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Cognitive factors associated with adherence to oral anti-estrogen therapy: Results from the Cognition in the Study of Tamoxifen and Raloxifene (Co-STAR) Study

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Abstract

Little is known about the cognitive factors associated with adherence to anti-estrogen therapy. Our objective was to investigate the association between domain-specific cognitive function and adherence among women in a clinical prevention trial of oral anti-estrogen therapies. We performed a secondary analysis of Co-STAR, an ancillary study of the STAR breast cancer prevention trial in which postmenopausal women at increased breast cancer risk were randomized to tamoxifen or raloxifene. Co-STAR enrolled non-demented participants ≥65 years old to compare treatment effects on cognition. The cognitive battery assessed global cognitive function (Modified Mini-Mental State Exam), and specific cognitive domains of verbal knowledge, verbal fluency, figural memory, verbal memory, attention and working memory, spatial ability, and fine motor speed. Adherence was defined by a ratio of actual time taking therapy per protocol ≥80% of expected time. Logistic regression was used to evaluate the association between cognitive test scores and adherence to therapy. The mean age of the 1,331 Co-STAR participants was 67.2±4.3 years. Mean 3MS score was 95.1 (4.7) and 14% were non-adherent. In adjusted analyses, the odds of non-adherence were lower for those with better scores on verbal memory [OR (95% CI): 0.75 (0.62, 0.92)]. Larger relative deficits in verbal memory compared to verbal fluency were also associated with non-adherence [1.28 (1.08, 1.51)]. Among non-demented older women, subtle differences in memory performance were associated with medication adherence. Differential performance across cognitive domains may help identify persons at greater risk for poor adherence.

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Keywords

adherence; cancer; cognition; elderly; tamoxifen; women

Introduction

Anti-estrogen therapy is effective as primary prevention for women at high risk for breast cancer and as treatment to prevent recurrence among women diagnosed with estrogen receptor (ER)-positive breast cancer(1-3). Long-term benefits of adjuvant anti-estrogen therapy are substantial among these women – an estimated 40% reduction in recurrence risk and 30% reduction in mortality, among both older and younger women(1). Nonetheless, adherence rates remain suboptimal in clinical practice(4-8), ranging from 50-85% and decreasing over time(4, 6-10). Importantly, non-adherence is associated with increased mortality(11). Efforts to maximize adherence are needed to ensure treatment benefits in clinical practice.

Multiple factors appear to be associated with non-adherence over time. Extremes of age (including age >75 years), increasing comorbidity, depressive symptoms, lower stage disease at treatment initiation, presence of treatment side effects, longer expected time on treatment, and increased treatment cost have all been associated with non-adherence to anti-estrogen therapy(4-7, 9-13). Additional associated factors include poor perceived communication with health care professionals, perceived lack of control, less than desired role in decision-making, or negative beliefs about treatment. Known risk factors are diverse and likely have differing implications for intentional versus non-intentional adherence(5, 12, 14-16). Understanding such risk factors may ultimately improve outcomes by guiding development of practice patterns and testable interventions to maximize adherence to effective therapies.

Cognitive impairment, a prevalent and often unrecognized condition, is an understudied risk factor for poor adherence in clinical trials and practice. Large-scale studies of medication adherence and cognition are lacking, with little attention focused specifically on anti-cancer therapy(17). Small studies in other chronic illnesses have shown associations between adherence and cognitive function, most consistently with the domains of attention, memory, and executive functioning(17-22). Studies in healthy community-dwelling elders found associations between subtle changes in global cognitive functioning and medication adherence, executive function, and working memory(23, 24).

The relationship between cognitive function, medication adherence, and older age is particularly relevant to cancer care, since most patients diagnosed or at risk for cancer are older and also have a higher prevalence of cognitive impairment(25, 26). The Co-STAR trial(27) provides a unique opportunity to investigate this relationship in a large cohort of non-demented older women taking long-term anti-cancer therapy. The aim of this analysis is to investigate the association between domain-specific cognitive function and adherence to anti-estrogen therapy among older women enrolled in Co-STAR, an ancillary study to a breast cancer primary prevention trial.

