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Cognitive changes associated with endocrine therapy for breast cancer

Kunal Agrawal, B.Sc.,

Division of Genitourinary Malignancies, Department of Medical Oncology & Experimental Therapeutics, City of Hope Comprehensive Cancer Center

Susan Onami, B.A.,

Division of Genitourinary Malignancies, Department of Medical Oncology & Experimental Therapeutics, City of Hope Comprehensive Cancer Center

Joanne E. Mortimer, M.D., F.A.C.P.[Director], and

Women's Cancer Program, Vice Chair and Professor, Department of Medical Oncology & Experimental Therapeutics, City of Hope Comprehensive Cancer Center

Sumanta Kumar Pal, M.D.[Assistant Professor]

Division of Genitourinary Malignancies, Department of Medical Oncology & Experimental Therapeutics, City of Hope Comprehensive Cancer Center

Abstract

Endocrine therapy in the setting of breast cancer has undoubtedly advanced clinical outcomes in this disease, but treatment with endocrine therapy is accompanied by a wide spectrum of side effects. It is of prime importance to understand and characterize these toxicities to facilitate clinical decision-making. Somewhat surprisingly, there is a relative paucity of data pertaining to cognitive changes associated with endocrine therapy. In this article we review cognitive associated with two classes of endocrine therapy: (1) selective estrogen receptor modulators (SERMs; tamoxifen and raloxifene) and (2) aromatase inhibitors (AIs; anastrozole, letrozole, and exemestane). Companion studies to the Multiple Outcome of Raloxifene Evaluation (MORE), the Study of Tamoxifen and Raloxifene (STAR) and National Surgical Adjuvant Breast and Bowel Project (NSABP) P-1 trials provide relevant data to understand the effect of SERMs on cognition. In contrast, substudies of the Arimidex, Tamoxifen Alone or in Combination (ATAC), Tamoxifen and Exemestane Adjuvant Multinational (TEAM) and Breast International Group (BIG) 1–98 trials juxtapose cognitive effects of AIs against those of tamoxifen. These and other studies are examined herein to provide a comprehensive overview of the effect of endocrine therapy on cognition.

INTRODUCTION

In 2009, approximately 194,280 cases of breast cancer were diagnosed.¹ An estimated two-thirds of these patients had hormone-receptor positive disease, with an even larger

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Corresponding Author: Sumanta Kumar Pal, M.D., Assistant Professor, Division of Genitourinary Malignancies, Department of Medical Oncology & Experimental Therapeutics, City of Hope Comprehensive Cancer Center, Duarte, CA 91010, Phone: (626) 256-4673, Fax: (626) 301-8233, spal@coh.org.

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proportion amongst older adults.² The majority of patients with estrogen- or progesterone-receptor positive breast cancer will receive endocrine therapy, whether as adjuvant treatment or in the case of metastatic disease as primary treatment.³ Furthermore, some of these therapies have been investigated as potential preventative measures for women at high risk of developing breast cancer. Two major types of endocrine therapies include selective estrogen receptor modulators (SERMs; e.g., tamoxifen and raloxifene) and, more recently, aromatase inhibitors (AIs; e.g., anastrozole, letrozole, and exemestane). While tamoxifen has represented the mainstay of endocrine therapy for decades, clinical studies of AIs have firmly established the role of these agents in several settings, with improved disease-free survival observed relative to tamoxifen in large, randomized trials.^{4,5}

Although hormone receptor positivity is the best indication of responsiveness to these endocrine therapies, effectiveness will vary among patients. Therefore, it is of great importance in identifying markers which will indicate responsiveness to endocrine therapies in order to minimize side effects and optimize therapy for the patient. In ongoing research, certain toxicities associated with endocrine therapies have been examined as biomarkers for response. For instance, the extent of vasomotor symptoms incurred with tamoxifen or AI use appears to correlate with clinical outcome.^{6,7} Findings such as these underscore the potential implications and critical importance of understanding toxicities associated with endocrine therapy. In contrast to other side effects, there is a relative paucity of data related to the impact of endocrine therapy on cognition. Herein, data pertaining to SERM- and AI-induced changes on cognitive function are described.

PRECLINICAL DATA

The influence of estradiol and related mediators on neuronal development and neuroprotection has been well illustrated in preclinical studies. For extensive reviews on estrogen and its role in neuroprotection see Brann *et al*⁸ and Bryant *et al*⁹, the latter focusing on potential mechanisms. Morphometric analysis of hippocampal neurons suggests that estradiol at physiologic concentrations can stimulate dendritic branching.¹⁰ Notably, the hippocampus is thought to play a pivotal role in establishing long-term memory. While this study found that treatment of neurons with the SERM raloxifene or the estrogen receptor dimerization inhibitor fulvestrant did not significantly affect dendritic branching, separate studies using a human neuroblastoma cell line (SH-SY5Y) suggest that endocrine therapy may limit the neuroprotective effect of estradiol.¹¹ 17 β -estradiol was shown to increase synthesis of neuronal nitric oxide synthase (NOS1) and thereby increase cell viability; however, growth was inhibited when treated with fulvestrant.

