Memory and Spatial Cognition in Breast Cancer Patients Undergoing Adjuvant Endocrine Therapy

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Keywords

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Summary

Introduction: It is generally accepted that estrogens play a protective role in cognitive function. Therefore, it can be expected that subtotal estrogen deprivation following aromatase inhibition will alter cognitive performance.

Methods: In a cross-sectional study we investigated 80 postmenopausal women with breast cancer. Memory and spatial cognition were compared across 4 treatment groups: tamoxifen only (TAM, $n = 22$), aromatase inhibitor only (AI, $n = 22$), TAM followed by AI ('SWITCH group', $n = 15$), and patients with local therapy (LT) only (surgery and radiation, $n = 21$). Duration of the 2 endocrine monotherapy arms prior to the assessment ranged from 1 to 3 years. The 'SWITCH group' received 2–3 years TAM followed by at least 1 year and at most 3 years of AI. Memory and spatial cognition were investigated as planned comparisons. Investigations of processing speed, attention, executive function, visuomotor construction and self-perception of memory were exploratory. **Results:** With regard to general memory, AI patients performed significantly worse than the LT group ($p = 0.013$). Significant differences in verbal memory did not remain significant after p -value correction for multiple testing. We found no significant differences concerning spatial cognition between the groups. **Conclusion:** AI treatment alone significantly impairs general memory compared to the LT group.

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Introduction

Adjuvant endocrine therapy substantially reduces recurrence rates and improves overall survival in women with hormone receptor-positive early breast cancer. However, in the clinical routine, numerous patients with breast cancer complain of memory and concentration problems.

Estrogen receptors have been documented in various parts of the brain [1]. Estrogens play an important role in the regulation of growth and differentiation of axons, dendrites and synapses [2], support long-term potentiation in the hippocampus [3, 4] and influence serotonergic, noradrenergic, dopaminergic and cholinergic activities [5]. The glutamate system, which is involved in learning and memory, also is regulated by estrogens [6]. Estrogens also act as antioxidants [4, 7]. Neuroprotective function has been demonstrated in lab animal studies, as the expression of aromatase is increased in the brain after injury [8]. Estrogens are also discussed as a target for therapeutic approaches in neurodegenerative and mental diseases [9].

A number of studies in animals and in humans show influences of sex hormones, especially estrogens, in memory and spatial cognition caused by changing of hormone levels during life span, menstrual cycle, pregnancy, menopause, hormone therapy or ovariectomy [10–14]. Therefore, in our study we focused mainly on these 2 domains.

The mechanism for endocrine therapy in patients with hormone receptor-positive breast cancer may be described as follows: tamoxifen (TAM) as an estrogen receptor (ER) modulator binds to ERs in competition with estradiol; thus, transcription is altered. Tumor cells are arrested in a non-proliferative state but, depending on the molecular profile of its target tissue, TAM may also act similarly to estradiol as an agonist [15]. AIs, however, work by inhibiting the activity of the aromatase, which is needed to convert androgens to estrogens [16]. Patients on AI are nearly completely deprived of estrogens.

Fig. 1. Consort diagram.

Against the background of the neurophysiological findings concerning protective effects of estrogens, increasing interest has developed with regard to the cognitive effects of endocrine therapy – especially with respect to the almost complete estrogen depletion caused by AIs. Preceding study results concerning profile, extent and duration of cognitive impairments in patients undergoing endocrine therapy are inconsistent [17]. In contrast to previous studies we assessed cognitive abilities in postmenopausal breast cancer patients undergoing differentiated endocrine protocols. The exclusion of premenopausal women and those who were treated with chemotherapy should avoid the impact of some known confounders. Since it is known that 17β -estradiol regulates hippocampal plasticity [9] as well as memory and spatial cognition [18], we assessed these domains. We wanted to confirm the hypothesis that a nearly complete estrogen deprivation by AI would affect memory and spatial cognition of these patients.

Material and Methods

Participants

A cross-sectional study was used to investigate 92 postmenopausal women with breast cancer recruited from 2 breast cancer centers. Patients were excluded for premenopausal status, organic brain diseases (even before cancer onset), a history of mental disorders (e.g. stroke, major depression, etc.), medication affecting the central nervous system (CNS), previous chemotherapy treatment and treatment with gonadotropin-releasing hormone (GnRH) agonists (ovarian function suppression), below average IQ (IQ score less than 85), alcohol or drug abuse (present or past), any metastases, or age above 80 years. The age limit was defined to exclude age-related cognitive dysfunctions like dementia. To compare cognitive task performance we constituted 4 treatment groups in the context of a quasi-experimental design: We investigated patients undergoing therapy with TAM only (n = 22), AI only (n = 22), patients who 'switched' from TAM to an AI ('SWITCH group', n = 15) and breast cancer patients who had received only local therapy (LT) such as surgery or radiation (n = 21) (see consort diagram, fig. 1).

