Effects of Tamoxifen and Exemestane on Cognitive Functioning of Postmenopausal Patients With Breast Cancer: Results From the Neuropsychological Side Study of the Tamoxifen and Exemestane Adjuvant Multinational Trial

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ABSTRACT

Purpose
To evaluate the influence of adjuvant tamoxifen and exemestane on cognitive functioning in postmenopausal patients with breast cancer (BC).

Patients and Methods
Neuropsychological assessments were performed before the start (T1) and after 1 year of adjuvant endocrine treatment (T2) in Dutch postmenopausal patients with BC, who did not receive chemotherapy. Patients participated in the international Tamoxifen and Exemestane Adjuvant Multinational trial, a prospective randomized study investigating tamoxifen versus exemestane as adjuvant therapy for hormone-sensitive BC.

Results
Participants included 80 tamoxifen users (mean age, 68.7 years; range 51 to 84), 99 exemestane users (mean age, 68.3 years; range, 50 to 82), and 120 healthy controls (mean age, 66.2 years; range, 49 to 86). At T2, after adjustment for T1 performance, exemestane users did not perform statistically significantly worse than healthy controls on any cognitive domain. In contrast, tamoxifen users performed statistically significantly worse than healthy controls on verbal memory (P < .01; Cohen’s d = .43) and executive functioning (P = .01; Cohen’s d = .40), and statistically significantly worse than exemestane users on information processing speed (P = .02; Cohen’s d = .36). With respect to visual memory, working memory, verbal fluency, reaction speed, and motor speed, no significant differences between the three groups were found.

Conclusion
After 1 year of adjuvant therapy, tamoxifen use is associated with statistically significant lower functioning in verbal memory and executive functioning, whereas exemestane use is not associated with statistically significant lower cognitive functioning in postmenopausal patients with BC. Our results accentuate the need to include assessments of cognitive effects of adjuvant endocrine treatment in long-term safety studies.

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INTRODUCTION

Adjuvant endocrine therapy is widely prescribed for patients with hormone-sensitive breast cancer (BC) and contributes to an improved survival. Ongoing trials are exploring the optimal duration of adjuvant endocrine therapy, as well as the most effective choice and sequence of agents. Although generally well tolerated, endocrine treatments have adverse effects which are of clinical concern and predictive for nonadherence. The toxicity profiles are class and agent specific, and concern menopausal symptoms, effects on bone density, changes in lipid profile, increased risk of endometrial cancer, cardiovascular disease, and venous thrombosis.

Whether the various endocrine treatments affect cognitive functioning is largely unknown. Preclinical data indicate that estrogens exert neurotrophic and neuroprotective actions in the brain. Although the mechanisms of action of estrogens in the brain are not completely understood, evidence is growing that estrogens favor neuronal differentiation and survival by acting through estrogen receptors (ERs). As ERs are
Effects of Tamoxifen and Exemestane on Cognitive Functioning

present in the hippocampus and the frontal lobe, structures that are important for cognitive functioning, it is plausible that estrogens are involved in cognitive functioning.

From neuropsychological studies, partial support for the neuroprotective influence of estrogens can be derived. For example, estrogen deprivation after removal of the ovaries in premenopausal women was associated with decreased verbal memory performance, while estrogen replacement therapy (ERT) in this setting was associated with stable cognitive performance. In addition, a recent case-control study suggested that long-term estrogen deprivation due to premature menopause after ovariectomy increases the risk for dementia later in life.

Harmful effects of estrogens on the brain have also been suggested. In a randomized, placebo-controlled trial ERT increased the risk of dementia and stroke in women older than 65 years of age, suggesting that estrogens are only neuroprotective during a critical time period around menopause and have no, or even detrimental effects in elderly women. Furthermore, neuropsychological studies suggest that not all cognitive functions are equally influenced by estrogens, but that the influence mainly concerns aspects of memory, information processing speed, and executive functioning.

In view of the literature evoking an effect of estrogens on brain functioning, it is theoretically plausible that endocrine treatment for postmenopausal BC, aiming at estrogen deprivation, also might influence brain functioning and cognition. However, only few and predominantly small studies evaluated such effects. Generally, these studies provided indications for small detrimental effects of the selective estrogen receptor modulator (SERM) tamoxifen on cognition, but yielded inconclusive results with respect to the aromatase inhibitor (AI) anastrozole.

