Psychopharmacology (2006) 185: 84–92
DOI 10.1007/s00213-005-0274-2

ORIGINAL INVESTIGATION

**Clarice Gorenstein · Stefania Caldeira de Carvalho · Rinaldo Artes · Ricardo Alberto Moreno · Tania Marcourakis**

# Cognitive performance in depressed patients after chronic use of antidepressants

Received: 26 July 2005 / Accepted: 16 November 2005 / Published online: 17 February 2006


**Abstract** *Rationale:* Depressive disorders are conditions that often require continuous treatment, and it is therefore important to evaluate the consequences of prolonged administration. There are few studies assessing cognitive functions of depressed patients after long-term use of antidepressants. *Objectives:* This study evaluated the cognitive performance of depressed patients treated with antidepressants for at least 6 months. *Methods:* Patients with major depression (DSM-IV) using imipramine for 2.4±0.6 years (mean±SE), clomipramine for 2.8±1.2 years, fluoxetine for 1.8±0.3 years and sertraline for 1.5±0.3 years were compared to matched controls (sex, age and educational level) without any psychiatric diagnosis. Memory evaluation consisted of episodic, implicit and working memory tests as well as metamemory assessment. *Results:* (a) Psychomotor performance of patients taking imipramine was worse than that of controls in inserting pins and a visual reaction time task; on the performance of tapping the difference from controls varied according to dose/weight for patients taking clomipramine and fluoxetine. (b) For memory tests, differences between patients taking sertraline and controls were observed in the number of digits and words recalled; the difference between patients and controls varied according to dose/weight on the number of familiar words correctly completed for patients taking clomipramine and on digit span backward for those taking sertraline. (c) Metamemory was worse in all patient groups irrespective of patients' clinical state. *Conclusions:* The impairment in psychomotor and memory performances associated with these antidepressants seems to be of low intensity and of questionable clinical relevance.

**Keywords** Clomipramine · Imipramine · Fluoxetine · Sertraline · Depressive disorder · Cognition

C. Gorenstein · S. C. de Carvalho
Departamento de Farmacologia,
Instituto de Ciências Biomédicas,
Universidade de São Paulo,
São Paulo, SP, Brazil

C. Gorenstein (✉) · R. A. Moreno
Instituto de Psiquiatria, Hospital das Clínicas,
Faculdade de Medicina (LIM-23),
Universidade de São Paulo,
Rua Dr. Ovídio Pires de Campos, 785, Térreo,
05403-010 São Paulo, SP, Brazil
e-mail: cgorenst@usp.br
Tel.: +55-11-30696958
Fax: +55-11-30696958

R. Artes
Ibmec,
São Paulo, SP, Brazil

T. Marcourakis
Centro de Investigações em Neurologia,
Hospital das Clínicas,
Faculdade de Medicina (LIM-15),
Universidade de São Paulo,
São Paulo, SP, Brazil

## Introduction

Complaints concerning memory deficits and performance impairment in cognitive tasks are relatively common in patients with major depressive disorder (Burt et al. 1995; Veiel 1997; Elliott 1998). Whether such complaints are symptoms of depression and residual after clinical remission following effective antidepressant treatment or whether they are side-effects of some antidepressant drugs (Fava 2003) remains unclear. A combination of these two possibilities cannot be dismissed; that is, an antidepressant might have a deleterious effect on cognition which is compounded with a cognitive residual symptom, consequently masking any possible benefits of recovery in the cognitive functions. In fact, many antidepressants exhibit pharmacological properties that can explain why such a dysfunction should be an expected treatment outcome. Memory processes are influenced by numerous neurotransmission systems such as cholinergic, serotonergic and dopaminergic systems that are affected by most antidepressant agents. As antidepressants are frequently prescribed for months or even years, it is important to evaluate the consequences of this prolonged administration on cognitive functioning, as

deleterious effects might have an important negative impact on everyday living activities.

To date, results from assessment of cognition in healthy volunteers and patients using tricyclic (TCA) (Deptula and Pomara 1990; Thompson 1991; Knegtering et al. 1994; Amado-Boccara et al. 1995) and selective serotonin reuptake inhibitor (SSRI) antidepressants (Fudge et al. 1990; Hale and Pinninti 1995; Schmitt et al. 2001) have been inconclusive. Methodological differences in variables such as drugs, doses, duration of treatment, diagnosis and tasks probably contribute to these inconsistencies (Deptula and Pomara 1990; Peselow et al. 1991; Thompson 1991). Most studies are either single-dose or short-term treatment, which do not reflect clinical practice.

We have previously investigated the effects of TCA antidepressants on memory and psychomotor functions in panic disorder patients. No significant drug effects were observed after 8 weeks of treatment with clomipramine (mean dose 50 mg/day), imipramine (mean dose 114 mg/day) and active placebo (Marcourakis et al. 1993). In a subsequent study, we evaluated the consequences of chronic use (around 6 years) of therapeutic doses of clomipramine (mean dose 57 mg/day) on remitted out-patients with panic disorder/agoraphobia compared to healthy volunteers matching the patients' characteristics (Carvalho et al. 2002). Although there was no significant difference between groups regarding any of the variables, except for metamemory, duration of treatment was associated with poorer performance in implicit and working memory tests. In addition, poorer performance in central executive tests and metamemory was observed at higher clomipramine and desmethylclomipramine serum levels.

Regarding depressed patients, faster reaction times have been reported on a 75- to 150-mg dose of clomipramine administered for 3 weeks (Seppala et al. 1978). Hale and Pinninti (1995) found no changes in the psychomotor performance of depressed patients treated for at least 3 months. However, Bartfai et al. (1991) found impairment in verbal learning performance associated to higher clomipramine plasma levels in patients after 3 weeks of treatment with 150 mg/day.

