Cognitive performance following fluoxetine treatment in depressed patients post myocardial infarction


**Background:** As depression is a considerable risk factor for an unfavourable course of myocardial infarction (MI), antidepressant treatment of post-MI depression and, inherent to MI status, polypharmacy has become an important issue.

**Objective:** The present study is the first to evaluate cognitive side effects of fluoxetine, as part of a placebo-controlled double-blind trial, in patients with post-first MI depression.

**Methods:** Cognitive performance of 54 depressed patients post first-MI, treated with fluoxetine or placebo was compared. Cognitive performance was tested before and after 9 weeks of treatment using the Visual Verbal Learning Test, Concept Shifting Task, Stroop Colour-Word Test and Letter-Digit-Substitution Test.

**Results:** The median number of cardiovascular drugs taken by MI patients was 4.9. There were no differences between the fluoxetine and the placebo group on cognitive performance.

**Conclusion:** In sum, there were no negative side effects of fluoxetine compared with placebo on cognition in depressed MI patients, simultaneously treated with cardiac drugs.

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**Introduction**

Depression is a frequent comorbid condition of myocardial infarction (MI), increasing morbidity and mortality in the first 18 months post-MI (1–5). It may be important to treat depressed MI patients, although it is as yet unclear whether treatment of post-MI depression increases cardiac prognosis (6). Nevertheless, as research has shown that depression is predictive of quality of life 12 months later, it remains important to treat depressed MI patients (7,8). A poor emotional state in MI patients may also compromise compliance with medical advice (9) and participation in cardiac rehabilitation (10,11), as well as increasing health care consumption (5). The selective serotonin reuptake inhibitors (SSRIs) seem to be first choice of pharmacological antidepressive treatment because of less cardiotoxic side effects compared with tricyclics (12,13). The question remains whether cognitive side effects occur in administration of an SSRI in combination with cardiac drugs (14).

Until now possible cognitive side effects of SSRIs have not been evaluated in depressed MI patients. It is important to evaluate cognitive side effects in depressed MI patients. First, the majority of depressed patients are treated as outpatients and are expected to continue their professional life and normal everyday routine (14). It thus becomes necessary that antidepressive therapy minimally impairs cognitive function. Second, treatment compliance can be endangered if patients experience memory disturbances or psychomotor side effects in a situation where they have to take daily doses of different...
cardiac medications. Most studies evaluating cognitive side effects of SSRIs are performed with a single-dose administration in healthy volunteers (14). In such studies, SSRIs such as fluoxetine, fluvoxamine and sertraline had no effect on arousal and reactivity, car driving and sensori-motor performance, and interference susceptibility (15–17). In a population-based sample of 1488 adults, tricyclic antidepressants did not cause any measurable cognitive deficits (18). Very few studies investigated cognitive side effects of SSRIs in depressed patients. A 1-month administration of fluvoxamine did not impair memory assessed by a word decision test (19). In elderly depressed patients, fluoxetine 20 mg showed no impairment of cognition compared with 75 mg of amitriptyline in a double-blind trial (20). In 242 elderly depressed patients treated with paroxetine or fluoxetine, no deterioration of cognition was observed (21).

The aim of the present study was to evaluate cognitive side effects of an SSRI, fluoxetine, in depressed first-MI patients treated with cardiac medication, as part of a double-blind placebo controlled trial of the efficacy and safety of fluoxetine in post-MI depression (13). Care was taken to use memory-related neuropsychological tests, including attention and speed of information processing, with proved sensitivity for use in neuropsychiatric patients (22,23) and in drug-evaluation studies (24).

Materials and methods

All consecutive admissions to the first heart aid of the Maastricht University Hospital and an affiliated hospital within a 3-year period were selected. Patients with first-time MI, diagnosed by a cardiologist, were included. Inclusion criteria were age between 18 and 75 years, clinical picture typical of MI, ECG changes specific for MI and a maximum plasma concentration of aspartate aminotransferase (ASAT) twice the upper normal range (80 U/l) (25). The number of eligible patients was 556; 357 patients agreed to participate, and 199 (35%) patients refused to participate. Of these 357 patients, four died between 1 and 3 months post-MI, and 68 met the DSM-III-R criteria for major depression within the first 12 months post-MI.

Intervention

Before inclusion in the study, possible side effects of fluoxetine were explained to the patients, and written informed consent was obtained. Fluoxetine was studied according to a randomized, placebo-controlled, double-blind design. The antidepressant was prescribed for a treatment period of 9 weeks. Patients were randomly assigned to either fluoxetine 20 mg/day or placebo. This dose could be increased to 40 mg/d in week 3 and to 60 mg/d in week 6, depending on clinical response [≤50% decrease of the score on the Hamilton Depression Rating Scale, 17-item version (HAM-D)] (26).

Data collection

Age and education were collected at baseline. Cognitive function tests were assessed at baseline and after 9 weeks of treatment. We used a neuropsychological test battery which has been used extensively in neuropsychiatric patients and in drug studies (22,24). This test battery is very sensitive to subtle cognitive changes and consists of parallel versions which enable repeated testing with a great sensitivity. Earlier studies were often hampered by a lack of sensitive tests in parallel versions.