Fig. 2. Spatial cognition tests.

Assessment

Demographic data were obtained through standardized interviews and clinical data were gleaned from the electronic health record. Compliance with endocrine therapy was evaluated by interview. Only patients who reported a daily intake of the medication were included. Drug levels were not assessed.

Memory and spatial cognition (mental rotation, navigation: Virtual Pointing Task, Object in Location Test) were investigated as planned comparisons. Investigations of processing speed, attention, executive function, visuoconstruction and self-perception of memory were exploratory. We also assessed mood and premorbid intelligence to check potential confounding variables and to parallelize the groups. On an exploratory basis we were also interested in correlation between self-perception of memory and objective measures as well as self-perception, anxiety and depression.

As background measures, we used the following psychological tests: for self-perception of memory: the Memory Assessment Clinic Self-Report Scale [19]; for mood: the Mental State Scale [20] and the Hospital Anxiety and Depression Scale-D [21]; and for premorbid intelligence: the Multiple Choice Vocabulary Test [22].

Assessment of Cognitive Performance

Memory, spatial cognition, processing speed and attention were assessed using a battery of neuropsychological tests. The assessment took about 2 h. Following instruments were used: for visual attention and task switching (processing speed, executive function): Trail Making-Test A and B [23]; for memory and visuoconstruction: Wechsler Memory Scale-R Part 1 [24], and Rey-Osterrieth Complex Figure Test (copy trial and delayed recall) [25]; and for spatial cognition: Mental Rotation Test [26], Virtual Pointing Task [27], and Object in Location Test [27, 28], see figure 2. All tests used to assess spatial cognition were performed on a personal computer (PC).

For the Mental Rotation Test [26], patients were required to judge whether 2 rotated abstract block figures were congruent or different. Each stimulus was

Table 1. Characteristics of the patient sample

Parameter	LT, n = 21	TAM, n = 22	AI, n = 22	SWITCH, n = 15	Test statistic	p	Significant post hoc comparisons
Age, years, mean (SD)	64.9 (7.3)	62.6(8.7)	68.3 (5.1)	65.3 (7.9)	F=2.1	0.10	
Menopause, years, mean (SD)	13.4 (7.8)	12.2 (10)	18.1 (5.9)	15.6 (7.8)	F=2.24	0.09	
Education, n (%) ^a							
Secondary modern school	9 (42.8)	10 (45.5)	13 (59.1)	9 (60.0)	$\chi^2=2.97$	0.81	
Intermediate school	6 (28.6)	8 (36.4)	6 (27.3)	4 (26.7)			
Grammar school	6 (28.6)	4 (18.2)	3 (13.6)	2 (13.3)			
Professional level, n (%)							
Untrained	1 (4.8)	1 (4.5)	1 (4.5)	2 (13.3)	$\chi^2=9.36$	0.4	
Apprenticeship	10 (47.6)	12 (54.5)	16 (72.7)	9 (60.0)			
College of higher education	8 (38.1)	5 (22.7)	4 (18.2)	1 (6.7)			
University	2 (9.5)	4 (18.2)	1 (4.5)	3 (20.0)			
Employment, n (%)							
Fulltime	4 (19.0)	7 (31.8)	0	1 (6.7)	$\chi^2=22.15$	0.06	
Parttime	1 (4.8)	1 (4.5)	0	0			
Not employed	16 (76.2)	14 (63.6)	22 (100)	14 (93.3)			
MSS t value, mean (SD)	49.0 (8.8)	52.8 (8.8)	48.5 (10.5)	54.9 (15.8)	F=1.47	0.23	
Anxiety t value, mean (SD)	53.5 (10.3)	55.0 (11.6)	50.2 (11.9)	56.3 (14.2)	F=0.98	0.41	
Depression t value, mean (SD)	55.6 (10.1)	57.8(8.8)	57.0 (11.7)	58.5 (15.7)	F=0.23	0.87	
Intelligence, IQ, mean (SD)	115.4 (14.7)	112.3 (15.0)	112.6 (13.0)	114.6 (17.2)	F=0.21	0.88	
Family status, n (%)							
Married	12 (57.1)	19 (86.4)	16 (72.7)	10 (66.7)	$\chi^2=7.55$	0.58	
Separated	1 (4.8)	0	0	1 (6.7)			
Divorced	3 (14.3)	0	2 (9.1)	1 (6.7)			
Widowed	5 (23.8)	3 (13.6)	4 (18.2)	3 (20.0)			
HRT before BC, %	28.6	27.3	18.2	73.3	$\chi^2=13.56$	0.004**	SWITCH vs. all
Duration of treatment, months, mean (SD) ^b		21.5 (8.6)	24.1 (9)		t=-1.2	0.23	
Time since diagnosis, months, mean (SD) ^b	< 1	23.2 (9)	26.9 (10.1)	> 36–60	t=-1.28	0.21	
Duration of AI treatment, months, mean (SD) ^c			24.1 (9)	22.3 (11)	t= 0.53	0.6	