In this report we describe the results of a prospective study on the impact of tamoxifen and the AI exemestane on cognitive functioning in 179 Dutch postmenopausal patients with BC, participating in the randomized Tamoxifen and Exemestane Adjuvant Multinational (TEAM) trial. It was hypothesized that both tamoxifen and exemestane would detrimentally affect certain cognitive functions. We exploratory evaluated possibly distinctive effects on cognition of both agents. Furthermore, given the potential age-dependency of the effects of estrogen on cognitive functioning, we investigated the cognitive effects of tamoxifen and exemestane in younger (≤ 65 years) and older (> 65 years) patients separately.

PATIENTS AND METHODS

Study Population and Procedure

Eligible patients were Dutch postmenopausal women participating in the TEAM trial; an international, open label, randomized study comparing the efficacy and safety of 5 years of adjuvant exemestane (25 mg/d) with 2.5 to 3 years of tamoxifen (20 mg/d) followed by 2 to 2.5 years of exemestane.

Extended data on in- and exclusion criteria of the TEAM trial have been described elsewhere. In short, patients had histologically confirmed adenocarcinoma of the breast, positive estrogen and/or progesterone receptor status, and had undergone surgery with a curative intent. For this neuropsychological side study additional exclusion criteria included: adjuvant chemotherapy, not being fluent in the Dutch language, CNS disease or signs of dementia according to a dementia screening tool (7-minute screen). In order to take into account test-retest effects of neuropsychological tests, we also included a control group consisting of healthy female friends or relatives having approximately the same age as the participating TEAM patients. For this healthy control group, we aimed for a sample size of at least the sample size of the patient groups. Inclusion criteria for controls were: postmenopausal status, no history of CNS disease or malignant disease, fluent in the Dutch language and no signs of dementia according to the dementia screening tool. The neuropsychological study was approved by the central review board (Erasmus MC, Rotterdam) and the local medical ethic committees of all participating hospitals. All participants provided written informed consent.

Assessment

Initial neuropsychological assessments (T1) were performed after definitive breast surgery, and immediately before the start of adjuvant endocrine treatment. This point in time was chosen in order to minimize potential effects of other treatments on cognition in the interval between T1 and T2. Follow-up assessments were conducted after 1 year of endocrine treatment (T2). Healthy control women underwent the same assessments with a similar time interval of 1 year.

Cognitive Tests

A comprehensive test battery, existing of 18 test indices, was designed to assess a broad range of cognitive functions (Table 1). All tests were classified in one of eight cognitive domains. The Dutch Adult Reading Test was used to estimate premorbid verbal intelligence. Tests were selected for reliability, validity, sensitivity for effects of hormones, and suitability for older age groups.

Anxiety/Depression, Fatigue, and Menopausal Symptoms

Data on anxiety/depression, fatigue, and menopausal symptoms were included in the analyses because these symptoms might act as confounders in the analysis of cognitive performance and might be different at T1 and T2. For measuring symptoms of anxiety/depression, the 25-item Hopkins Symptom Checklist (HSCL) was used; and for fatigue, the three-item fatigue subscale of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC-QLQ-C30). Menopausal symptoms were assessed by the 18-item Endocrine Subscale of the Functional Assessment of Cancer Therapy-Breast questionnaire (FACT-B-ES). Participants rated all items on a 4-point (HSCL, EORTC-QLQ-C-30) or 5-point scale (FACT-B-ES). Results of self-reported cognitive functioning will be reported separately.

Statistical Analysis

SPSS for Windows version 15.0 (SPSS, Chicago, IL) was used for all analyses. Raw cognitive test scores were converted to standardized Z-scores based on the mean and standard deviation of the healthy control group. For T1, healthy control group data at T1 were used; for T2, healthy control group data at T2.

To decrease the number of outcome variables, the 18 Z-scores were combined into eight cognitive domain scores, expressed as the mean Z-score of tests that made up the particular cognitive domain. By definition, mean Z-scores and cognitive domain scores of the healthy control group were zero both at T1 and T2, and the T2 scores discounted for test-retest effects. Data from questionnaires were converted to scores according to standard scoring rules.

Changes from T1 to T2 and between groups were analyzed by using univariate analyses of covariance (ANCOVA) in which, for each of eight cognitive domains, the baseline score was the covariate. We chose for this method for its demonstrated power and its understanding that both T1 scores and these variables served as predictors. For T1, T2, and T2, the T2, and T2 scores discounted for test-retest effects. Data from questionnaires were converted to scores according to standard scoring rules.

