The SSRIs drug Fluoxetine, but not the noradrenergic tricyclic drug Desipramine, improves memory performance during acute major depression

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INTRODUCTION

Inappropriate negative mood, abnormal neurovegetative activities, and cognitive impairment are the three main symptoms in major depression disorder. In a comparison of depressed patients with a control group, significant deficits were found in a range of neuropsychological measures covering aspects of language function, memory (both recall and recognition) attention, and behavioral regulation [7]. Many clinical studies indicate that depressed patients also suffer from poor memory performance and that their memory significantly improves after treatment with antidepressants [7,10,19,25]. Improved memory formation in both verbal and nonverbal tasks has been repeatedly demonstrated in patients with major depression disorder [1,5,15,26,29]. Meta-analytic techniques that were used to synthesize data from 99 studies on recall and 48 studies on recognition in clinically depressed and nondepressed patients revealed a significant stable association between depression and memory impairment [25].

The most common neurochemical hypothesis to explain depressive illness is the monoamine hypothesis. This hypothesis associates depression with lowered actual or functional monoamine neurotransmitter concentrations at brain synapses. Therefore, treatment of depression may be achieved by restoring the monoamine levels or action to normal. Support for this hypothesis comes from the mechanism of action of the tricyclic antidepressant drugs; a large group of drugs that have been useful for treating a wide range of depressive states as well as for preventing relapse. The tricyclic drugs are reuptake inhibitors mainly of noradrenaline (NA) and serotonin (5-hydroxytryptamine, 5-HT). Different drugs show a preference for inhibition of reuptake of either NA or 5-HT, and the monoaminergic hypothesis of depression refers equally to both.

A new generation of antidepressant drugs was developed that shows selectivity for inhibition of reuptake of one of these monoamines. Among these new drugs, selective serotonin reuptake inhibitors (SSRIs) have a distinct and well-characterized mechanism of action, and these have become among the most prescribed antidepressant drugs [4,8,17,24].

However, comparing the effects of drugs of the SSRIs group with drugs of the tricyclic group, various studies found equal clinical improvement in patients with major depression. For example, an equal improvement of depression symptoms was found in major depression patients who received either the SSRI drug Fluoxetine or the noradrenergic drug Amitriptyline [18,29]. Similar findings were found when Fluoxetine and Mianserin [20] or Fluoxetine and Desipramine [6,32] were compared.

On the other hand, concerning memory performance, patients who received Amitriptyline did not perform as well as the Fluoxetine group in recent memory and in verbal learning tasks [18,29].

ABSTRACT: Accumulating evidence suggests that noradrenergic and serotonergic drugs are equally effective in ameliorating the depressive symptoms of major depression. Major depression is associated also with memory impairments, but the comparative effects of the antidepressant drugs on memory are not clear. We previously found that serotonergic neurotransmission is of particular importance for some aspects of episodic memory. We set out to test whether treatment with the selective serotonergic drug Fluoxetine (Prozac) would be advantageous in this respect over treatment with the selective noradrenergic tricyclic antidepressant drug Desipramine (Despresan). Seventeen patients with major depressive episode, randomly assigned for treatment with either Fluoxetine (n = 8) or Desipramine (n = 9), were assessed for their clinical situation and for memory performance at the beginning of treatment, after 3 weeks, and after 6 weeks of pharmacological treatment. We found that although clinically both drugs were equally effective, the improvement of memory performance in the Fluoxetine-treated patients was significantly greater compared with that of the Desipramine-treated patients. The results support the role of serotonin in memory. More studies in larger samples of patients are required, but it may be that in cases where memory impairment is a major symptom, it would be beneficial to consider serotonergic antidepressant drugs for treatment. Furthermore, in cases where, for various reasons, the treatment of choice is noradrenergic, it may be worthwhile to consider a supplementary serotonergic drug to improve memory deficits.

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KEY WORDS: Serotonin, Memory, Mood disorders.
Likewise, the spatial capacities, short-term and overall memory of patients who received Fluoxetine were improved, whereas patients who received Mianserin did not manifest an equivalent improvement [20].