Improvement in memory tests after short-term use of 150–300 mg of imipramine associated with remission of depressive symptomatology has been shown by several authors (Amin et al. 1980; Glass et al. 1981; Peselow et al. 1991). In contrast, Calev et al. (1989) found impairment in memory tests under similar methodological conditions.

Studies with SSRIs have demonstrated memory and psychomotor performance improvements after fluoxetine in adults (Hale and Pinninti 1995) and elderly depressed patients (Kerr et al. 1993; Geretsegger et al. 1994; Cassano et al. 2002). Sertraline, however, was investigated mainly in normal volunteers. The few studies on depressed patients have shown improvement in psychomotor performance after 4 months of treatment (mean dose 103 mg/day) (Hale and Pinninti 1995).

The aim of this study is to evaluate the cognitive performance of depressed patients treated with TCA (clomipramine and imipramine) and SSRI (fluoxetine and sertraline) antidepressants for at least 6 months.

## Materials and methods

### Subjects

*Patients* Fifty-six out-patients (42 women) from the Institute of Psychiatry, School of Medicine, University of São Paulo, aged 20–61 years (mean±SE 40.7±1.4 years), with 11.5±0.8 years of education and users of therapeutic doses of antidepressants for at least 6 months [imipramine ($n$=15, mean±SE 230±23 mg/day, range 75–350 mg/day) for 2.4±0.6 years, clomipramine ($n$=9, 219±24 mg/day, 100–325 mg/day) for 2.8±1.2 years, fluoxetine ($n$=14, 54±6 mg/day, 20–80 mg/day) for 1.8±0.3 years and sertraline ($n$=18, 157±18 mg/day, 50–300 mg/day) for 1.5±0.3 years] participated in the study. Subjects were selected through the Structured Clinical Interview for DSM-IV (SCID; First et al. 1995), conducted by a trained psychiatrist, and met DSM-IV criteria for major depressive disorder (APA 1994). Exclusion criteria were use of any other psychotropic drug, severe psychiatric comorbidity along with the usual exclusion criteria for clinical trials (e.g. pregnancy, chronic clinical disorder, alcohol or illicit drug abuse).

*Healthy volunteers (controls)* Each patient was matched to a healthy subject with similar characteristics regarding sex, age and educational level. The final sample included 31 healthy subjects, 9 men, with mean age of 38.3±1.7 years and mean educational level of 11.2±0.8 years. In some cases, the same control was matched to a number of patients each receiving different drug treatments. They were screened through the Self-Report Questionnaire (SRQ-20; Harding et al. 1980; Brazilian validation by Mari and Williams 1986) and the SCID. Subjects having any psychopathology over the past year and those who had used psychotropic drugs in the last 3 years were also excluded. Volunteers were recruited via advertisement and were paid for their participation.

The study was approved by the Hospital's Ethics Committee, and all subjects signed informed consent forms.

### Procedure

*Rating scales*

The following instruments were used: Clinical Global Impression scale (CGI scale—Guy 1976), State–Trait Anxiety Inventory (STAI—Spielberg et al. 1970; Biaggio and Natalício 1979), Beck Depression Inventory (BDI—Beck et al. 1961) and Hamilton Depression Rating Scale (HDRS—Hamilton 1960). Healthy volunteers answered only the STAI and BDI.

*Experiment day*

Patients and healthy volunteers were instructed to arrive at the laboratory in the morning, between 7:00 and 9:00 a.m., and were asked to refrain from smoking just before the tests, as well as to abstain from consuming alcohol 24 h before evaluation.

The test battery consisted of subjective and objective memory evaluations (episodic, implicit and working memory) and tasks of selective attention, association skills, sedation and motor functions. Patients and controls underwent training on the psychomotor tasks to achieve their best performance. A number of tests were computer-based: the Vienna Test System (supplier Dr. G. Schuhfried Ges.M. B.H, Mödling, Austria, 1995) and the PSS CogReHab (Psychological Software Services Inc., Cognitive Rehabilitation, 1995). All subjects answered the STAI state form and then started the test battery which lasted around 2 h. Tests were applied in the same order to all subjects, where the number following the test name (below) indicates the order of application of that particular measure. The same investigator (SCC) collected all the data.

*Memory tests*

*Subjective Memory Questionnaire (SMQ)*[1] This is a self-reporting rating scale assessing individual perceptions of general everyday-life memory abilities (for instance: *How good is your memory for*: names of people; faces; appointments; giving messages to people; etc.), on a five-point scale (very bad to very good), adapted from Bennett-Levy and Powell (1980). Score is the mean of 45 questions.

*Verbal recall*[2,9] A short 14-item story (Correa and Gorenstein 1988) had to be recalled immediately after its verbal presentation and again about 30–40 min later, to assess short- and long-term episodic memories, respectively. This was scored according to the number and accuracy of items recalled.

*Word appreciation task (word preference)*[3] Twenty common words written individually on cards (1 card/5 s) were shown to the subjects (e.g. abacate, delegado). They were asked to read the words aloud and rate how much they liked each word, on a five-point scale. The objective was to expose those words which could then be used later in the word stem completion test, although no mention was made of the fact that memory on these words would be tested subsequently. Digit span, as a distracter task, was given after word presentation.

*Digit span forward and backward*[4] Scores were the number of digits in the last correctly reproduced sequence (Wechsler 1945). These tasks assess working memory: forward span evaluates the phonological loop, while backward span, the central executive (Gathercole 1998).