Because anxiety/depression, fatigue, and menopausal symptom ratings might act as confounders, the ANCOVA procedure was repeated on the understanding that both T1 scores and these variables served as predictors.

To investigate possible age differences with respect to the cognitive effects of tamoxifen and exemestane, we repeated the ANCOVA procedure, adjusted for T1 scores in two subgroups separately: women age ≤ 65 years and women older than 65 years. Effect sizes were expressed by Cohen’s d. For all analyses, a
two-sided P value lower than .05 was required for significance. P values for the
direct comparison between tamoxifen and exemestane should be interpreted
as exploratory in nature, as no hypothesis could be formulated on the basis of
the literature for differences between the two therapies in effect on cognition.
The sample-sizes of the two patient groups (80 and 99 persons, respectively)
provided 76% power (type I error rate of 5% and two-sided tests) to detect a
between-group difference of 0.4 standard deviation. This was a lower bound
that could be regarded as adherent.4

### Patients and Controls

Ninety-two patients allocated to tamoxifen, 114 patients allocated to exemestane, and 124 healthy controls underwent cognitive assessments at T1. Data at T2 were provided by 90% of the participants (80 tamoxifen users, 99 exemestane users, and 120 healthy controls). More patients than healthy controls were lost to follow-up (12.7% v 3.2%, respectively), without a statistically significant difference between tamoxifen (13.0%) and exemestane (12.4%) users (Fig 1). The participants who were lost to follow-up were significantly older (72.3 v 67.6 years; P ≤ .01) and had a lower intelligence quotient (93.9 v 102.7; P = .02) than participants who completed both assessments.

After controlling for age and IQ, there were no statistically significant differences in cognitive performance (at T1) between participants who were lost to follow-up and participants who completed both assessments. Furthermore, both groups did not differ significantly with respect to anxiety/depression and fatigue ratings (at T1).

Between T1 and T2, the endocrine therapy was changed by 12 patients (6.7%). Six tamoxifen users changed to exemestane, and six exemestane users changed to either tamoxifen (n = 4), anastrozole (n = 1), or letrozole (n = 1). The predominant reason for changing endocrine therapy was bothering adverse effects. Self-reported adherence to the study medication was not statistically significant different between tamoxifen and exemestane users (Table 2). In view of the literature that considers taking medication for more than 80% of the days as an acceptable adherence, all patients could be regarded as adherent.4

### Cognitive Test Results: Baseline Assessment (T1)

The baseline cognitive domain scores of patients are included in Table 3 for illustrative purposes, and have been described and discussed elsewhere.39 In summary, the patient group, as a whole, had after adjustment for covariates such as age, IQ, ongoing treatment for hypertension or diabetes mellitus, and anxiety/depression, a significantly worse overall cognitive functioning compared to healthy controls (P = .03). Considering the eight cognitive domains separately, the only significant lower performance in the patient group was in the verbal fluency domain (P < .01).

### Follow-Up Assessment (T2)

Raw test scores of T1 and T2 are presented in Appendix Table A1 (online only). The results of the intent-to-treat analyses are presented in Table 3. After 1 year of adjuvant therapy and adjusting for T1 scores, exemestane users did not perform significantly worse than healthy controls on any of the eight cognitive domains. In contrast, tamoxifen users performed worse than healthy controls on verbal memory (P = .01; Cohen’s d = .43) and executive functioning (P = .01; Cohen’s d = .40). Furthermore, compared to exemestane users, tamoxifen users scored lower on information processing speed (P = .02; Cohen’s d = .36). For visual memory, reaction speed, motor speed, working memory, and verbal fluency no significant differences between the groups were found.