Henry et al. [13] found evidence that pretreatment with biogenic amine precursors was associated with improvement in memory function in major depression. There is also evidence that serotonergic neurotransmission is important for cognitive performance.

The hippocampus, which is known to be involved in learning and memory processes, is among the regions richest in serotonin receptors [2,3]. There are indications that drugs that act on serotonergic systems influence human and animal cognition, and that modification of serotonergic neurotransmission interferes with cognitive function [12,14,31,34]. There is also evidence for a functional interaction between the central cholinergic and serotonergic neural systems, as well as evidence that this interaction plays an important role in the mediation of cognitive performance [9,11,21,22,30,34].

The serotonergic and noradrenergic drugs were found to be equally effective in ameliorating the depression symptoms of patients. However, it may be the case that the serotonergic drugs are advantageous over the noradrenergic drugs in their effects on major depression-associated memory deficiency. Establishing such a memory-related advantage of the serotonergic treatment is of clinical importance, as it may be a factor in the choice of the most appropriate pharmacological treatment of depressed patients. Furthermore, memory-related advantage of the serotonergic drugs would support the notion of a role for serotonin in mediating memory processes.

The purpose of this work was to compare the improvement in performance of memory tasks between patients with major depression who were treated with either the selective serotonergic drug Fluoxetine (Prozac) or with the selective noradrenergic tricyclic antidepressant drug Desipramine (Deprexan).

### MATERIALS AND METHODS

#### Participants

The study sample included 27 patients with recurrent major depressive disorder, randomly selected from a pool of patients, refer by General Practitioner, to the ambulatory services of Shalvata Mental Health Center, affiliated with Tel-Aviv University. Of these, five refused to participate and five were excluded during the study because of lack of cooperation and/or worsening of clinical symptoms (see Table 1). The diagnosis was based on the criteria of the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, and was made by two independent senior psychiatrists. The inclusion criteria were: age 25–50 years, severe or moderate nonpsychotic depressive episode with a score of more than 21 on the Hamilton Depression Rating Scale (HAMD), duration of the present depressive episode no longer than 5 months, no more than two previous antidepressive drugs given for the current episode, and no medication for 3–5 days before first assessment. Exclusion criteria were: psychotic state, significant past head injury, severe neurological disease or physical illness, history of drug addiction or alcoholism, electroconvulsive therapy in the last year, an abnormal finding on physical examination or laboratory tests (done by the General Practitioner) severe suicide risk, or suicide attempt in the last year.

#### Measures

**Clinical assessment of depression symptoms.** Two assessment tests were used:

- HAMD: rates the severity of 17 depression symptoms.  
- Clinical Global Impression (CGI): a global assessment of the severity of the illness according to the psychiatrist’s clinical experience.

**Assessment of memory performance.** The battery of memory tests was compounded from:

- The Rivermead Behavioral Memory Test (RBMT; [38]): this test was employed to measure a variety of aspects of everyday memory functions. It consists of 12 subtests, including: recognition memory for pictures and faces, logical memory (free recall of a story), orientation, prospective memory (remembering to retrieve an object and ask a question), spatial memory (recall a route), and short-term and delayed memory (remembering a name and other details) [16,35,38].
- Rey-Osterrieth Complex Figure Test (CFT): this test investigates visual and spatial memory and perceptual organization. The patient is first instructed to copy a complex figure, and then, when the figure and his initial drawing have been removed, he is asked to draw the figure again as he recalls it. Scoring system is based on appraisal of accuracy of each unit that composes the figure and appraisal of its relative position within the whole design [23,36].
- Paired Associates: this test measures memory skills in a process of learning. After the patient reads aloud 10 paired words from cards, he is presented with the first word from each pair and tries to recall its match. If he does not recall, the examiner gives him the right answer. The sequence is repeated five times or until the patient remembers all 10 pairs [33].
- Digit Span forward: this subtest from the Wechsler Adult Intelligence Scale (WAIS-R; [37]) was employed as a measure of short-term memory [16].
- Digit Symbol: this subtest from the W AIS-R test [37] is a paper-and-pencil coding task that was used to assess complex psychomotor speed, concentration, and attention.
- Digit Span backward: this subtest from the WAIS-R test [37] is a measure of working memory.