*Word stem completion*[5] Thirty-two word stems consisting of three letters written individually on cards were shown, and subjects were instructed to complete them as fast as they could with "the first word that came to mind". Sixteen of these stems were allowed to be completed with words from the word appreciation task (familiar; e.g. aba_____ for abacate; del_____ for delegado) and 16 with different words (new). Scores were the number of stems completed with familiar words, a measure of priming (implicit memory; Graf and Schacter 1985; Tulving and Schacter 1990). Time taken to complete the stems with familiar words and with non-exhibited words (new) was also measured. This capacity to process language appears to be a function of the central executive (Gathercole 1998).

The non-conscious nature of this test was checked by asking the subjects about their impression of the objective of the test and through the priming effect, which can be demonstrated by the reduced latency for recollection of familiar words correctly completed, as compared to new words (Tulving and Schacter 1990).

*Visual recall (from Memory I, PSS)*[10] These short-term visual memory tasks consisted of an immediate identification of words (in the same sequence) or digits (in any order) presented on the screen. Although this is called a 'visual' test, it is assumed that the information could be acquired by the visuospatial sketchpad and by the articulatory loop through a rehearsal process (Gathercole 1998).

*Psychomotor tests*

*Digit–Symbol Substitution Test (DSST)*[6] This is a subtest of the Wechsler Adult Intelligence Schedule involving coding skills (Wechsler 1955); it was scored for the number of substitutions correctly performed in 90 s.

*Cancellation Task (CT)*[7] This is a measure of focused attention at speed (Bond and Lader 1972); it was scored for the time taken to cross out digit 4 at a frequency of 40 in 400 random digits. Time was corrected for the number of errors (for each error, 1 s was added to the total score).

*Symbol Copying Test (SCT)*[8] This test consists of copying the same symbols used in the DSST to measure its motor component; it was scored for the number of symbols correctly copied in 90 s (Wechsler 1955).

*Tapping (from Vienna Test System)*[11] This is a measure of motor sedation. Subjects tap a sensor on a sensitive panel as fast as possible for 32 s. Score was the total number of taps.

*Inserting pins (from Vienna Test System)*[12] This is used to assess hand and finger dexterity, with a rapid and precise manipulation of 5-cm pins. The time to pick up the pins from a tray and insert them inside 25 holes on a board was measured.

**Table 1** Rating scales scores of patients with major depression during chronic use of antidepressants and their respective controls (mean±SE)

| Scales | Clomipramine | | Imipramine | | Sertraline | | Fluoxetine | |
|---|---|---|---|---|---|---|---|---|
| | Patients ($n$=9) | Controls ($n$=9) | Patients ($n$=15) | Controls ($n$=15) | Patients ($n$=18) | Controls ($n$=18) | Patients ($n$=14) | Controls ($n$=14) |
| STAI trait | 54.0±2.2*** | 33.7±2.7 | 48.6±2.4*** | 33.3±1.3 | 44.2±3.0*** | 30.8±1.2 | 50.0±2.9*** | 31.9±1.7 |
| STAI state | 40.1±3.1** | 27.8±1.6 | 36.7±1.8** | 31.5±1.4 | 38.0±2.4* | 31.3±1.4 | 38.8±2.4* | 30.3±1.8 |
| Beck Depression Inventory | 19.9±2.5*** | 5.1±1.6 | 14.5±1.9[a] | 3.5±1.2 | 12.4±3.2** | 2.6±0.7 | 12.7±1.8*** | 3.0±1.0 |
| Hamilton Depression Inventory | 10.2±1.4 | | 6.5±1.2 | | 8.1±1.9 | | 6.5±1.7 | |
| Clinical Global Impression | | | | | | | | |
| Severity of illness | 2.3±0.4 | | 1.2±0.2 | | 1.9±0.3 | | 1.6±0.3 | |
| Global improvement | 1.3±0.2 | | 0.7±0.2 | | 1.2±0.2 | | 0.9±0.2 | |
| Therapeutic effects | 3.0±0.2 | | 3.6±0.2 | | 3.4±0.2 | | 3.6±0.2 | |
| Side-effects | 2.1±0.3 | | 1.7±0.1 | | 1.6±0.2 | | 1.9±0.3 | |

*STAI* State–Trait Anxiety Inventory
Statistical differences refer to the comparison between patients and controls: *$p\leq0.05$; **$p\leq0.01$; ***$p\leq0.001$
[a]The difference varies according to dose/weight (as dose/weight increased, the mean difference between patients and controls increased)

*Reaction times (from Foundations I, PSS)*[13] These tasks address visual and auditory attention skills (focusing, sustaining and dividing attention) and their integration with basic executive functioning (simple discrimination, initiation, inhibition and differential responding). Stimuli are randomly presented on the screen, at an interval of 1–3 s, and the response is to press the mouse button as quickly as possible to the required stimulus.

### Statistical analysis

To compare patients' and healthy volunteers' performance, separate repeated-measures ANOVA models (Neter et al. 1996) for each drug were adjusted to data, and the appropriate $F$ tests were applied; to control the effect of the dose, the dose/weight ratio was included in the model as a covariate. The final model is equivalent to applying a standard regression model to the difference between patient and their own control. The repeated-measures model is recommended, given that each patient had been paired to a specific control subject with similar characteristics (case–control design). We chose to apply separate tests because in some cases, the same control subject was paired to different patients from different drug groups. This procedure would avoid breaching of any of the assumptions of independence among controls in the statistical model.

The model adjustment was carried out in two steps. In the first step, a complete model with dose/weight covariate was adjusted. If the covariate effect was non-significant, then the paired $t$ test was applied. If the covariate was significant, we analysed the influence of dose/weight on the difference between patients and controls through the parameter estimates.

Pearson's correlation coefficients were calculated to investigate association between (a) performance and length of use of antidepressants, (b) dose/weight and severity of illness and (c) scores in the subjective and objective memory tasks.