^aGerman: secondary modern school = Hauptschule, intermediate school = Sekundarschule, grammar school = Gymnasium.

^bOnly the monotherapy groups were compared.

^cOnly AI treatment times were compared.

MSS = Mental State Scale, LT = local therapy, TAM = tamoxifen, AI = aromatase inhibitor, SWITCH = TAM→AI, BC = breast cancer, SD = standard deviation, HRT = hormone replacement therapy, est. = estimated.

**Significant p < 0.01.

a 2-dimensional image of a 3-dimensional object and was then shown at different orientations rotated around the vertical axis. Patients had to rotate the figure in their mind to compare 4 response-choice figures to the target figure. They had to complete 2 runs within a time limit (10 min every run, 2 min break between the runs). We used 2 methods of scoring: 'lenient' in which every right answer counted; and 'strict' in which answers were only valid if both figures are identified correctly.

For the Virtual Pointing Task (navigation without landmarks) [27], patients 'walked' through a virtual park. They were instructed to remember the position of the starting point. Finally, they were requested to position the compass to the 'home' direction. This test was administered at 2 different speeds and 3 different levels of difficulty (a total of 6 runs).

For the Object in Location Test (navigation with landmarks adapted from an animal trial: the Morris Water Maze Experiment [28], the task involved the exploration of a virtual island. Patients were required to find a treasure chest. Landmarks on the island could be used as assistance. After this, they started again from different positions on the island. The position of the chest did not change.

Statistical Analysis

The data analysis was performed with the Statistical Package for the Social Sciences (SPSS), version 17.0. Performance differences between the groups were compared using ANOVA (analysis of variance). For parameters not following the normal distribution, the Kruskal-Wallis test as a non-parametric method was used. If a significant effect was detected by ANOVA, multiple comparison tests (post hoc tests, e.g. Bonferroni test) were used. In a case of statistically significant differences of the means, the effect size (Cohen's d) was calculated. In addition, we used ANCOVA (analysis of covariance) to control age as a potential confounder (age as independent variable (covariate), memory as dependent variable, and the 4 treatment groups as fixed factors). The level of significance was established at 0.05, 2-tailed. Group differences of nominal data were calculated by the Chi² test. Because of the multiple comparisons in our study we used the Benjamini-Hochberg correction [29] to reduce the number of false-positives results with a critical value for the false discovery rate of 0.2. The Pearson product-moment correlation coefficient was calculated to assess the correlation of mood (values of anxiety, depression and mental state scale), self-reported cognitive func-

Table 2. Self-perception of memory (exploratory)