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### TABLE 1

<table>
<thead>
<tr>
<th>Gender</th>
<th>Age (Years)</th>
<th>No. of Previous Episodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>F 4, M 4</td>
<td>44.5 ± 5.6</td>
<td>14 ± 0.65</td>
</tr>
<tr>
<td>F 3, M 6</td>
<td>49.6 ± 5.3</td>
<td>12 ± 0.83</td>
</tr>
</tbody>
</table>

Values are mean ± SD. F, Female; M, Male.
Procedure
All patients were assessed for their clinical status and for memory tasks performance at the beginning of treatment, 3 weeks, and after 6 weeks after the beginning of the pharmacological treatment. The patients’ psychiatrists established clinical assessment, and an examiner (a psychology intern) assessed memory performance. Both the psychiatrist and the patient knew the name of the medication, but this information was withheld from the examiner. Patients were given Desipramine in a dosage of 125–200 or Prozac 20 mg with no changes in dosage after the first 5 days. No other medication was taken by the patients.

RESULTS

Clinical Assessment
The level of depression at the beginning of the study (baseline) was assessed either by the HAMD or the CGI results in the first session. No difference was found in the baseline level of depression between the two groups (Tables 2 and 3).
Significant improvement in the severity of the depression, as measured by the HAMD and CGI, was found among patients from both groups at the second and third session compared with the first (Tables 2 and 3; Fig. 1). There was no significant difference between the two groups at either the second or third sessions.

An Analysis of Memory Performance

Tables 4 and 5 display data from all memory tests in both groups, including means and standard errors in each session and results from the paired Mann–Whitney test (Wilcoxon) concerning comparisons of the first, second, and third sessions.

It is evident from Tables 4 and 5 that in the Prozac group there was a significant improvement in the total sum of RBMT subtests, in the sixth week versus the first (p < 0.04) and a tendency for a significant improvement by the third week (p < 0.07). In the Paired Associates test, there was also a significant improvement in the sixth week versus the first (p < 0.05), and in the CPT there...
TABLE 4
MEAN AND STANDARD ERROR OF THE DIFFERENT MEMORY TESTS IN EACH SESSION, AND RESULTS FROM THE PAIRED MANN–WHITNEY TEST (WILCOXON), FROM COMPARISONS OF THE THREE SESSIONS, IN THE PROZAC GROUP

<table>
<thead>
<tr>
<th>Test</th>
<th>Pretreatment</th>
<th>At 3 Weeks</th>
<th>At 6 Weeks</th>
<th>Wilcoxon at 3 Weeks Versus Pretreatment</th>
<th>Wilcoxon at 6 Weeks Versus Pretreatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>RBMT (total sum of subtests)</td>
<td>58.2 ± 2.3</td>
<td>63.2 ± 4</td>
<td>64.2 ± 4.1</td>
<td><em>p = 0.07</em></td>
<td><em>p &lt; 0.05</em></td>
</tr>
<tr>
<td>CFT</td>
<td>23.2 ± 2.6</td>
<td>24.5 ± 2.5</td>
<td>26.7 ± 2.2</td>
<td><em>p = 0.54</em></td>
<td><em>p = 0.15</em></td>
</tr>
<tr>
<td>Paired Associates</td>
<td>8.8 ± 3.1</td>
<td>9.2 ± 3</td>
<td>12.5 ± 4.3</td>
<td><em>p = 0.43</em></td>
<td><em>p &lt; 0.05</em></td>
</tr>
<tr>
<td>Digit Span</td>
<td>7.12 ± 0.67</td>
<td>6.38 ± 0.59</td>
<td>7 ± 0.53</td>
<td><em>p = 0.94</em></td>
<td><em>p = 0.81</em></td>
</tr>
<tr>
<td>Digit Symbol</td>
<td>44.75 ± 6.37</td>
<td>40.88 ± 6.59</td>
<td>36.12 ± 5.99</td>
<td><em>p = 0.07</em></td>
<td><em>p &lt; 0.01</em></td>
</tr>
</tbody>
</table>

RBMT, Rivermead Behavioral Memory Test; CFT, Rey–Osterrieth Complex Figure Test.

was a tendency for improvement in the sixth week, though without statistical significance. Parallel improvement was not found in the Deprexan group. In the Digit Symbol test, there was a significant decrease in performance in the sixth week versus the first one, in both groups.