Results were expressed as mean±standard error of the mean (SE). A 5% significance level ($\alpha$) was considered for all statistical analyses.

## Results

Table 1 shows rating scale scores of patients and their respective controls. Statistically significant differences between patients and controls were found for all antidepressants in STAI trait (clomipramine: $F$=62.969, $df$=1,7, $p$<0.001; imipramine: $F$=23.906, $df$=1,14, $p$<0.001; sertraline: $F$=21.425, $df$=1,17, $p$<0.001; fluoxetine: $F$=33.030, $df$=1,13, $p$<0.001), STAI state (clomipramine: $F$=13.572, $df$=1,7, $p$=0.008; imipramine: $F$=10.730, $df$=1,14, $p$=0.006; sertraline: $F$=5.415, $df$=1,17, $p$=0.033; fluoxetine: $F$=6.181, $df$=1,13, $p$=0.027) and the BDI (clomipramine: $F$=42.899, $df$=1,7, $p$<0.001; sertraline: $F$=8.922, $df$=1,17, $p$=0.008; fluoxetine: $F$=20.233, $df$=1,13, $p$=0.001). For patients taking imipramine, the difference on BDI varied according to dose/weight. As dose/weight increased, the mean difference between patients and controls increased. For a dose/weight of zero, the difference is estimated as −1.3±5.9 ($F$=0.050, $df$=1,13, $p$=0.826). For every one unit increase, the difference increased by 3.6±1.6 ($F$=4.845, $df$=1,13, $p$=0.046).

Comparison of healthy volunteers' and patients' psychomotor performance (Table 2) showed some statistically significant differences between patients and controls. Volunteers performed better than patients taking imipramine in inserting pins ($F$=5.299, $df$=1,10, $p$=0.044) and in the differential response of the visual reaction time test ($F$=6.536, $df$=1,14; $p$=0.023).

For patients taking clomipramine, the difference on tapping varied according to dose/weight. For a dose/weight

**Table 2** Performance on psychomotor tests of patients with major depression during chronic use of antidepressants and their respective controls (mean±SE)

| | Clomipramine | | Imipramine | | Sertraline | | Fluoxetine | |
|---|---|---|---|---|---|---|---|---|
| | Patients (*n*=9) | Controls (*n*=9) | Patients (*n*=15) | Controls (*n*=15) | Patients (*n*=18) | Controls (*n*=18) | Patients (*n*=14) | Controls (*n*=14) |
| DSST (*n* substitutions) | 47.3±3.6 | 49.0±5.7 | 49.5±2.6 | 50.3±3.9 | 50.1±3.0 | 50.6±3.7 | 52.6±4.7 | 57.6±3.8 |
| SCT (*n* symbols) | 122.7±6.4 | 115.7±9.4 | 129.3±6.1 | 123.1±8.2 | 131.1±4.4 | 127.6±7.4 | 136.4±8.0 | 131.3±9.0 |
| CT time (s) | 72.9±5.9 | 65.7±7.9 | 63.7±3.0 | 58.8±4.6 | 58.8±2.2 | 60.5±2.9 | 63.2±4.1 | 61.7±5.0 |
| Tapping (*n*/32 s) | 183.0±5.1[a] | 199.5±6.5 | 195.7±9.0 | 203.6±4.4 | 194.7±4.1 | 200.8±3.8 | 198.1±3.7[a] | 204.8±3.9 |
| Inserting pins (s) | 43.7±1.5 | 40.7±1.7 | 42.0±1.2* | 40.0±1.3 | 41.0±1.0 | 39.4±0.9 | 41.0±0.9 | 40.1±1.2 |
| Reaction times (ms) | | | | | | | | |
| Simple choice visual reaction | 497.9±18.5 | 488.3±23.5 | 459.9±16.0 | 458.1±16.4 | 466.1±19.2 | 469.8±15.2 | 501.3±31.9 | 455.9±14.1 |
| Visual reaction/auditory prestimulus | 403.8±20.6 | 381.1±21.7 | 381.3±12.1 | 358.3±16.0 | 388.8±14.5 | 369.2±14.2 | 391.9±17.8 | 365.8±11.5 |
| Visual reaction/differential response | 521.3±28.8 | 476.6±21.0 | 496.6±15.8* | 453.3±10.5 | 505.0±17.8 | 470.8±8.8 | 502.1±22.8 | 495.1±14.7 |
| Simple choice auditory reaction | 558.3±50.2 | 522.4±35.4 | 493.9±33.1 | 467.3±27.5 | 511.2±35.9 | 465.9±22.7 | 505.1±40.1 | 488.6±17.1 |
| Auditory reaction/visual prestimulus | 371.3±32.2 | 294.2±20.9 | 315.8±15.6 | 282.9±12.4 | 297.1±14.4 | 294.4±11.2 | 304.3±14.6 | 298.1±13.2 |

*DSST* Digit–Symbol Substitution Test, *SCT* Symbol Copying Test, *CT* Cancellation Task
Statistical differences refer to the comparison between patients and controls: *$p \leq 0.05$
[a]The difference varied according to dose/weight (as dose/weight increased, the mean difference between patients and controls decreased)