	LT, n = 21	TAM, n = 22	AI, n = 22	SWITCH, n = 15	Test statistic	(p)	Significant post hoc comparisons
Ability scale							
Personal long-term memory, mean (SD) ^a	3.7 (0.5)	3.6 (0.6)	3.5 (0.47)	3.6(0.7)	F = 0.5	(0.68)	
Memory of numbers, mean (SD)	3.1 (0.9)	3.2 (0.7)	3.4 (0.6)	3.3 (0.6)	F = 0.9	(0.44)	
Memory for daily tasks, mean (SD)	3.9 (0.6)	3.4 (0.6)	3.6 (0.5)	3.9 (0.6)	F = 3.7	(0.016*)	LT better than TAM
Semantic memory/word recall, mean (SD)	3.3 (0.6)	3.2 (0.6)	3.4 (0.6)	3.4 (0.6)	F = 0.45	(0.72)	
Topographic memory, mean (SD)	3.6 (0.6)	3.4 (0.8)	3.4 (0.6)	3.6 (0.4)	F = 0.8	(0.49)	
Frequency scale							
Attention/concentration, mean (SD) ^a	3.8 (0.5)	3.8 (0.7)	4.1 (0.5)	3.7 (0.7)	F = 0.11	(0.49)	
Semantic memory for words and facts, rank ^b	46.7	34.3	43.9	35.7	$\chi^2 = 4.3$	(0.23)	
General forgetfulness, rank ^b	47.7	41.9	51.6	12.17	$\chi^2 = 31.1$	(0.000**)	all better than SWITCH

^aMean of the 5-step rating scale: low values indicate the self-perception of high memory deficits.

^bNo normal distribution.

LT = local therapy, TAM = tamoxifen, AI = aromatase inhibitor, SWITCH = TAM→AI, SD = standard deviation.

*Significance $p < 0.05$, **significance $p < 0.01$.

tion (8 subscales) and test data (general memory, verbal memory and visual memory) of the sample as whole (all groups), assuming the data were normally distributed. Otherwise, the Spearman's rank correlation coefficient was used.

Results

The groups did not differ significantly with regard to demographic characteristics such as age, time since menopause, education, professional level, employment, mental state, anxiety, depression, intelligence and family status. Significantly more patients of the 'SWITCH group' had previously received hormone therapy (HT) for postmenopausal symptoms before diagnosis of breast cancer compared to all other groups ($p = 0.004$) (table 1). However, in most cases, HT was discontinued months to years prior to breast cancer diagnosis and the duration was highly heterogeneous (range 3–180 months). The 2 monotherapy groups (TAM and AI) did not show significant differences concerning the duration of HT. The same applied to time since diagnosis and duration of AI therapy in the groups AI and 'SWITCH group' (table 1).

Overall, the AI group showed more impaired abilities concerning verbal and general memory than the control group. However, after correction for multiple tests using the Benjamini-Hochberg method, only the value concerning general memory remained significant. Furthermore, we noticed some interesting results with regard to executive function, visuoconstruction and self-perception.

Self-Perception of Memory (Exploratory)

Most patients perceived their own memory performance as average. Self-perception of memory correlated negatively with anxiety and depression but not with the objective test data. Taking into account the fact that we have many correlation data, the results should be interpreted with caution. In terms of memory self-assessment, appreciable differences between the groups were found in these 2 domains. The 'SWITCH group' perceived a lower mean concerning forgetfulness than all the other groups. Lower values indicate the self-perception of higher memory deficits. The LT group had a better self-perception concerning their memory of daily tasks on the ability scale compared to the TAM group (table 2).

Memory (Planned Comparisons)

Women who solely received AI without any TAM treatment in the past showed a significant impairment of general memory in comparison to the LT group ($p = 0.013$, $d = 1.15$ large effect). Concerning verbal memory and visuoconstruction, the AI group performed worse than any other group ($p = 0.037$, respectively) (see table 3). Adjusting for multiple comparisons, the differences did not remain significant. It is remarkable that many of the patients investigated showed below average memory performances compared with normative data of matched healthy women (scores less than 85 are below average). This applied particularly to the AI group. AI patients showed values below average for general memory 36.4%, verbal memory 54.5% and attention 31.8%.

Table 3. Results for memory, visuoconstruction, attention and executive functioning