Visual Verbal Learning Test (27,28). A visual version of the Auditory-Verbal Learning Test (AVLT) (29) was used. In The Netherlands, this is the most used memory test, and its psychometric properties are quite similar to the California Verbal Learning Test (29) and the AVLT (29,30) with the exception that the words are presented visually to control for hearing loss. In this Dutch version, a set of 15 frequently used monosyllabic meaningful words is presented in a fixed order at a rate of one every 2 s in three consecutive trials. After each trial, the patient is required to recall as many words as possible with no restriction concerning the order of the recalled words. The dependent variable is the total number of words recalled over the three trials (VVLTtot). Twenty minutes after the last presentation, the patient is again requested to recall as many words as he or she can remember (VVLTdel). This test measures memory storage and retrieval of verbal information in episodic memory.

Concept Shifting Task (29,31). This test is derived from the Trail Making Test, which is used to measure the ease of shifting between different sets of attention (32). The advantage above the Trail Making Test is that the effect of motor function is limited, so that the influence of simple motor speed on test performance is controlled for. It consists of four test sheets, that each contains 16 small circles grouped in a larger circle. On the first test sheet, empty circles
have to be crossed out as fast as possible (CST0). On the other three test sheets, the circles contain numbers (CSTA), letters (CSTB) or both (CSTC), appearing in a fixed random order. Patients are requested to cross out the items in the right order. The dependent variable is the time needed for each part (31).

**Stroop Colour-Word test (29).** The Stroop Colour-Word test (SCWT) tests selective attention and interference susceptibility. The test is made out of three cards displaying 40 stimuli each, i.e. colour names (SCWT1), coloured patches (SCWT2) and colour names printed in incongruously coloured ink (SCWT3). For the last card (SCWT3), the colour of the ink has to be named instead of the colour name. This task is sensitive to interference. The dependent variables are the seconds needed to complete each task.

**Letter-Digit Substitution Test (29,31).** This test is a modification of the Symbol-Digit-Modalities Test. The patients are supplied with a code at the top of the page where a digit corresponds to a letter. Then they have 60 s to fill in blanks with corresponds to the correct codes. This test measures the speed of processing general information obtained by visual perception, attention and memory. The dependent variable is the total number of letters written correctly within the one minute (LDSTt1ot).

These cognitive tests assess the following theoretical underlying cognitive constructs, memory-(VVTt1ot, VVTtdel) and attention-related aspects such as cognitive flexibility (ability to shift between the two sequences; CSTC), interference susceptibility (ability to ward off distractions, SCWT2), sensorimotor speed (simple cognitive speed; CST0, CSTA, CSTB, SCWT1 and 2) and speed of general informatting processing (LDSTt1ot) (33).

Depression, measured by the HAMD scale, 17 items was assessed at baseline and after 9 weeks of treatment. Blood samples were collected for fluoxetine and norfluoxetine plasma concentrations after 3, 6 and 9 weeks of treatment.

**Analyses**

Statistical analyses were carried out using SPSS 6.0 Windows software (34). Because the study described in our manuscript is part of a double-blind placebo-controlled study of the efficacy of fluoxetine in depressed post-MI patients, the power calculations were a priori based on depression efficacy measures. The power calculation on the depression outcome is published in Strik et al. 2000 (13). For the present study, the required sample size was estimated using the guidelines described by Knapp and Miller (35). In case of the absence of previous cognitive outcome data in depressed post-MI patients, we used data of normal controls (31). Effect size of cognitive tests was estimated by choosing one standard deviation of a healthy male and female population, aged between 53 and 62 years, with a medium education level. If, furthermore, the level of significance α is set on 0.05, the power β is set at 0.95, and the cognition hypothesis is tested one tailed, the required sample size is 46 (23 per group).

For the outcome on the cognitive tests, ANCOVA was applied using endpoint scores of the cognitive testbattery as the dependent variable and baseline scores of cognition, age, gender, education and HAMD difference between baseline and week 9 as covariants. A two-tailed P-value ≤0.05 was considered to be significant. Patients were only included in the analyses, if they had assessment data at baseline and week 9.

**Results**

**Patients**

Of the 68 patients diagnosed with major depression, 12 refused to participate at a later stage, and two were excluded due to heart failure. The nonparticipants did not differ from the included patients with regard to age, gender and maximum serum ASAT. Fifty-four patients were included in the study, of whom 31 were diagnosed with major depressive episode at 3 months, 17 at 6 months and 6 at 12 months post-MI. Fifty-four patients were randomized to fluoxetine (n = 27) or placebo (n = 27). There were 38 males and 16 females. Mean age was 54.1 years (SD 11.3) in the fluoxetine and 58.7 years (SD 10.1) in the placebo group; mean education level was 28 (SD 2.2) on an 8-point scale (36) in the fluoxetine group and 3.0 (SD 2.1) in the placebo group; and mean HAMD score was 22 (SD 3.5) in the fluoxetine and 21.2 (SD 3.7) in the placebo group. There were no statistically significant differences between fluoxetine and placebo groups with regard to age, gender, education or severity of depression (using HAMD scale) (Table 1).