Memory performance index (MPI). The results so far indicate that the serotonergic treatment was advantageous over the noradrenergic treatment, with respect to the improvement in the performance of memory tasks. However, a careful examination of the performance in the different tasks revealed that several of the tests were, in effect, not sufficiently discriminative.

We thus set out to calculate an MPI that would be based only on the more discriminative tasks, i.e., those with high initial variability as indicated by stepwise regression (F(7, 18) = 1741,

TABLE 5
MEAN AND STANDARD ERROR OF THE DIFFERENT MEMORY TESTS IN EACH SESSION, AND RESULTS FROM THE PAIRED MANN–WHITNEY TEST (WILCOXON), FROM COMPARISONS OF THE THREE SESSIONS, IN THE DEPREXAN GROUP

<table>
<thead>
<tr>
<th>Test</th>
<th>Pretreatment</th>
<th>At 3 Weeks</th>
<th>At 6 Weeks</th>
<th>Wilcoxon at 3 Weeks Versus Pretreatment</th>
<th>Wilcoxon at 6 Weeks Versus Pretreatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>RBMT (total sum of subtests)</td>
<td>57.9 ± 2.2</td>
<td>58.7 ± 2.3</td>
<td>58.9 ± 2.5</td>
<td><em>p = 1</em></td>
<td><em>p = 0.73</em></td>
</tr>
<tr>
<td>CFT</td>
<td>20.6 ± 3.9</td>
<td>19.4 ± 3.7</td>
<td>19.7 ± 3.8</td>
<td><em>p = 0.64</em></td>
<td><em>p = 0.81</em></td>
</tr>
<tr>
<td>Paired Associates</td>
<td>9.7 ± 3.1</td>
<td>11.7 ± 4.6</td>
<td>10.8 ± 5</td>
<td><em>p = 0.93</em></td>
<td><em>p = 1</em></td>
</tr>
<tr>
<td>Digit Span</td>
<td>5.78 ± 0.22</td>
<td>7 ± 0.7</td>
<td>6.44 ± 0.41</td>
<td><em>p &lt; 0.05</em></td>
<td><em>p = 0.09</em></td>
</tr>
<tr>
<td>Digit Symbol</td>
<td>44.11 ± 7.73</td>
<td>41.44 ± 7.18</td>
<td>37.11 ± 6.56</td>
<td><em>p = 0.31</em></td>
<td><em>p &lt; 0.05</em></td>
</tr>
</tbody>
</table>

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In order to select those memory tests that contribute significantly to the variability between individual performance, a stepwise regression was performed on all the tests. Stepwise regression yielded seven variables that have significant standardized coefficients (β). Taken together, the performance in these seven tests explains 99% of the variability. The performance in these tests was thus used to build the MPI.

TABLE 6
SETTING UP THE MEMORY PERFORMANCE INDEX (MPI)

<table>
<thead>
<tr>
<th>Model</th>
<th>Unstandardized Coefficients</th>
<th>Standardized Coefficients (β)</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B</td>
<td>SE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Constant)</td>
<td>23.302</td>
<td>3.604</td>
<td>6.47</td>
<td>0.000</td>
</tr>
<tr>
<td>Digit Span</td>
<td>1.009</td>
<td>0.022</td>
<td>0.578</td>
<td>45.80</td>
</tr>
<tr>
<td>CFT (Rey)</td>
<td>1.064</td>
<td>0.053</td>
<td>0.293</td>
<td>20.26</td>
</tr>
<tr>
<td>Paired Association</td>
<td>0.990</td>
<td>0.049</td>
<td>0.288</td>
<td>20.34</td>
</tr>
<tr>
<td>RBMT subsets</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Name</td>
<td>1.893</td>
<td>0.149</td>
<td>0.149</td>
<td>11.17</td>
</tr>
<tr>
<td>F. name</td>
<td>1.269</td>
<td>0.343</td>
<td>0.043</td>
<td>3.70</td>
</tr>
<tr>
<td>Story</td>
<td>2.480</td>
<td>0.505</td>
<td>0.056</td>
<td>4.91</td>
</tr>
<tr>
<td>D. story</td>
<td>2.278</td>
<td>0.657</td>
<td>0.036</td>
<td>3.47</td>
</tr>
</tbody>
</table>

