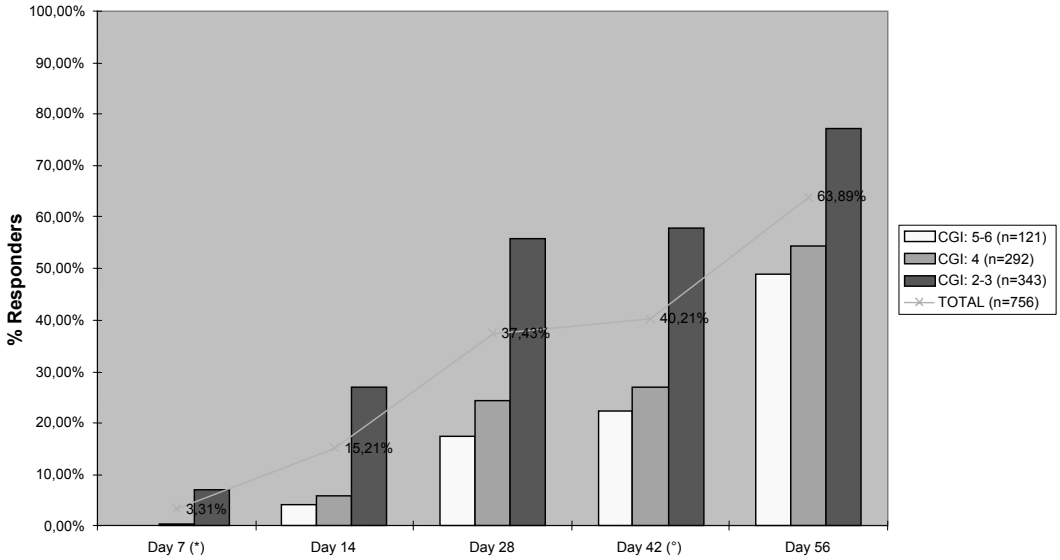

Figure 3. Course of treatment response rate according to illness severity

Safety assessment

Safety was assessed on the ITT population (n=811) and results are displayed on table 2. 37 patients (4.5 %) alleged side effects sufficient to withdraw from the study and, on the whole, 205 patients (25.3%) experienced at least one side effect during the study period. Most of these were neurovegetative (gastrointestinal complaints, dizziness) but also psychological (insomnia) and they were rated as mild (see Table 2).

A series of repeated multivariate analyses of covariance were performed on heart rate and blood pressure measurements controlling for the effect of age. Table 3 and 4 and figure 4 and 5 show a sustained decrease of these parameters during the whole study period reaching significance for systolic blood pressure (p<0.05). These effects were observed both in responding as well as non-responding patients, and were somewhat more marked in responders for heart rate (p=0.058).

Table 2. Psychic, neurological, neurovegetative symptoms recorded by patients

Neurovegetative	668	110	33	0.4524
Psychological	750	36	25	0.4104
Neurological	781	21	9	0.0522
Other	797	14	0	0.5385 (*)
Total	606	123	82	0.0478 (*)

(*) UKU scales scores

Table 3. Reductionof Heart Rate and Blood Pressure over time

	Day 0	Day 7	Day 14	Day 28	Day 56
Heart Rate (n=663)	77.6 +/- 8.8	77.4 +/- 9.1	76.9 +/- 9.0	76.6 +/- 9.0	76.2 +/- 8.6
Systolic BP (n=665)	140.3 +/- 16.2	139.6 +/- 16.3	138.4 +/- 15.9	138.1 +/- 15.1	137.1 +/- 14.5
Diastolic BP (n=665)	81.7 +/- 8.4	81.6 +/- 8.3	80.8 +/- 8.4	80.4 +/- 8.5	79.9 +/- 8.1

		Citalopram		Day *
	Age	Response	Day (°)	Response (°)
Heart Rate (n=663)	p<0.05	p<0.01	p=0.082	p=0.058
Systolic BP (n=665)	NS	NS	p<0.05	NS
Diastolic BP (n=665)	p<0.05	p<0.05	NS	NS

p values are Greenhouse-Geisser corrected

Table 4. Blood Pressure reduction over time

	Day 0	Day 7	Day 14	Day 28	Day 56
Syst BP-Non Resp	141	141	139.4	139.3	138.1
Syst BP-Resp	139.8	138.7	137.7	137.3	136.4
Diast BP-Non Resp	82.3	82.4	81.5	80.9	80.6
Diast BP-Resp	81.2	81	80.3	80	79.4