Parameter	LT n = 21	TAM n = 22	AI n = 22	SWITCH n = 15	Test statistic	p	Significant post hoc comparisons	Effect size
Memory, mean (SD) ^a								Cohens d
WMS-R indices	105.3	99.5	89.2	101.5	F=3.8		LT better	1.15 (CI
General Memory	(14.5)	(17.5)	(13.4)	(20.3)		0.013*	than AI	0.51–1.79)
WMS-R indices	101.1	95	84.3	92.3	F=3	0.037 ^d	LT better	0.97 (CI
Verbal memory	(16.7)	(19.4)	(18)	(21.5)			than AI	0.33–1.6)
WMS-R indices	108.9	105.4	100.4	108.5	F=2			
Visual Memory	(10.9)	(14.4)	(11.7)	(13.9)		0.126		
ROCF (delay) pt	17.0	17.9	14.5	13.9	F=1.7	0.2		
Visual Memory	(6.4)	(7.6)	(6.3)	(4.2)				
Visuoconstruction ^b								
ROCF (copy) pt. rank ^c	45.3	43.4	28.6	47.0	$\chi^2=8.5$	(0.037)	(all better than AI)	nd
Attention ^b								
WMS-R indices	90.1	98.5	88.7	99.9	F=2.77	(0.047)	(TAM better than AI SWITCH better than AI)	nd
Attention	(17.5)	(16.3)	(14)	(10.3)				
TMT A	39.1	33.9	41.6	35.5	F=1.97	(0.13)		
Visual attention	(10.4)	(10.4)	(14.5)	(8.7)				
Executive functioning ^b								
TMT B	90.1	98.5	88.7	99.9	F=2.77	(0.59)		
Task switching	(17.5)	(16.3)	(14)	(10.3)				

^aPlanned comparisons.

^bExploratory.

^cNo normal distribution, thus ANOVA not possible, mean only for information.

^dDid not remain significant after correction by false discover rate.

LT = local therapy group, TAM = tamoxifen, AI = aromatase inhibitor, SWITCH: TAM→AI, WSM-R = Wechsler Memory Scale revised, ROCF = Rey-Osterrieth Complex Figure Test, TMT = Trail Making Test, CI = confidence interval, SD = standard deviation, pt = points, Cohens d = effect size, nd = not done.

*p < 0.05.

Differences of age between the groups were not significant. Furthermore, compared scores were already age-adjusted indices. In addition, an ANCOVA was performed with the 4 treatment conditions as between-groups factor and age as the covariate. We did not find any effects of age with regard to memory (general memory: p = 0.58, verbal memory: p = 0.29, visual memory: p = 0.92). Group differences with regard to general memory remained significant (p = 0.026).

Spatial Cognition (Planned Comparisons)

No significant differences were seen with respect to navigation and mental rotation. The majority of participants showed low performances on this test. For the 3 learning trials and the test run of the Object in Location Task (navigation with landmarks), no significant mean differences in terms of time required, length of path, average deviation angle (average heading error) and success (treasure chest found) were detected. With regard to the Virtual Pointing Task (navigation without landmarks), we did not find any significant results when the results of all runs were averaged (table 4). An ANCOVA was performed with the 4 treatment conditions as

the between-group factor and age as the covariate. We did not find significant effects of age on spatial cognition (Mental Rotation Test: strong p = 0.34, mild p = 0.68, Virtual Pointing Task: estimation error p = 0.68, orientation time p = 0.51, Object in Location Task: average heading error p = 0.46).

Attention, Processing Speed and Visuoconstruction (Exploratory)

The AI group performed worse than the TAM and the 'SWITCH' groups concerning attention (table 3). AI patients performed worse than the other groups concerning visuoconstruction. These results should be analyzed in more detail in further studies.

Discussion

The results of our study suggest that women who are completely estrogen deprived without any TAM treatment in the past achieved a significant lower mean in general memory compared to the control group. Considering the potentially protective effects of estro-

Table 4. Results for spatial cognition

	LT n = 21	TAM n = 22	AI n = 22	SWITCH n = 15	Test statistic	p
Mental rotation test, mean (SD)						
Total strict (max 24 pt)	6.1 (3.8)	7.1 (3.2)	6.4 (2.1)	6.8 (4.4)	F = 0.32	0.83
Total lenient (max 48 pt)	21.4 (5.6)	23.5 (6.5)	24.4 (4.4)	23.9 (6.0)	F = 1.1	0.81
Object in location task (navigation with landmarks)						
Mean time, s	36.8	38.1	43.1	45.4	$\chi^2 = 1.7$	0.63
Length of path ^a	32.8	41.0	46.3	42.0	$\chi^2 = 3.75$	0.29
Average heading error in ° mean (SD)	48.7 (14.6)	52 (14.5)	59.0 (15.3)	55.2 (15.2)	F = 1.8	0.15
Number of detected treasure chests ^a	42.3	42.4	42.2	32.7	$\chi^2 = 5.9$	0.12
Path integration, mean (SD)						
Navigation time, s	28,732	19,997	24,756	23,407	2.47	0.069
Runs 1–3, mean summarized	(11,319)	(6,209)	(12,338)	(12,010)		
Estimation error ^b in °	11.7 (4.1)	10.9 (3.6)	12.0 (3.2)	9.9 (2.5)	1.36	0.26
Runs 1–3, mean summarized						

^aNo normal distribution, rank.^bDifference from real and estimated angle divided by 6.