The as-treated analysis showed significantly worse functioning in tamoxifen users compared to healthy controls on the same cognitive

<table>
<thead>
<tr>
<th>Cognitive Domain</th>
<th>Cognitive Tests</th>
<th>Outcome Variable</th>
<th>Score Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verbal memory</td>
<td>Rey auditory verbal learning test&lt;sup&gt;34&lt;/sup&gt; (Dutch shortened version)</td>
<td>1. Total of three trials</td>
<td>0-45</td>
</tr>
<tr>
<td></td>
<td>Visual association test&lt;sup&gt;26&lt;/sup&gt;</td>
<td>2. Total for long delay trial</td>
<td>0-15</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. Total of two trials</td>
<td>0-24</td>
</tr>
<tr>
<td>Visual memory</td>
<td>Wechsler memory scale revised-visual memory subtest&lt;sup&gt;26&lt;/sup&gt;</td>
<td>4. Points awarded according to scoring criteria</td>
<td>0-41</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5. Points awarded according to scoring criteria</td>
<td>0-41</td>
</tr>
<tr>
<td>Information processing speed</td>
<td>Stroop card 1&lt;sup&gt;27&lt;/sup&gt;</td>
<td>6. Seconds to complete</td>
<td>0+</td>
</tr>
<tr>
<td></td>
<td>Stroop card 2&lt;sup&gt;27&lt;/sup&gt;</td>
<td>7. Seconds to complete</td>
<td>0+</td>
</tr>
<tr>
<td></td>
<td>Trailmaking A&lt;sup&gt;28&lt;/sup&gt;</td>
<td>8. Seconds to complete</td>
<td>0+</td>
</tr>
<tr>
<td>Executive functioning</td>
<td>Stroop card 3&lt;sup&gt;27&lt;/sup&gt;</td>
<td>9. Seconds to complete</td>
<td>0+</td>
</tr>
<tr>
<td></td>
<td>Trailmaking B&lt;sup&gt;28&lt;/sup&gt;</td>
<td>10. Seconds to complete</td>
<td>0+</td>
</tr>
<tr>
<td>Manual motor speed</td>
<td>Fepsy finger tapping&lt;sup&gt;29&lt;/sup&gt;</td>
<td>11. Mean score of 5 trials of 10 sec</td>
<td>0+</td>
</tr>
<tr>
<td></td>
<td>Dominant hand</td>
<td>12. Mean score of 5 trials of 10 sec</td>
<td>0+</td>
</tr>
<tr>
<td></td>
<td>Nondominant hand</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verbal fluency</td>
<td>Letter fluency (D, A, and T)&lt;sup&gt;30&lt;/sup&gt;</td>
<td>13. Total score of 3 letters/1 min each</td>
<td>0+</td>
</tr>
<tr>
<td></td>
<td>Category fluency (animals/professions)&lt;sup&gt;31&lt;/sup&gt;</td>
<td>14. Total score animals/1 min</td>
<td>0+</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15. Total score professions/1 min</td>
<td>0+</td>
</tr>
<tr>
<td>Reaction speed</td>
<td>Fepsy reaction times&lt;sup&gt;29&lt;/sup&gt;</td>
<td>16. Mean msec/50 trials</td>
<td>0+</td>
</tr>
<tr>
<td></td>
<td>Dominant hand</td>
<td>17. Mean msec/50 trials</td>
<td>0+</td>
</tr>
<tr>
<td></td>
<td>Nondominant hand</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Working memory</td>
<td>WAIS III letter-number sequencing&lt;sup&gt;32&lt;/sup&gt;</td>
<td>18. Total correct trials</td>
<td>0-21</td>
</tr>
</tbody>
</table>

Abbreviation: WAIS, Wechsler Adult Intelligence Scale.
domains, with slightly larger effect-sizes (verbal memory: \( P < .01; \) Cohen’s \( d = .46 \); executive functioning: \( P < .01; \) Cohen’s \( d = .44 \)), and worse cognitive functioning in tamoxifen users compared to exemestane users not only on information processing speed \( (P < .01; \) Cohen’s \( d = .47 \)), but also on executive functioning \( (P = .03; \) Cohen’s \( d = .34 \); data not shown). Additional adjustment for anxiety/depression, fatigue, and menopausal symptom scores did not change these results.