**Table 3** Performance on memory tests of patients with major depression during chronic use of antidepressants and their respective controls (mean±SE)

| | Clomipramine | | Imipramine | | Sertraline | | Fluoxetine | |
|---|---|---|---|---|---|---|---|---|
| | Patients (*n*=9) | Controls (*n*=9) | Patients (*n*=15) | Controls (*n*=15) | Patients (*n*=18) | Controls (*n*=18) | Patients (*n*=14) | Controls (*n*=14) |
| Subjective Memory Questionnaire (mean) | 2.9±0.2** | 3.8±0.1 | 3.0±0.1*** | 3.9±0.1 | 3.0±0.1*** | 3.9±0.1 | 3.1±0.1*** | 3.9±0.1 |
| Verbal recall, immediate (*n* items) | 12.3±0.5 | 11.8±0.8 | 11.5±0.6 | 11.6±0.5 | 12.2±0.5 | 12.6±0.3 | 12.4±0.5 | 12.5±0.6 |
| Verbal recall, delayed (*n* items) | 11.1±0.8 | 11.4±0.9 | 10.7±0.6 | 10.7±0.6 | 12.0±0.5 | 12.1±0.4 | 11.6±0.7 | 12.4±0.6 |
| Digit span forward (*n* digits) | 5.7±0.3 | 5.6±0.3 | 5.7±0.3 | 5.9±0.3 | 5.4±0.3 | 5.8±0.3 | 6.1±0.3 | 6.1±0.3 |
| Digit span backward (*n* digits) | 4.2±0.4 | 4.1±0.3 | 4.5±0.3 | 3.9±0.2 | 3.9±0.2[a] | 4.4±0.3 | 4.6±0.4 | 4.7±0.3 |
| Visual recall (*n* digits recalled) | 7.2±0.3 | 7.1±0.4 | 7.3±0.4 | 7.2±0.4 | 7.0±0.3* | 7.7±0.4 | 7.9±0.3 | 7.8±0.4 |
| Visual recall (*n* words recalled) | 4.9±0.2 | 4.7±0.2 | 4.9±0.3 | 5.3±0.3 | 4.7±0.2* | 5.4±0.3 | 5.4±0.2 | 5.2±0.3 |
| Word stem completion | | | | | | | | |
| Familiar words correctly completed (*n*) | 7.9±0.7[a] | 8.1±0.7 | 6.6±0.5 | 7.3±0.6 | 6.6±0.5 | 7.3±0.5 | 7.7±0.7 | 8.0±0.7 |
| Time to complete (s) | | | | | | | | |
| Familiar words | 1.20 ±0.16***[,b] | 1.03 ±0.08***[,b] | 1.17 ±0.10***[,b] | 1.08 ±0.06**[,b] | 1.19 ±0.11***[,b] | 1.11 ±0.06**[,b] | 1.23 ±0.16***[,b] | 0.98 ±0.04***[,b] |
| New words | 1.33±0.08 | 1.20±0.07 | 1.39±0.07 | 1.28±0.08 | 1.38±0.09 | 1.35±0.07 | 1.42±0.14 | 1.27±0.08 |

Statistical differences refer to the comparison between patients and controls: *$p \leq 0.05$; **$p \leq 0.01$; ***$p \leq 0.001$
[a]The difference varies according to dose/weight (as dose/weight increased, the mean difference between patients and controls decreased)
[b]Intragroup priming effect (familiar × new)

of zero, the difference is estimated as −66.3±19.6 ($F$=11.451, $df$=1.6, $p$=0.015). For every one unit increase, the difference decreased by 14.7±5.6[1] ($F$=6.700, $df$=1.6, $p$=0.041). As we have an estimated difference of −66.3 for a zero dose/weight level and an increase of 14.7 for each additional unit of dose/weight, we may conclude that the mean difference between patients and controls tends to decrease for almost all variation intervals of dose/weight in the sample. For fluoxetine, we observed similar behaviour; for a dose/weight of zero, the expected difference for tapping is estimated as −37.2±8.0 ($F$=21.630, $df$=1,10, $p$=0.001). For every one unit increase, the expected difference varies 42.2±9.6 ($F$=19.359, $df$=1,10, $p$=0.001).

Few differences between patients and controls were found in objective memory (Table 3). In the sertraline group, patients performed worse than controls on the number of digits ($F$=5.781, $df$=1,17, $p$<0.05) and the number of words on the visual recall tests ($F$=5.231, $df$=1,17, $p$<0.05). Also, for patients taking sertraline, the difference on digit span backward varied according to dose/weight. As dose/weight increased, the mean difference between patients and controls decreased. For a dose/weight of zero, the difference is estimated as 0.77±0.60 ($F$=1.612; $df$=1,16, $p$=0.222). For every one unit increase, the difference decreased by −0.55±0.23 ($F$=5.420, $df$=1.6, $p$=0.033).

For patients taking clomipramine the difference in the number of familiar words completed in the word stem completion test varied according to dose/weight. As dose/weight increased, the mean difference between patients and controls decreased. For a dose/weight of zero, the difference is estimated as 7.44±1.74 ($F$=18.313, $df$=1,6, $p$=0.005). For every unit increase, the difference decreased by −2.43±0.50 ($F$=23.358, $df$=1.6, $p$=0.003).

Intragroup priming effect was shown through prompter recollection of familiar words correctly completed, when compared to new words, for all groups. For patients, it was possible to adjust a single model of ANOVA ($F$=12.253, $df$=1,51, $p$=0.001). For controls, as the same person was used in different treatments, we applied a different model for each treatment (clomipramine: $F$=33.849, $df$=1,7, $p$=0.001; imipramine: $F$=9.278, $df$=1,14, $p$=0.009; sertraline: $F$=10.615, $df$=1,17, $p$=0.005; fluoxetine: $F$=24.354, $df$=1,13, $p$<0.001).

In the SMQ, patients' self-evaluation was worse than controls for all antidepressants (Table 3; clomipramine: $F$=13.315, $df$=1,7, $p$<0.01; imipramine: $F$=21.724, $df$=1,14, $p$<0.001; sertraline: $F$=37.488, $df$=1,16, $p$<0.001; fluoxetine: $F$=23.255, $df$=1,12, $p$<0.001).