Materials and Methods

Study of Tamoxifen and Raloxifene (STAR) – Design

STAR was a multi-center, randomized clinical trial of oral tamoxifen 20 mg/day or oral raloxifene 60 mg/day for a maximum of 5 years, among 19,747 postmenopausal women 35

years of age or older at increased risk for breast cancer according to the modified Gail model(28). The primary outcome was breast cancer prevention.

Cognition in the Study of Tamoxifen and Raloxifene (Co-STAR) – Design

Co-STAR examined the cognitive effects of tamoxifen and raloxifene in a subset of women enrolled in the STAR trial(27). The methods have been described in detail elsewhere(27). Co-STAR enrolled 1,498 women, age 65 and over, without a diagnosis of dementia, from 153 sites. All participants were fluent in English and provided written informed consent for Co-STAR at each participating site. Co-STAR was coordinated at the Wake Forest School of Medicine, approved by its Institutional Review Board and sponsored by the National Institute on Aging. Co-STAR enrollment began in October 2001, 18 months after STAR enrollment started, and continued until the unmasking of STAR in June 2006. Age-eligible women were allowed to join Co-STAR any time during their first 4 years of STAR follow-up. Therefore, most participants did not receive cognitive assessments until after study drugs had been initiated. The baseline Co-STAR visit corresponds to an on-treatment visit for 1,225 participants and to a pretreatment visit for 273 women.

Study Population

The Co-STAR cohort for this secondary analysis included the 1,331 women who met the following criteria: 1) their first Co-STAR visit was within 5 years after their randomization in STAR; 2) they had no protocol-specified reason for discontinuation at the time of baseline Co-STAR evaluation; and 3) were compliant with their assigned treatment when enrolled in Co-STAR. By restricting the analyses to women who were adherent at the time of their Co-STAR evaluation, we also limited the potential confounding between adherence and treatment effects on cognitive function. Tamoxifen and raloxifene have similar effects on cognitive function, which appeared to occur relatively early during treatment and may have stabilized by the time most women entered Co-STAR(27,29).

Measures

Medication Adherence—Medication adherence (measured by pill count) was assessed at each 6-month clinic visit during the STAR primary prevention trial. In this secondary analysis, we defined participants as being adherent to anti-estrogen therapy if they followed the protocol regimen≥80% of their expected time on therapy. Participants who withdrew consent or were lost to follow-up within 4 years of STAR randomization without having a protocol-specified event, or who were randomized but never returned for a follow-up visit, were classified as non-adherent; their expected time on therapy was defined as 5 years. As such, loss of follow-up for any non-protocol-specified reason was incorporated into the adherence outcome. For all other participants, their actual and expected times on therapy were defined as a function of their follow-up and any protocol-specified reasons for stopping (which could include invasive and non-invasive breast cancer or other invasive cancers, pulmonary embolism, deep vein thrombosis, stroke, transient ischemic attack, and atrial fibrillation).

Cognitive Battery—A standardized 70- to 90-minute neuropsychological test battery (Table 1) similar to the cognitive battery used in the Women's Health Initiative Study of Cognitive Aging (WHISCA) was administered yearly by centrally trained and certified examiners according to standardized procedures(30). The battery included tests of general cognitive functioning plus tests of specific cognitive domains. Details about the individual cognitive tests, rationale for categorization of domains, and quality assurance of the measures, are reported elsewhere(30). Raw scores for individual tests within each domain were standardized and the means of domain component scores were used in all analyses of

cognitive domains. Individual test comparisons used raw mean scores. Only cognitive testing data from the baseline Co-STAR visit were used for this analysis.