LT = local therapy, TAM = Tamoxifen, AI = aromatase inhibitor, SWITCH = TAM→AI, SD = standard deviation, pt = points.

*p < 0.05.

gens on CNS function, these findings seem to be consistent. However, with regard to spatial cognition, we generally did not find significant results when subtests were summarized.

Overall, no differences were observed between the ‘SWITCH’ and the TAM group in our study. The results may be limited by the fact that patients in the ‘SWITCH group’ had previously received more HT for postmenopausal symptoms before the diagnosis of breast cancer than patients in the other groups. The extent to which previous HT has an impact on patient performance is unknown. Some previous studies concluded that healthy women who had received HT in the past, but not at the time of assessment, achieved better cognitive performances than the control group [30, 31]. The effect of a previous HT on cognition should be clarified in further studies.

Similar results concerning endocrine therapy and cognition were shown by Bender et al. [32, 33] and Collins et al. [34], who also found deterioration of cognition under AI treatment. However, Phillips et al. [35] and Jenkins et al. [36] showed conflicting results. Phillips et al. [35] noticed that the AI group performed significantly better than the TAM group when a composite score was calculated, but both groups performed below age norms in most domains. Jenkins et al. [36] ascertained in their prevention study that there were no statistically significant differences in cognitive function between the AI group and the placebo group at any time point.

One of the advantages of our study is the separation of the different options of endocrine therapy in each treatment group. All women were postmenopausal. The groups were statistically parallel, apart from history of HT in the past. A comprehensive assessment of spatial cognitive ability was not performed in previous studies. In addition, confounders such as chemotherapy were excluded, even if the magnitude of the impact of chemotherapy is still controversial [17, 37]. In a meta-analysis of 17 studies on chemotherapy-induced cognitive impairment in patients with breast can-

cer, Jim et al. [38] reported an impairment of verbal and visuospatial ability compared to healthy controls.

One major limitation of this study was the cross-sectional design. Measurement occurred at 1 time point only, and the results provide no information about the sequence of the events, e.g. we do not know whether patients were already impaired before onset of treatment. Another limitation may be seen in the number of measured data, which necessitated adjusting p values. This involves the risk that potential differences remain undetected. Generally, a differentiation between patients receiving chemotherapy and endocrine therapy is essential, because chemotherapy is a potential confounder [37, 38]. Different types of endocrine therapy – antiestrogens and AIs – should be studied separately. In addition, the steroidal AI exemestane with its androgenic properties could show an advantage in cognitive functioning when compared with TAM or non-steroidal AIs such as anastrozole and letrozole [39]. Moreover, the time interval since menopause may have an effect on cognitive functioning. It is conceivable that women who have been postmenopausal for many years may tolerate a complete estrogen deprivation better than those who are barely postmenopausal. Against this background, it was remarkable to find significant results even though AI patients were on average 15 years postmenopausal. Further studies should clarify whether a shorter period since menopause would modify the cognitive effects of AIs. Furthermore, body weight may play a role in endocrine therapy. It is not known whether obese women are subject to complete estrogen suppression with AIs. Different results have been found in various studies [40–42]. In TAM treatment, the level of the active metabolites may have impact on effects and side effects including cognitive impairment. Therefore, poor metabolizers, e.g. due to CYP2D6 polymorphisms, should be studied separately from normal metabolizers. Another important factor is reduced compliance for endo-

crine therapy in patients with breast cancer. A number of studies have shown different discontinuation rates [43–45]. Highest discontinuation rates of 49.7% were found by Fontein et al. [45] in the first 6 months of treatment. Although compliance was assessed in the pre-test interview, in planning future studies we suggest assessing compliance pharmacologically (by drug level measurement) to gain a better estimate of the true impact of endocrine therapy.

In conclusion, adverse effects on cognitive function through adjuvant endocrine treatment can frequently be detected and may be of clinical relevance. These side effects may influence patient coun-

selling with regard to AI use for adjuvant treatment in early breast cancer, e.g. by preferring shorter over longer AI treatment periods. In the future, prospective trials with larger samples will be necessary to elucidate this observation further. However, adjustment for potential confounders is important.

Disclosure Statement

The authors indicated no potential conflicts of interest.

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