Endocrine therapy may also affect neurotransmission. In a female ovariectomized rat model, it was demonstrated that treatment with estradiol significantly increased serotonergic production by the dorsal raphe nucleus (located in the midline of the brainstem).¹² Substantial increases in 5-hydroxytryptamine_{2A} receptor (5-HT_{2A}R) and serotonin transporter (SERT) mRNA were recorded. Co-treatment with tamoxifen completely abrogated these rises.

Moreover, the physiologic effects of estrogenic signaling modulation have been demonstrated in preclinical models. In one series of experiments, female Sprague-Dawley rats were ovariectomized and exposed to a number of different treatments including estradiol.¹³ The cognitive function of these animals was assessed using latency maze tests; greater latency was observed in ovariectomized rats as compared to the non-ovariectomized control group. Latency was reduced with estradiol treatment, suggesting that estrogen may have a protective effect against cognitive impairment. Interestingly, studies in male rats produced different results. In one series of experiments, male Sprague-Dawley rats were

treated with either letrozole (2.5 mg/kg) or vehicle alone, with improved performance on latency maze tests with letrozole intake.¹⁴

The cited laboratory data offer potential mechanisms for estrogen-mediated changes in cognitive function. However, clinical data are necessary to understand the scope and magnitude of cognitive changes associated with endocrine therapies in human subjects. The remainder of this review is devoted to clinical data that have massed on this topic.

CLINICAL DATA: SERMs

One of the largest datasets documenting the effect of SERMs on cognitive function is derived from the Multiple Outcomes of Raloxifene Evaluation (MORE) study.¹⁶ This trial included a total of 7,478 postmenopausal women with osteoporosis treated at over 180 sites in 25 countries. Patients were randomly assigned to one of three treatment arms: (1) raloxifene at 60 mg oral daily, (2) raloxifene at 120 mg oral daily, or (3) placebo. Women were also supplied with daily calcium and vitamin D. Six tests of cognitive function were utilized in this study (Table 1), with assessments performed at baseline and at 6 months, 1 year, 2 years, and 3 years after initiation of treatment. Cognitive decline was defined as a change in overall score from baseline to 3 years, with the overall score falling within the worst 10% of the population assessed. Characteristics amongst women randomized to the 3 groups were similar, with a mean age of 66 and an average of 19 years elapsed since menopause. Approximately 30% of patients in each arm had received prior estrogen therapy. With respect to cognitive testing, no difference in mean scores was observed amongst the treatment arms at baseline or after 3 years of therapy. Women taking raloxifene did have a lower risk of cognitive decline as assessed by the Word List Recall Test (relative risk, RR, 0.77; 95% CI 0.59–1.00; P=0.05). However, a similar phenomenon was not observed with any of the other cognitive tests administered. Overall, it did not appear that 3 years of therapy with raloxifene had an overall effect on cognitive function in postmenopausal women with osteoporosis.

A second large dataset examined both the effects of tamoxifen and raloxifene in a population of postmenopausal patients. The National Surgical Adjuvant Breast and Bowel Project (NSABP) Study of Tamoxifen and Raloxifene (STAR) trial randomized 19,747 women age 35 years or older who had an increased risk of breast cancer (by the Gail model) to either tamoxifen (20 mg oral daily) or raloxifene (60 mg oral daily).^{17,18} A substudy (designated the CoSTAR trial) enrolled 1,498 women over the age of 65 without a concomitant diagnosis of dementia. Subjects performed an 83-minute standardized test battery including multiple domains. Several commonly utilized testing algorithms were incorporated into this battery, including: (1) the Positive and Negative Affect Schedule (PANAS; to assess changes in affect), (2) the Geriatric Depression Scale (GDS; to assess for depression) and (3) the Modified Mini-Mental State Examination (3MSE; to assess global cognitive function). Patients were assessed at the time of enrollment in Co-STAR, as well as after 1 and 2 years. Based on data assimilated from previous studies, the investigators hypothesized that patients randomized to receive raloxifene would have improved cognitive performance relative to patients receiving tamoxifen. Interestingly, this was not found to be the case. Outcomes on cognitive testing were similar in both groups.