Model Summary

<table>
<thead>
<tr>
<th>SE of the Estimate</th>
<th>Adjusted R²</th>
<th>R²</th>
<th>R</th>
<th>Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.3282</td>
<td>0.998</td>
<td>0.999</td>
<td>1.000</td>
<td></td>
</tr>
</tbody>
</table>

* Dependent variable: MPI
An improvement in memory performance, which became significant 6 weeks after the beginning of the treatment, was found only in the Prozac-treated group. No improvement was observed in the Deprexan-treated group. No difference in MPI was found between the two groups at the beginning of the study \( t(153) = 0.19, p > 0.844 \). The mean for the Prozac group was 80.2 ± 7.31 and for the Deprexan group 77.9 ± 8.73. Figure 2 demonstrates the improvement in memory performance, as measured by the MPI, in the course of the three sessions, for both groups. Analysis of variance (ANOVA) revealed a significant effect of time on MPI \( F(2, 23) = 8.3, p < 0.001 \). A post-hoc Student’s Newman–Keuls test for improvement between the first and the third sessions was significant \( p < 0.001 \). The improvement mean between the first session (pre) and the last session (6w) \((pre-6w)/pre\) was \(-18.2 ± 6.5\).

In the Deprexan group, no significant memory improvement was found \( F(2, 26) < 1 \), and the improvement mean between the pre-session and the sixth-week session was:

\[-1.1 ± 3.1\].

A comparison of the mean improvement in memory performance for both treatments showed that the improvement was significantly greater in the Prozac group than in the Deprexan group \( t(15) = 2.46, p < 0.02 \).

Figure 3 demonstrates the difference in the improvement in memory performance between the two groups.

**DISCUSSION**

The purpose of the present study was to compare the improvement in performance of memory tasks among major depressive patients during acute episode who were treated with either the selective serotoninergic drug Fluoxetine (Prozac), or the selective noradrenergic tricyclic antidepressant drug Desipramine (Deprexan). While both groups showed a comparable improvement in measures of depression, we found that 6 weeks after the beginning of treatment only patients treated with Fluoxetine exhibited a significant improvement in memory tasks performance. In contrast, patients who were treated with Desipramine showed no similar improvement, and there was a significant difference between the two groups 6 weeks after the beginning of treatment.

It is important to note that the improvement in memory performance in the Fluoxetine group did not result from the improvement in the level of depression, because both groups exhibited a similar improvement in the clinical symptoms of depression. The findings support previous evidence for a role of the serotoninergic system in memory performance. The results are in accordance with previous findings that tryptophan depletion, which reduces brain serotonin levels, produces selective memory impairments and, more specifically, suggest that serotoninergic deficiency contribute to depression-associated memory impairments. In conclusion, the results suggest that in cases in which memory impairment is a major symptom associated with the depression, the treatment of choice would be a serotoninergic specific drug. Furthermore, in cases in which, for various reasons, the treatment of choice is noradrenergic, it may be worthwhile to consider supplementary serotoninergic treatment, to improve memory deficits. Clearly, more extensive studies with larger samples will be required to validate this possibility, but similar results in previous findings strongly support our conclusions.

In addition, we examined only patients during the acute phase of depression. It is possible that improvement in memory with the noradrenergic drug develops more slowly. It remains to be tested whether this difference between treatments is transient or long lasting.

Nevertheless, even if the advantage of the serotoninergic treatment is confined to the first few weeks of treatment, it is worthwhile to take this into consideration. Memory improvement will no doubt contribute significantly to the well-being of these patients during the first, sensitive phase of the treatment.

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