### Table 2. Sociodemographics of the Tamoxifen Users, the Exemestane Users, and the Healthy Controls

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Tamoxifen Users (n = 80)</th>
<th>Exemestane Users (n = 99)</th>
<th>Healthy Controls (n = 120)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, years</td>
<td>68.7</td>
<td>68.3</td>
<td>66.2</td>
<td>.031</td>
</tr>
<tr>
<td>SD</td>
<td>7.6</td>
<td>6.8</td>
<td>7.9</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>51-84</td>
<td>50-82</td>
<td>49-88</td>
<td>.07</td>
</tr>
<tr>
<td>Mean IQ</td>
<td>100.7</td>
<td>100.5</td>
<td>105.8</td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>20.0</td>
<td>18.6</td>
<td>19.0</td>
<td></td>
</tr>
<tr>
<td>Mean T1-T2 interval in months</td>
<td>12.4</td>
<td>12.2</td>
<td>12.3</td>
<td>.25</td>
</tr>
<tr>
<td>SD</td>
<td>1.2</td>
<td>1.4</td>
<td>0.6</td>
<td></td>
</tr>
<tr>
<td>Underwent radiotherapy</td>
<td>47 (58.8)</td>
<td>68 (68.7)</td>
<td>—</td>
<td>.16</td>
</tr>
<tr>
<td>Ever-use of hormone replacement therapy</td>
<td>14 (17.5)</td>
<td>20 (20.2)</td>
<td>23‡ (19.2)</td>
<td>.79</td>
</tr>
<tr>
<td>Self-reported adherence$\dagger$</td>
<td>100%</td>
<td>70%</td>
<td>74%</td>
<td>.28</td>
</tr>
<tr>
<td>99%-100%</td>
<td>56%</td>
<td>19%</td>
<td>21%</td>
<td></td>
</tr>
<tr>
<td>95%-99%</td>
<td>5%</td>
<td>6%</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>83%-94%</td>
<td>4%</td>
<td>5%</td>
<td>1%</td>
<td></td>
</tr>
<tr>
<td>&lt; 83%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: SD, standard deviation; IQ, intelligence quotient.

*\( P \) values for analysis of variance (for age, IQ and T1-T2 interval) and \( \chi^2 \) test (for self-reported adherence).

$\dagger$Post hoc tests: tamoxifen versus controls: \( P = .03; \) exemestane versus controls: \( P = .04; \) tamoxifen versus exemestane: \( P = .71 \).

\( n = 119 \).

$\dagger$Self-reported therapy adherence was assessed by two questions: (1) have you (temporarily) stopped taking the study medication, and if so, what was/are the start and the end date(s) of these period(s)? and (2) how often (each week, month, or in the whole interval between T1 and T2) have you forgotten to take the study medication? Self-reported adherence to the study medication was calculated as the proportion of the days that the patients reported taking their tablets over the period between T1 and T2.
Exploratory intent-to-treat analyses showed that in the younger age group (≤65 years) tamoxifen users (n = 30) performed significantly worse than healthy controls (n = 60) on executive functioning (P = .01; Cohen’s d = .54), while in the older age group (>65 years) tamoxifen users (n = 50) performed worse than healthy controls (n = 60) on verbal memory (P < .01; Cohen’s d = .58), and information processing speed (P = .03; Cohen’s d = .44). In addition, only in the older age group tamoxifen users performed worse than exemestane users (n = 64) on information processing speed (P = .01; Cohen’s d = .54; data not shown). For all significant differences, the effect sizes were small-to-medium.

**DISCUSSION**

This prospective study evaluated cognitive functioning during adjuvant therapy with tamoxifen or exemestane in postmenopausal patients with hormone-sensitive BC. We observed that 1 year of exemestane treatment did not result in significantly negative effects on cognitive functioning. In contrast, 1 year of tamoxifen treatment was associated with worse performance regarding verbal memory and executive functioning. For information processing speed, we observed a significant difference between tamoxifen and exemestane users due to an increased performance in the exemestane group and a decreased performance in the tamoxifen group. The effect sizes of all significant differences were small-to-medium and were higher in the as treated analyses compared with the intent-to-treat analyses, confirming the robustness of the effects. Adjustment for menopausal symptoms, anxiety/depression ratings and fatigue did not influence the results.

The observed differences between tamoxifen and exemestane with respect to cognitive effects might imply different mechanisms of action of the drugs in the brain. Tamoxifen exerts tissue-dependent estrogenic and antiestrogenic actions after binding to the estrogen receptor (ER), but whether it has estrogenic or antiestrogenic qualities on brain tissue is not known. Our results support the results of earlier studies performed in postmenopausal patients with BC, which suggested a detrimental effect of tamoxifen on cognitive functioning. Also, the cognitive domains that were vulnerable for the effects of tamoxifen in our study (verbal memory, information processing speed, and executive functioning) overlap with those found affected in earlier studies and indeed are associated with brain structures known to be rich of ERs (ie, hippocampus and frontal lobe).