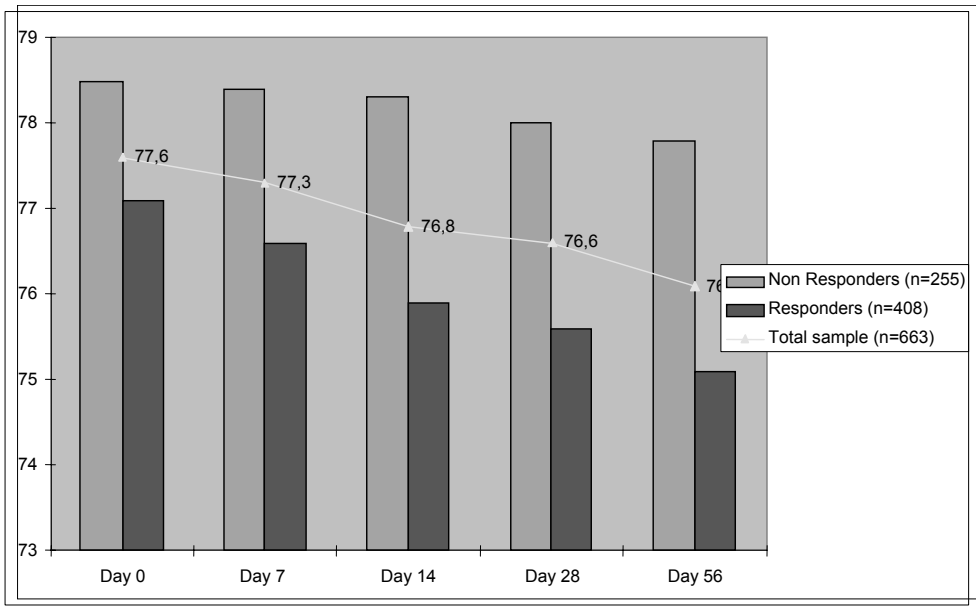

Figure 4. Sustained decrease of heart rate over time

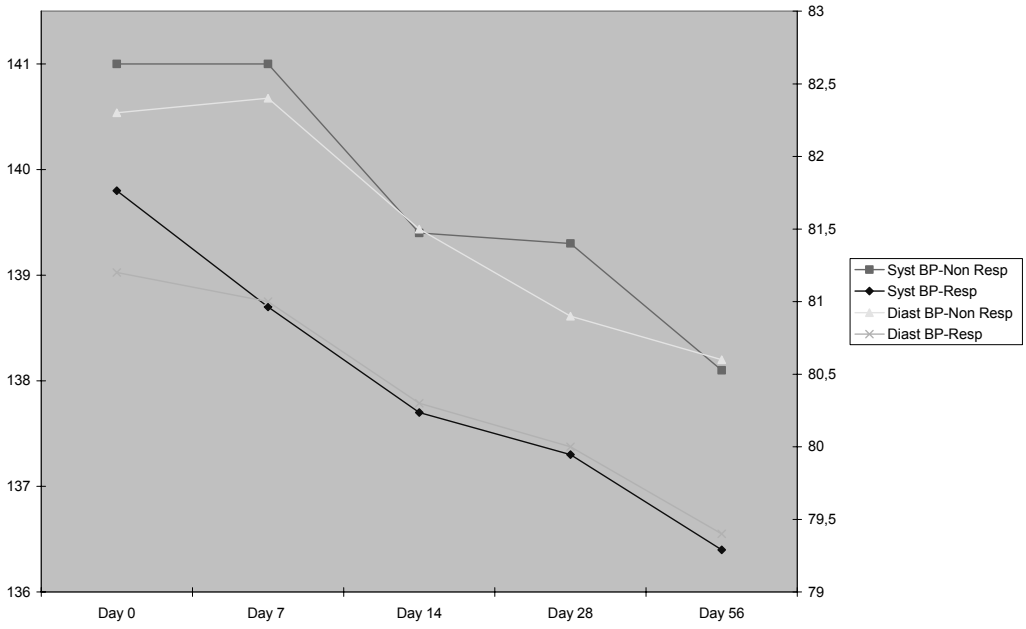

Figure 5. Sustained decrease of Blood Pressure over time

DISCUSION

Although widely prescribed, this study is the only Open Clinical Study of Citalopram in Elderly Patients. Because of the internal validity of the methodology controlled clinical trials are the best way to investigate the efficacy of a treatment. But the extrapolation of results from clinical controlled trials to every day clinical practice is sometimes more difficult because patients entering clinical controlled trials are selected patients that may represent only a subgroup. The interest of open studies is that being less selective they

represent better than controlled trials what can happen in a naturalistic setting and therefore have better external validity (Staner 1994, Thase 1999).