Covariates—We considered as covariates any measured baseline characteristics that might confound the relationship between cognitive function and medication adherence. The covariates measured on a continuous scale included age at STAR randomization, time between STAR randomization and first Co-STAR assessment, expected time on drug therapy, and Geriatric Depression Scale score(31). Categorical covariates were treatment assignment (tamoxifen versus raloxifene), race, self-report of comorbid conditions (diabetes, heart disease, vision impairment, prior non-breast cancer malignancy), number of medications taken prior to STAR entry, and education level. A history of heart disease was defined as participant self-report of angina, heart attack, or heart failure. Self-reported vision impairment was defined by history of cataracts, glaucoma, or macular degeneration.

Statistical Analyses

Differences between adherent and non-adherent women in covariates and cognitive test scores were described with means and percentages and compared using t-tests and chi-square tests. Logistic regression was used to assess multivariable relationships. A stepwise backwards elimination approach was used to identify a subset of potentially influential covariates from those selected a priori as potential confounders. The association between medication adherence and each cognitive domain was assessed without and with adjustment for this subset. Stepwise backwards elimination was also used to identify a subset of cognitive domains that were jointly associated with medication adherence without and with covariate adjustment. Additional models were fit to characterize the relationship and assessed for goodness of fit using the Akaike information criterion (AIC). Final models are adjusted for relevant confounding covariates (treatment type, time between STAR randomization and first Co-STAR visit, Geriatric Depression Scale score and expected time on therapy). To assess the impact of pretreatment versus post-treatment cognitive assessment on our analysis results we: 1) compared mean baseline cognitive test scores between subjects whose assessment was done before starting study drug with those whose assessment occurred after starting study drug; and 2) conducted a sensitivity analysis by applying the final model to the subset of patients whose baseline cognitive battery was administered after initiation of study drug.

Results

A total of 1,479 participants had their first Co-STAR visit within 5 years after STAR randomization. Among them were 148 individuals who enrolled into Co-STAR after they stopped or were supposed to stop the protocol therapy. We excluded these women from the analysis, and report here results from the 1,331 women who were on protocol therapy and compliant to their treatment schedule at the time of Co-STAR enrollment. The mean time between STAR randomization and Co-STAR enrollment was 26±18 months. The mean age of the Co-STAR cohort was 67.2±4.3 years, and 94.7% were white. These women were well educated (66.7% college educated) and reported low comorbidity (<10% heart disease or diabetes). Eighty-six percent (N=1,148) of our sample were adherent. While on the protocol regimen, participants took an average of 84% of their required pills. Among non-adherent participants, 21% stayed on therapy <20% of expected time, 18% stayed on therapy ≥20% but<40% of expected time, 19% stayed on therapy ≥40% but <60% of expected time, and 43% stayed on therapy ≥60% but <80% of expected time. Compared to the adherent women (Table 2), the non-adherent population was slightly older, had been on protocol medication for less time when enrolled on Co-STAR, and had slightly higher depression scores at

baseline. In addition, more women in the non-adherent group took tamoxifen (versus raloxifene) and had diabetes.

The baseline scores for individual cognitive tests and cognitive domains are presented in Table 3. Overall, women were high-functioning, with a baseline mean 3MS score of 95.1±4.7 (maximum score of 100) for the entire cohort. There were only small differences in individual test scores between adherent and non-adherent women. Adherent women performed statistically better on the Long Delay of the California Verbal Learning Test (CVLT). When comparing cognitive domain scores between the adherent and non-adherent populations, non-adherent women performed worse on verbal memory (p=0.04).

The stepwise selection identified the following covariates as being independently related to treatment adherence: treatment type (tamoxifen versus raloxifene), time between STAR randomization and first Co-STAR visit, Geriatric Depression Scale score, and expected time on therapy. Among cognitive domains, verbal fluency and verbal memory were associated with adherence in multivariable modeling (Model 1, Table 4). A score in the domain of verbal memory that was 1 unit higher was associated with 25% lower odds of non-adherence. After controlling for verbal memory, a score in verbal fluency that was 1 unit higher was associated with 24% higher odds of medication non-adherence. The remaining cognitive domain scores were not associated with adherence.