In the acute phase, two patients dropped out from the fluoxetine group and five from the placebo group due to lack of effect, loss to follow-up, or medical reasons. The HAMD score decreased significantly in both groups. Efficacy and cardiac safety of fluoxetine in this patient
group is discussed elsewhere (13). Overall, the a-priori difference in antidepressive efficacy between fluoxetine and placebo treatment of four points on the HAMD score was not met. However, there were significantly more respondents during fluoxetine treatment than during placebo treatment at week 25. Furthermore, compared with placebo, fluoxetine was especially effective with reference to HAMD score of patients diagnosed with mild depression.

Medication
All patients taking fluoxetine had repeated fluoxetine plasma levels > 4 μg/l. The mean fluoxetine dose was 47.3 mg/day (SD = 19.1).

Comedication (Table 2) consisted of platelet aggregation inhibitors (PAI) (n = 42, 77.8%), lipophilic beta-blockers (n = 33, 61.1%), benzodiazepines (n = 28, 51.9%), isosorbide nitrate (n = 23, 42.6%), cholesterol-lowering medication (n = 22, 40.7%), angiotensin converting enzyme (ACE) inhibitors (n = 16, 29.6%), calcium channel blockers (n = 15, 27.8%), diuretics (n = 13, 24.1%), anti-aggregation agents (other than PAI) (n = 6, 11.1%) and hydrophilic beta-blockers (n = 5, 9.3). The median number of cardiovascular drugs taken was 4.9, ranging from 1 to 9, excluding trial medication. There were no significant differences in specific drugs between groups. All patients were antidepressant and antipsychotic drug free prior to starting the study.

Cognitive performance
In Table 3, the mean scores at baseline of the cognitive tests are summarized for the two groups. Because of missing data, the number of patients is different for each group. There were no differences in mean scores of the different tests of the cognitive battery at baseline and week 9. Also after correction for several confounders, i.e., gender, age, education, difference in HAMD between baseline and week 9, and test performance at baseline, end points of the mean cognitive tests scores, i.e. VLT (memory storage and retrieval), CST (ease of shifting between different sets of items), SWIT (selective attention and interference susceptibility) and LDST (speed of processing general information obtained by visual perception, memory and attention) were not statistically significant different (Table 4).

Discussion
The present study is the first to investigate cognitive side effects of fluoxetine in a double-blind, placebo-controlled design in patients with major depression after first MI, also treated with cardiac drugs. We found that there were no differences in cognitive performance between depressed MI patients treated with fluoxetine compared with those treated with placebo, although patients simultaneously had to take a median number of 4.9 cardiac drugs per day.

In literature, fluoxetine was already reported to have no negative effect on neurocognitive functions.
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*Baseline measures vs. week 9.

performance or sedative side effects (14). However, cognitive side effects of fluoxetine were mainly tested in young, healthy volunteers in a single-dose administration (14). There is one study in which cognitive effects of fluoxetine were evaluated in elderly depressed patients and compared with paroxetine using the the Mini Mental State Examination and The Sandoz Clinical Assessment Geriatric scale (SCAG) (37), which may be less sensitive than the neurocognitive testbattery, measuring memory, speed and cognitive flexibility, used in our study (22,24). This study found that both fluoxetine and paroxetine improved cognitive function. Another study by Nebes et al. (1999) (38), who evaluated toxicity of paroxetine in 29 older depressed patients, found that acute treatment with paroxetine was not associated with any cognitive impairment. Patients’ performance improved on several timed tasks, but memory performance remained unchanged, as in our study.

No studies on fluoxetine have been performed in patients with MI, treated for several weeks. Our study was the first to evaluate cognitive side effects of fluoxetine in depressed patients aged 37–75 years, with 50% of this patient sample being 55 years and older, with a frequently occurring somatic illness being MI and treated for 9 weeks with placebo or fluoxetine up to 60 mg/day.

It was already been found that baseline cognition of the depressed MI patients was not different from baseline cognition in nondepressed MI patients (39) or healthy controls (matched for gender, age and education) (31). Hence, it is unlikely that cognitive functioning will further improve during treatment. Data

on the interaction between treatment and pre-existing cognitive functioning are inconsistent (38). One study showed that cognitively intact patients showed an improvement in performance following treatment with nortryptiline (40), while others did not find an association between treatment outcome and cognitive function at baseline (41).

Second, one has to consider the role of psychoactive effect of the cardiac drugs taken by the patients in the present study. It is very difficult to analyse the separate contribution of each individual substance and their interactions on its influence on cognitive performance. However, there were no statistically significant or clinically relevant differences in the number of cardiac medication in both groups. The only drug that was different was the trial medication fluoxetine/placebo, but this did not lead to differene in cognitive performance (Table 3).

In sum, there were no negative side effects of fluoxetine compared with placebo on cognition in depressed MI patients, simultaneously treated with cardiac drugs.

Acknowledgment

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References