The AI exemestane causes nearly complete estrogen deprivation by blocking estrogen biosynthesis. Our results suggest that in postmenopausal BC patients such estrogen deprivation does not result in measurable cognitive effects. As our study is the first to evaluate the cognitive effects of exemestane our data can only be compared with results obtained from studies with the AI anastrozole. For anastrozole, however, data about its impact on cognition are conflicting. One cross-sectional study suggested detrimental effects on verbal memory and information processing speed in patients with BC using anastrozole and/or tamoxifen (n = 94) compared with healthy controls (n = 35). Another cross-sectional study in patients with BC suggested detriments on verbal and visual memory in exemestane users (n = 15) compared to tamoxifen users (n = 16). A prospective study suggested that patients with BC taking anastrozole (n = 14) were more likely to show cognitive decline after 5 to 6 months of use than healthy controls (n = 28). A prospective prevention study in postmenopausal women being at increased risk for BC reported no cognitive impairment in women taking anastrozole (n = 79) compared to placebo (n = 74) after 6 months and 2 years of therapy.

An explanation for potentially different effects on cognition between anastrozole and exemestane might be sought in the different pharmacologic properties of both agents. Exemestane and its metabolites have mild androgenic properties, contrary to anastrozole. Because androgens might be beneficial for performance in several
cognitive domains, detrimental effects on cognitive function of estrogen deprivation might be limited, or even prevented by the androgenic properties of exemestane. As the reported data for anastrozole are not congruent, it is important to obtain further data on this issue in studies in patients with BC comparing different AIs directly with respect to their impact on cognition.

Our exploratory analyses of the younger (≤ 65 years) and older (> 65 years) women separately showed larger effects, comprising more cognitive domains, in the older patients with BC, suggesting a possible age-dependency of the effects of tamoxifen on cognition.

Despite the consistent finding of detrimental cognitive effects of tamoxifen in studies conducted until now, including this study, the mechanisms of action of tamoxifen on the brain are insufficiently known. Potential mechanisms to evaluate in future research should include the effects of tamoxifen on the two ERs, ERα and ERβ, which are also differentially expressed in various parts of the brain, this distinction might be relevant for tamoxifen as well. In addition, tamoxifen may act as an antagonist and as an agonist of ERs, or via mechanisms that are independent of genomic actions. Finally, more research is needed to clarify the role of age with respect to the effects of tamoxifen on cognition.

The strengths of this study include the relatively large sample size compared to other neuropsychological studies in patients with cancer, and the randomized allocation to either tamoxifen or exemestane resulting in very similar patient groups. Inclusion of baseline cognitive assessments made it possible to adjust for pre-existing cognitive differences between the groups. Furthermore, because none of the patients received chemotherapy, the results are not confounded by potential cognitive alterations induced by chemotherapy.

A limitation of our study is the relatively short observation period, covering 1 year of adjuvant endocrine treatment, while the recommended therapy duration at this moment is 5 years with the consideration of extended endocrine therapy in case of high-risk BC. Another point of concern might be our finding of lower cognitive functioning of patients compared with healthy controls at T1. Cognitive problems before the start of systemic treatment are described in earlier studies. Although we have attempted to take the cognitive differences at T1 into account by means of a statistical adjustment, there is no guarantee that such a statistical adjustment is sufficient to manage the differences completely.

In conclusion, our results suggest that compared with healthy controls, exemestane did not result in the same cognitive decline over time that was seen in patients with BC taking tamoxifen. Although the impact of the observed cognitive effects on daily life of patients has yet to be determined, intact cognitive functioning is known to be an important precondition for independent living and well-being. In view of the already widespread and potentially even longer use of endocrine treatment for patients with BC in the future, and the fact that the choice for a specific endocrine agent and therapy sequence among others is based on the safety profile, our results justify continuing research into the cognitive effects of endocrine therapy and stress the need for more detailed knowledge about differential effects of these therapies on neuropsychological functioning.

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO’s conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Employment or Leadership Position: None Consultant or Advisory Role: None Stock Ownership: None Honoraria: None Research Funding: Christina M. Schilder, Pfizer Expert Testimony: None Other Remuneration: None

CONCLUSION

Tamoxifen and exemestane are effective endocrine therapies on neuropsychological functioning. To this end, the study showed detrimental cognitive effects of tamoxifen on cognition, while exemestane did not result in such effects. The differences at T1 into account by means of a statistical adjustment, there is no guarantee that such a statistical adjustment is sufficient to manage the differences completely.

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