This model suggested that a relative deficit in verbal memory compared to verbal fluency may be an important predictor of non-adherence. Thus, we created a new variable that equaled a participant's difference between the verbal memory and the verbal fluency domain scores, and included this variable in the regression model (Model 2, Table 5). Directly accounting for such differences offered a better fit than the model with both variables together (Akaike information criteria, AIC, 848.5 vs. 850.1). After adjustment for other important covariates identified earlier (treatment type, time between STAR randomization and first Co-STAR visit, Geriatric Depression Scale score, and expected time on therapy), the difference between the verbal memory and verbal fluency domain scores was a highly significant predictor of adherence (beta=0.25, p-value=0.004). Addition of the individual memory or fluency domain scores did not significantly improve this model. The model indicates that the odds of non-adherence increased in proportion to the relative decrement in verbal memory compared to verbal fluency.

We found no differences in mean cognitive test domains between women who completed their first cognitive assessment before or after initiation of study drug. The final logistic regression model (Model 2) was applied to the subset of women without true baseline assessment; the significance, direction, and magnitude of the effect for all covariates were similar to our original findings. Thus, the subset of women with true baseline cognitive assessment was not influential in the model building process (data not shown).

Discussion

Among non-demented older women enrolled in a breast cancer primary prevention trial, those not adherent to protocol treatment scored below the mean on verbal memory, and above the mean on verbal fluency (after adjusting for relevant confounding characteristics). The difference between verbal memory and verbal fluency performance was independently associated with adherence. There are two important implications from this analysis: 1) very subtle changes in cognitive function may impact adherence to oral therapy, even among a selected population of highly motivated individuals; and 2) differential performance in specific cognitive domains may identify patients at higher risk for non-adherence.

Patients with clinically meaningful impairments detected on standardized cognitive screening tools would always be considered at risk for poor adherence in clinical practice, due in large part to deficits in memory or executive functioning(21). However, our finding of an association between subclinical cognitive impairment and adherence suggests a more nuanced relationship than has been traditionally appreciated. Our finding is consistent with results of a small study in non-demented healthy elders in which a small change (mean 4 point difference) on the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) was associated with a 4-fold increased risk of medication non-adherence(23).

Our analysis further suggests that subtle impairment in verbal memory may have relevance for medication adherence. A similar finding was reported previously in a small study of women taking anastrazole as adjuvant therapy(17). This relationship has implications for how medication instructions are provided in clinical practice. If this finding is validated in other studies, interventions to improve adherence may benefit from focusing on providing written instructions and resources, not just verbal instructions. It also has implications for development of brief screening tools to most efficiently identify at-risk patients for closer monitoring and targeted adherence interventions. In contrast to verbal memory, we find no association between the attention/working memory domain and adherence, as reported in other studies(17, 24). Possible explanations for this result include unique characteristics of our population (highly educated, clinical trial cohort), differences in predictors of long-term versus short-term adherence, or characterization of memory domains across studies.

The relative decrement in verbal memory compared to verbal fluency was more important in predicting non-adherence than the absolute level of verbal memory. Relative differences in domain-specific test scores are independently predictive of incident dementia(32). Verbal memory may be an early marker of underlying cognitive impairment, while deficit in verbal fluency may occur relatively late(33, 34). This pattern has been associated with the development of Alzheimer's disease and may be a mechanism by which to explain our study findings (35). Our study adds to the literature by suggesting that differential performance on specific cognitive domain tests may be a risk factor for future dementia, and may impact treatment adherence (and hence clinical outcomes) years before cognitive impairment is clinically diagnosed.

This is among the largest studies to investigate the association between cognitive function and medication adherence in older adults. In addition, several attributes of the Co-STAR database strengthen the analysis. Specifically, the comprehensive cognitive battery provides a unique opportunity to evaluate the associations between individual cognitive domains and adherence. The longitudinal follow-up provides a more meaningful adherence outcome than shorter-term studies. Use of a homogeneous, highly educated cohort minimizes the confounding effects of education. Finally, the extensive and complete data available on comorbid conditions, including screening for affective disorders, enables us to evaluate cognition in the context of comorbidity and health status.