To better investigate the influence of clinical state in this questionnaire, patients were classified as remitted (HDRS ≤6) or not remitted (HDRS ≥7). There was no difference between ratings of SMQ according to clinical state for all drug groups, and both remitted and non-remitted patients evaluated their memory as worse than controls ($p$<0.01).

[1] We expect a variation of 14.7±5.6 for each increase of one unit on the dose/weight covariate. A similar interpretation may be made for fluoxetine.

Significant Pearson's correlation coefficients were found between duration of treatment and performance on the CT for clomipramine ($r$=−0.773, $p$=0.025) and sertraline ($r$=−0.510; $p$=0.03). No significant correlation was found between dose/weight and severity of illness, global improvement or therapeutic effects on the CGI scale. Scores in the SMQ were correlated to objective memory tasks only in patient group for verbal delayed recall for patients taking clomipramine ($r$=0.775, $p$=0.024) and time to complete new words for patients taking sertraline ($r$=−0.493, $p$=0.037).

## Discussion

Few studies have evaluated the impact of antidepressants on memory and psychomotor performances after prolonged therapy. In the current study, we did observe some impairment in psychomotor and memory performances, after chronic use of clomipramine, imipramine, sertraline and fluoxetine at their therapeutic doses, by depressed patients.

A qualitative inspection showed that patients' performance was around 95% of controls' for most tests. This low intensity of effect on performance is of questionable clinical relevance.

The indications that imipramine affects memory performance to some degree is suggested by the significant impairment in a visual reaction time compared to controls. The finding that as fluoxetine and clomipramine dose/weight ratio increases, the difference of performance of patients and controls decreases in tapping test might be consistent with previous reports of improvement in performance after fluoxetine treatment (Fudge et al. 1990; Hale and Pinninti 1995). It is interesting to note that for clomipramine and sertraline, the duration of treatment was associated to better performance on CT.

Regarding memory, depressed patients did not perform significantly worse than controls in most of the objective tests. Patients taking fluoxetine and clomipramine did not show impairment in memory tests. Although those on clomipramine and sertraline performed worse than controls in some tests, higher dose/weight ratio was associated with decrease in the difference between patients and controls. These data suggest that higher drug levels may ameliorate the performance of depressed patients in long-term treatment with some antidepressant medications. In fact, the dose/weight effect seems not to be related to the depressive state, as there was no correlation between dose/weight and severity of illness, global improvement or therapeutic effects on the CGI scale. Also, there was no impairment in priming, attested by the statistical difference in the number of familiar words correctly completed in all groups. This is in agreement with the fastest times to complete with familiar rather than new words recorded in patients and controls.

The lack of a consistent memory impairment observed here is in contrast with the common memory complaints seen among patients in antidepressant treatment. A few

studies (e.g. Allen et al. 1991; Meyers et al. 1991; Sakulsripong et al. 1991) have explored antidepressant effects on metamemory, i.e. the knowledge and judgment by the individual of his/her own capacity to acquire, retain and recall information (Flavell 1971). Metamemory may involve self-perception of general memory abilities in daily activities or more specific aspects related to the use of strategies to improve memory or task performance appraisal. Most studies have assessed metamemory in healthy and depressive subjects to evaluate the validity of this measure in predicting memory impairment related to aging, affective status and performance in objective tasks (Derouesne et al. 1999; Kalska et al. 1999).

Although few differences were observed between volunteers and patients in the objective memory tests, in the subjective assessment, patients in all drug groups self-evaluated their memory as being worse than controls (average vs good). Indeed, subjective ratings of memory performance often have weak correlation with objective laboratory tasks (Bennett-Levy and Powell 1980; Derouesne et al. 1999; Kalska et al. 1999). This is consistent with our finding of just two significant correlations between subjective and objective memory tests (verbal delayed recall for patients taking clomipramine and time to complete new words for patients taking sertraline).

As the memory complaint might be associated to the depressive state, patients were divided according to their clinical condition into remitted and non-remitted. There was no difference between the memory performance rating of these two subgroups, which suggests that the level of depressive symptomatology alone cannot explain this finding. In fact, these patients were not severely depressed; in most of them, the severity of illness was rated as borderline to mild, except for the clomipramine group (mild to moderate), according to the CGI scale. HDRS scores showed that depression could be considered as remitted in most patients using imipramine and fluoxetine (HDRS $\leq$7) and as mild and moderate in those belonging to the clomipramine and sertraline groups (HDRS 8–24). Accordingly, in the BDI, most patients evaluated themselves as mildly to moderately depressed (10–18, Beck et al. 1988), except for those in the clomipramine group (moderate to severe). STAI trait scores were mostly approaching the upper value of the normal range (33–49; Gorenstein et al. 1995a) for all groups except clomipramine, while state anxiety was considered normal for all groups of patients. As expected, patients showed higher clinical scale scores than their respective controls whose rating scale scores were within the normal range.

The possibility that a cognitive depressive distortion underlies the memory complaints in these patients cannot be ruled out. Depressed patients usually show a depressive perception that leads to a biased negative evaluation of themselves and of the world; this is expected to be improved by an effective treatment (Niederehe and Yoder 1989; Derouesne et al. 1999; Kalska et al. 1999). However, functional recovery takes longer to occur than symptomatological remission (Furukawa et al. 2001), and this could explain why remitted and non-remitted patients evaluated their memory as being worse than controls.