Our study shows that for elderly patients with depressive symptoms, when taking citalopram, there is a highly significant difference for all efficacy parameters between baseline and each of the visits indicating an improvement in the depressive symptamatology of the patient. The largest improvement compared to baseline occurs in the first 4 weeks of treatment.

Safety evaluation of treatment is of capital importance when the studied population concerns elderly patients. They are more sensitive to the side effects and antidepressant medication might aggravate some of the somatic disorders that are frequently found in elderly. Our demographic data confirms that 86.7% of the population referred by general practitioners and 87.4% of those referred by psychiatrists and geriatricians were taking one or more concomitant medications.

Safety records of patients evaluated by geriatricians and psychiatrists show that only few (six) patients were withdrawn from the study because of adverse events. For one of them the relationship to the treatment was stated to be unlikely. The largest number of side effects recorded was noted in the neurovegetative or psychological subclass. Side effects are highest at week 2 and decrease gradually at each visit until the end of the study. At week 2, 24.4% of patients reported side effects and 9.3% at week 8. An average of 0.3 side effects per patient is recorded at week 2 and 0.1 at week 8. UKU Global Impression scores are very low throughout the whole study period (median=0) which means that in general the existing side effects are assessed as having no to only little interference with daily functioning. For the population referred by general practitioners, the same trend can be observed. The number of side effects is highest at day 7 and subsequently the number gradually decreases at each visit until the end of the study. At day 7, a total of 99 patients (14.5%) reported side effects recorded as possibly or probably related whereas at day 60 this number was reduced to 12 (1.9%)

The average starting dose of the test medication was 19.24 mg. The average end dose was 19.75 mg. There was a decrease in dosage for 3% of patients and an increase for 18%. Information on somatic parameters shows that unlike with depressed patients treated with tricyclic antidepressants (TCAs), the mean weight of the study population at each of the visits was not significantly different from weight at baseline.

Elderly depressed patients are at risk of cardiovascular morbidity and mortality. 87% of our sample were taking concomitant medication and cardiovascular medication. Antihypertensive medication was the associated treatment most frequently found. Risk factors other than those associated with old age have been documented in many studies such as the notion that having a psychiatric illness such as depression increases one's risk for developing ischemic heart disease (Musselman 1998). Biological psychiatry reflect important alterations that contribute to the increased vulnerability of depressed patients to cardiovascular diseases. Many depressed patients exhibit sympathoadrenal hyperactivity (Davidson 2009). Elevated values were observed in patients with co-morbid panic disorder (Barton 2007). Sympathoadrenal hyperactivity contributes to the development of cardiovascular diseases through effects of catecholamines upon the heart, blood vessels and platelets. Elevations of Plasma norepinephrine (NE) levels are found most frequently in subjects with high cardiac output and borderline hypertension who later proceed to established highly resistant hypertension (Lund-Johansen 1983). Even normotensive depressed patients have been found to exhibit greater heart rates at rest, after orthostasis, and after exercise in comparison with normal controls. These depressed patients also exhibited increased plasma concentration of NE at rest.

Interestingly, in our study the systolic blood pressure of elderly depressed patients treated with citalopram significantly decreases compared to baseline. Heart rate decreased with a statistical significance of 0.058 in responders. These results suggest that citalopram may not only improve quality of life in depressed elderly patients but perhaps even increase longevity reducing sympathoadrenal hyperactivity associated with depression.

CONCLUSION

Our study confirms that in a naturalistic setting citalopram appears to be a good and safe alternative in the treatment of depressive symptoms in the elderly. With few side effects, Citalopram significantly improves compared to baseline the clinical condition of elderly patients suffering from depressive symptoms. Slight decrease in blood pressure and heart rate suggests that citalopram may reduce sympathomedullary hyperactivity and the related increased cardiovascular morbidity and mortality associated with depression.

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