This study also has several limitations. Adherence was measured by pill count; no electronic monitoring devices were available. Degrees and patterns of non-adherence were not assessed. Participants were not representative of the general population in several ways: 1) all subjects were enrolled on a clinical treatment trial, suggesting they were motivated and more likely to be adherent; 2) they were at high risk for the occurrence of breast cancer; and 3) they were highly educated and high-functioning. These biases may have minimized potential detectable associations between cognition and adherence; however, they also strengthen the potential significance of our findings. Furthermore, most participants underwent cognitive testing after initiation of study drug, because of Co-STAR's design. Finally, adherence patterns in a primary prevention trial may differ from those in a cancer

treatment trial, limiting extrapolation to oncology practice. However, signals detected in this healthy population may provide clues to links between cognition and adherence in the many women receiving adjuvant anti-estrogen therapy after a diagnosis of breast cancer.

Future Directions

Our results demonstrate that adherence is a complex behavior exhibiting nuanced associations with cognition. Additional research in less highly selected populations is needed to confirm our observations and further examine the role of independent and relative cognitive deficits in adherence. Understanding the relationships between subclinical cognitive deficits and adherence will be critical to ensure optimal outcomes for cancer prevention and treatment for an aging population with an ever-increasing arsenal of oral therapies. Ultimately, this line of work should help identify efficient screening tools for clinicians to identify patients at risk for non-adherence, and develop interventions to improve and monitor adherence to oral therapies.

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Table 1

Summary of cognitive measures

Cognitive Measures	Outcome Variable	Maximum Score
Global Cognitive Function		
Modified Mini Mental Status Exam (3MS)	Total score	100
Verbal Knowledge		
Primary Mental Abilities-Vocabulary (PMA-V)	Total correct minus 1/3 of the number incorrect	N/A
Verbal Fluency Domain		
Letter Fluency (F, A, S)	Total correct	N/A
Category Fluency (vegetables, fruits)	Total correct	N/A
Figural Memory Domain		
Benton Visual Retention Test (BVRT)*	Total figures with errors**	26
Verbal Memory Domain		
California Verbal Learning Test (CVLT)	Total of 3 List A learning trials	48
	Total for List B trial	16
	Total for short-delay trial	16
	Total for long-delay trial	16
Attention and Working Memory Domain		
Digits forward	Total correct trials	14
Digits backward	Total correct trials	14
Spatial Ability Domain		
Card rotations	Total correct minus total	160
Fine Motor Speed Domain		
Finger tapping, dominant hand	Total score	N/A
Finger tapping, non-dominant hand	Total score	N/A

*higher scores indicate worse function

**includes additions of designs

Table 2

Distribution of baseline characteristics by adherence status

	Non-adherent (N=183)		Adherent (N=1148)		
Characteristic	**Mean**	**SD**	**Mean**	**SD**	**p-value**
Age (in years)	68.2	4.0	67.0	4.4	<0.001
Time between STAR randomization and Co-STAR enrollment (months)	10.2	12.3	29.0	17.9	<0.001
GDS score[1]	1.6	2.1	1.3	1.9	0.05
Expected time on treatment (months)	54.9	7.6	56.7	8.3	0.006
	N	%	N	%	
Treatment					
Tamoxifen	115	62.8	526	45.8	<0.001
Raloxifene	68	37.2	622	54.2	
Race					
Other	13	7.1	58	5.1	0.25
White	170	92.9	1090	94.9	
History of diabetes	18	9.8	73	6.4	0.08
History of heart disease	18	9.8	95	8.3	0.48
Impaired vision	71	38.8	452	39.4	0.88
Prior malignancy (not breast cancer)	9	4.9	60	5.2	0.86
Number of medications					
Missing	0	0.0	1	0.1	0.31
0	7	3.8	77	6.7	
1	50	27.3	267	23.3	
2	52	28.4	335	29.2	
3	36	19.7	264	23.0	
≥4	38	20.8	204	17.8	
Education					
High school grad or less	70	38.3	373	32.5	0.18
Some college	51	27.9	392	34.2	
College grad	62	33.9	383	33.4	

[1]GDS = Geriatric Depression Scale;3 participants had a missing GDS score.