Another explanation is that the lack of sensitivity of the tasks used masked objective memory impairment in patients' memory performance. This test battery was shown to be useful for the detection of deleterious effects on memory induced by acute or chronic benzodiazepine administration (Curran and Gorenstein 1993; Hindmarch 1994; Gorenstein et al. 1995b; Pompeia et al. 1996; Buffett-Jerrott et al. 1998), as well as by TCA treatment (Peselow et al. 1991; Hale and Pinninti 1995). However, it is possible that these tests are not sensitive enough for weaker effects or to detect intermittent impairments consistent with the anomia and paraphasia reported by depressed patients (Georgieff et al. 1998).

We should note that the lack of a prospective design is a methodological limitation of this study. The possibility of influence of patients' pretreatment clinical condition on the results cannot be ruled out. Although a prospective design confirmation study in a large sample is desirable, it has several time-consuming implications: it is impossible to predict which patient will have a chronic outcome; those who will need long-term medication treatment; those who will have treatment compliance; those who will not need antidepressant association or combination with other drugs (e.g. benzodiazepines or potentiation strategies); and, mainly, those who will respond to the first antidepressant trial. This is probably why most studies to date have been either single-dose or short-term treatment, which do not reflect clinical practice.

In conclusion, long-term use of these antidepressants does not consistently impair memory and psychomotor performances. The impairments associated with these drugs seem to be of low intensity, where their clinical relevance remains questionable. The fact that impairment of patients' performance was not associated to duration of treatment with any of these drugs corroborates the safety of long-term antidepressant treatment. It is difficult to predict the impact on daily life of any alterations reported by the patients, activities for which more complex cognitive skills are used.

**Acknowledgements** The authors acknowledge FAPESP (SCC), CNPq (RA, CG), PRONEX (RA) and PROTEM (RA) for their grants. The research was conducted at LIM-15, LIM-23 and AMBAN, HCFMUSP.

We hereby declare that the experiments comply with the current laws of Brazil, the country in which they were performed.

## References

Allen D, Curran HV, Lader M (1991) The effects of repeated doses of clomipramine and alprazolam on physiological, psychomotor and cognitive functions in normal subjects. Eur J Clin Pharmacol 40:355–362

Amado-Boccara I, Gougoulis N, Poirier Littre MF, Galinowski A, Loo H (1995) Effects of antidepressants on cognitive functions: a review. Neurosci Biobehav Rev 19:479–493

Amin MM, Khan P, Lehmann HE (1980) The differential effects of viloxazine and imipramine on performance tests: their relationship to behavioural toxicity. Psychopharmacol Bull 16:57–58

APA (1994) Diagnostic and statistical manual of mental disorders, 4th edn. American Psychiatric Association, Washington, DC

Bartfai A, Asberg M, Martensson B, Gustavsson P (1991) Memory effects of clomipramine treatment: relationship to CSF monoamine metabolites and drug concentrations in plasma. Biol Psychiatry 30:1075–1092

Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J (1961) An inventory for measuring depression. Arch Gen Psychiatry 4: 561–571

Beck AT, Steer RA, Garbin MG (1988) Psychometric properties of the Beck Depression Inventory: twenty-five years of evaluation. Clin Psychol Rev 8:7–100

Bennett-Levy J, Powell GE (1980) The Subjective Memory Questionnaire (SMQ). An investigation into the self-reporting of 'real-life' memory skills. Br J Soc Clin Psychol 19:177–188

Biaggio AMB, Natalício L (1979) Manual para o inventário de ansiedade traço-estado (IDATE). Centro Editor de Psicologia Aplicada (CEPA), Rio de Janeiro

Bond AJ, Lader MH (1972) Residual effects of hypnotics. Psychopharmacologia 25:117–132

Buffett-Jerrott SE, Stewart SH, Teehan MD (1998) A further examination of the time-dependent effects of oxazepam and lorazepam on implicit and explicit memory. Psychopharmacology (Berl) 138:344–353

Burt DB, Zembar MJ, Niederehe G (1995) Depression and memory impairment: a meta-analysis of the association, its pattern, and specificity. Psychol Bull 117:285–305

Calev A, Ben-Tzvi E, Shapira B, Drexler H, Carasso R, Lerer B (1989) Distinct memory impairments following electroconvulsive therapy and imipramine. Psychol Med 19:111–119

Carvalho SC, Marcourakis T, Artes R, Gorenstein C (2002) Memory performance in panic disorder patients after chronic use of clomipramine. J Psychopharmacol 16:220–226

Cassano GB, Puca F, Scapicchio PL, Trabucchi M (2002) Paroxetine and fluoxetine effects on mood and cognitive functions in depressed nondemented elderly patients. J Clin Psychiatry 63: 396–402

Correa DD, Gorenstein C (1988) Bateria de testes de momória (I). Critérios de elaboração e avaliação. Arq Bras Psicol 38:24–35

Curran HV, Gorenstein C (1993) Differential effects of lorazepam and oxazepam on priming. Int Clin Psychopharmacol 8:37–42

Deptula D, Pomara N (1990) Effects of antidepressants on human performance: a review. J Clin Psychopharmacol 10:105–111

Derouesne C, Lacomblez L, Thibault S, LePoncin M (1999) Memory complaints in young and elderly subjects. Int J Geriatr Psychiatry 14:291–301

Elliott R (1998) The neuropsychological profile in unipolar depression. Trends Cogn Sci 2:447–454

Fava M (2003) Symptoms of fatigue and cognitive/executive dysfunction in major depressive disorder before and after antidepressant treatment. J Clin Psychiatry 64(Suppl 14):30–34

First MB, Spitzer RL, Gibbon M, Williams JBW (1995) Structured Clinical Interview for DSM-IV Axis I Disorders—patient edition, version 2.0 (SCID-I/P). Biometrics Research Department, New York

Flavell JH (1971) First discussant's comments: what is memory development the development of? Hum Dev 14:272–278