Table 3

Distribution of cognitive measures at the first Co-STAR visit by adherence status

	Non-adherent (N=183)		Adherent (N=1148)		
Characteristic	**Mean**	**SD**	**Mean**	**SD**	**p-value**
Individual cognitive test[1]					
3MSE	94.9	5.5	95.2	4.5	0.53
BVRT	6.9	4.0	6.7	4.2	0.55
CVLT List A	27.5	6.1	28.4	6.3	0.06
CVLT List B	6.3	2.2	6.5	2.1	0.20
CVLT Long-Delay	8.6	2.9	9.0	3.0	0.05
CVLT Short-Delay	8.0	3.2	8.4	3.1	0.10
Letter Fluency	39.3	10.8	38.6	12.3	0.46
Category Fluency	29.3	6.4	29.0	6.3	0.63
Card Rotations	54.8	27.8	58.5	28.2	0.10
Digits Forward	7.8	2.0	7.7	2.1	0.95
Digits Backward	6.7	2.0	6.7	2.1	0.98
Finger Tapping Dominant	40.5	8.1	41.2	8.1	0.36
Finger Tapping Non-dominant	38.0	6.4	38.5	6.9	0.38
PMA Vocabulary	36.0	10.7	36.1	9.9	0.94
Cognitive domain					
Global Cognitive Function Domain	-0.05	1.19	0.01	0.97	0.53
Verbal Knowledge Domain	-0.00	1.07	0.00	0.99	0.94
Verbal Fluency Domain	0.03	0.90	-0.02	1.02	0.46
Figural Memory Domain	-0.04	0.97	0.01	1.02	0.55
Verbal Memory Domain	-0.13	0.98	0.03	1.00	0.04
Attention and Working Memory Domain	0.01	0.95	0.01	1.01	0.98
Spatial Ability Domain	-0.11	0.98	0.02	0.99	0.10
Fine Motor Speed Domain	-0.06	0.95	0.02	1.00	0.31

[1]Number of missing scores on cognitive tests: 3MSE=1, Letter Fluency=1, Category Fluency=1; Digits Forward and Backward=2; PMA vocabulary=3; BVRT=8; Finger Tapping Dominant=23 and Finger Tapping Non-dominant=30.

Table 4

Multivariable model (Model 1) of Co-STAR baseline characteristics associated with medication non-adherence

Covariate	Odds Ratio[1] (95% Confidence Interval)	p-value[2]
Verbal Memory Domain	0.75 (0.62, 0.92)	0.005
Verbal Fluency Domain	1.24 (1.02, 1.50)	0.03
Tamoxifen (versus raloxifene)	2.49 (1.74, 3.56)	<.0001
Time between enrollment in STAR and Co-STAR	0.93 (0.92, 0.94)	<.0001
Higher GDS[3] score	1.13 (1.04, 1.23)	0.007
Expected time on treatment	1.03 (1.01, 1.05)	0.003

[1] Odds ratios reflect adjustment for all covariates listed in the table

[2] Likelihood-ratio test

[3] GDS=Geriatric Depression Scale

Table 5

Multivariable model (Model 2) of Co-STAR baseline characteristics associated with medication non-adherence, including relative deficit in verbal memory

Covariate	Odds Ratio[1] (95% Confidence Interval)	p-value[2]
Relative deficit in verbal memory[3]	1.28 (1.08, 1.51)	0.004
Tamoxifen (versus raloxifene)	2.50 (1.75, 3.57)	<.0001
Time between enrollment in STAR and Co-STAR	0.93 (0.92, 0.94)	<.0001
Higher GDS score	1.13 (1.04, 1.23)	0.006
Expected time on treatment	1.03 (1.01, 1.05)	0.004

[1] Odds ratios reflect adjustment for all covariates listed in the table

[2] Likelihood-ratio test

[3] Relative deficit=Verbal Fluency Domain score – Verbal Memory Domain score