Fudge JL, Perry PJ, Garvey MJ, Kelly MW (1990) A comparison of the effect of fluoxetine and trazodone on the cognitive functioning of depressed outpatients. J Affect Disord 18:275–280

Furukawa TA, Takeuchi H, Hiroe T, Mashiko H, Kamei K, Kitamura T, Takahashi K (2001) Symptomatic recovery and social functioning in major depression. Acta Psychiatr Scand 103:257–261

Gathercole SE (1998) The development of memory. J Child Psychol Psychiatry 39:3–27

Georgieff N, Dominey PF, Michel F, Marie-Cardine M, Dalery J (1998) Anomia in major depressive state. Psychiatry Res 77: 197–208

Geretsegger C, Bohmer F, Ludwig M (1994) Paroxetine in the elderly depressed patient: randomized comparison with fluoxetine of efficacy, cognitive and behavioural effects. Int Clin Psychopharmacol 9:25–29

Glass RM, Uhlenhuth EH, Hartel FW, Matuzas W, Fischman MW (1981) Cognitive dysfunction and imipramine in outpatient depressive. Arch Gen Psychiatry 38:1048–1051

Gorenstein C, Pompeia S, Andrade L (1995a) Scores of Brazilian University students on the Beck Depression and the State Trait Anxiety Inventories. Psychol Rep 77:635–641

Gorenstein C, Bernik MA, Pompéia S, Marcourakis T (1995b) Impairment of performance associated with long-term use of benzodiazepines. J Psychopharmacol 9:313–318

Graf P, Schacter DL (1985) Implicit and explicit memory for new associations in normal and amnesic subjects. J Exp Psychol Learn Mem Cogn 11:501–518

Guy W (1976) ECDEU assessment manual for psychopharmacology, revisada edn. NIMH, Rockville, MD

Hale AS, Pinninti NR (1995) Critical flicker threshold and anticholinergic effects of chronic antidepressant treatment in remitted depressives. J Psychopharmacol 9:258–266

Hamilton M (1960) A rating scale for depression. J Neurol Neurosurg Psychiatry 23:56–62

Harding TW, de Arango MV, Baltazar J, Climent CE, Ibrahim HH, Ladrido-Ignacio L, Murthy RS, Wig NN (1980) Mental disorders in primary health care: a study of their frequency and diagnosis in four developing countries. Psychol Med 10: 231–241

Hindmarch I (1994) Relevant psychometric tests for antidepressants and anxiolytics. Int Clin Psychopharmacol 9(Suppl 1):27–33

Kalska H, Punamaki RL, Makinen-Pelli T, Saarinen M (1999) Memory and metamemory functioning among depressed patients. Appl Neuropsychol 6:96–107

Kerr JS, Fairweather DB, Hindmarch I (1993) Effects of fluoxetine on psychomotor performance, cognitive function and sleep in depressed patients. Int Clin Psychopharmacol 8:341–343

Knegtering H, Eijck M, Huijsman A (1994) Effects of antidepressants on cognitive functioning of elderly patients. A review. Drugs Aging 5:192–199

Marcourakis T, Gorenstein C, Gentil V (1993) Clomipramine, a better reference drug for panic/agoraphobia II. Psychomotor and cognitive effects. J Psychopharmacol 7:325–330

Mari JJ, Williams P (1986) A validity study of a psychiatric screening questionnaire (SRQ-20) in primary care in the city of Sao Paulo. Br J Psychiatry 148:23–26

Meyers BS, Mattis S, Gabriele M, Kakuma T (1991) Effects of nortriptyline on memory self-assessment and performance in recovered elderly depressives. Psychopharmacol Bull 27: 295–299

Neter J, Kutner MH, Nachtsheim CJ, Wasserman W (1996) Applied Linear Statistical Models, 4th edn. McGraw-Hill, Boston, MA

Niederehe G, Yoder C (1989) Metamemory perceptions in depressions of young and older adults. J Nerv Ment Dis 177:4–14

Peselow ED, Corwin J, Fieve RR, Rotrosen J, Cooper TB (1991) Disappearance of memory deficits in outpatient depressives responding to imipramine. J Affect Disord 21:173–183

Pompeia S, Gorenstein C, Curran HV (1996) Does potency determine amnestic effects of benzodiazepines? A dose–response comparison of flunitrazepam and nitrazepam. Behav Pharmacol 7:532–539

Sakulsripong M, Curran HV, Lader M (1991) Does tolerance develop to the sedative and amnesic effects of antidepressants? A comparison of amitriptyline, trazodone and placebo. Eur J Clin Pharmacol 40:43–48

Schmitt JA, Kruizinga MJ, Riedel WJ (2001) Non-serotonergic pharmacological profiles and associated cognitive effects of serotonin reuptake inhibitors. J Psychopharmacol 15:173–179

Seppala T, Linnoila M, Mattila MJ (1978) Psychomotor skills in depressed out-patients treated with L-tryptophan, doxepin, or chlorimipramine. Ann Clin Res 10:214–221

Spielberg CD, Gorsuch RL, Lushene RE (1970) Manual for the State–Trait Anxiety Inventory. Consulting Psychologists Press, Palo Alto, CA

Thompson PJ (1991) Antidepressants and memory: a review. Hum Psychopharmacol 6:79–90

Tulving E, Schacter DL (1990) Priming and human memory systems. Science 247:301–306

Veiel HO (1997) A preliminary profile of neuropsychological deficits associated with major depression. J Clin Exp Neuropsychol 19:587–603

Wechsler DA (1945) A standardized memory scale for clinical use. J Psychol 19:87–95

Wechsler DA (1955) Manual for the Wechsler adult intelligence scale. National Foundation for Educational Research, London