The effect of tamoxifen on cognitive function relative to placebo has been assessed in the NSABP Breast Cancer Prevention Trial (P-1).²⁰ In this landmark study including 13,388 women at an increased risk of breast cancer, treatment with tamoxifen for 5 years (20 mg oral daily) resulted in a reduced risk of breast cancer by 49% relative to placebo. A separate report documented the results of the P-1 Symptom Checklist (SCL) assessment.²¹ The SCL encompassed a number of self-reported domains, spanning cognition, musculoskeletal pain,

vasomotor symptoms, nausea, sexual problems, bladder problems, body image and vaginal symptoms. The cognitive assessment included questions related to ease of concentration, forgetfulness, avoidance of social affairs, and tendency towards accidents. At 1 year, patients receiving tamoxifen had a higher degree of worsening in vasomotor symptoms, bladder control and vaginal symptoms. However, there was little difference between groups in cognitive dysfunction.

While the aforementioned studies of SERMs do not highlight substantial changes in cognitive function accompanying therapy, one limitation is the extent of follow-up. Evaluations of cognitive function in the P-1, MORE and STAR studies were conducted during the period of active therapy.^{16,18,21} Presumably, cognitive changes could be incurred years after treatment with tamoxifen or raloxifene. To address this, a population-based case-control study was conducted in Los Angeles County, including 1,163 women between the ages of 55–75 diagnosed with primary breast cancer between 1987 and 1996.²² Those who had previously used tamoxifen were classified as short-term users (< 4 years) or long-term users (≥6 years), and were compared to never users. Furthermore, patients were classified as previous or current users of tamoxifen. A total of 3 clinical assessments were performed for each patient: (1) clock-drawing, (2) copying a box drawing, and (3) narrative writing to describe a picture. In the study population, 710 women had used tamoxifen, while 453 women were characterized as never users. Interestingly, women who had used tamoxifen for a standard term had more memory problems than never users (3.8% v 1.5%; $P=0.04$). Furthermore, a greater proportion of current users were noted to have deficiencies in memory (8%; $P=0.0003$). Importantly, there were no differences seen amongst never users and past users of tamoxifen, suggesting limited long-term sequelae. Clearly, larger studies are needed to confirm this observation.

Smaller studies have assessed the potential effect of SERMs on cognitive function in the pre-menopausal population. In one such study, 23 pre-menopausal women using tamoxifen for early breast cancer were compared to 23 age-matched women who were not receiving tamoxifen.²³ Patients were assessed using a battery of 8 cognitive and neuropsychological tests. Significantly lower processing speeds were observed in those patients receiving tamoxifen, and appeared to interfere with executive functioning. The study is challenged by a limited sample size and furthermore by a lack of baseline data. In such a small cohort, it is possible that baseline intelligence characteristics may have influenced the study results.

CLINICAL DATA: AIs

Anastrozole

The largest dataset describing changes in cognitive function with AI therapy is derived from the International Breast Intervention Study-II (IBIS-II).²⁴ In IBIS-II, postmenopausal women at an increased risk for breast cancer were randomized to receive either anastrozole (1 mg oral daily) or placebo for a total of 5 years. The primary endpoint of this study was incidence of invasive and non-invasive breast cancer. A substudy of IBIS-II assessed patients with a battery of tests assessing the following domains: (1) auditory/verbal learning, (2) logical memory, (3) complex figures, (3) letter cancellation, (4) letter/number sequencing, (5) spatial gain, (6) digit span, (7) executive function and (8) total verbal fluency. Patients were assessed at baseline, at 6 months, and at 2 years following initiation of study enrollment. A total of 227 women were consented for the study. A total of 207 women (91%) completed baseline and 6-month assessments, and 151 women (67%) completed 24 month assessments. Both arms were well balanced with respect to demographic characteristics. Interestingly, no differences in cognitive function were observed between the two treatment arms. Although at 6 months, a higher proportion of women receiving anastrozole were noted to have memory impairment, this was balanced

between groups by the 24 month assessment. Criticisms of the study include the fact that the population assessed was postmenopausal and therefore hypoestrogenic, and as such, the effects of aromatase inhibition on cognitive function could have been blunted.²⁵ Furthermore, as noted with the aforementioned studies involving SERMs, the duration of neurocognitive testing occurred during the period of treatment. Thus, the latent effects of anastrozole on cognitive function are challenging to interpret.

In the adjuvant setting, the Arimidex, Tamoxifen Alone or in Combination (ATAC) study provides the longest available follow-up comparing the clinical efficacy of tamoxifen to an AI (100 months at the time of most recent report).²⁶ In ATAC, 6,241 postmenopausal women with localized, invasive breast cancer who had completed local therapy were randomized to either tamoxifen (20 mg oral daily) or anastrozole (1 mg oral daily). In a substudy, 94 patients from the ATAC trial were compared to 35 non-cancer control patients.²⁷ Subjects were exposed to a cognitive test battery assessing verbal memory, visual memory, working memory, mood, processing speed and IQ. The study found that working memory, attention and visual memory did not differ between patients receiving endocrine therapy via the ATAC trial and non-cancer controls. However, patients receiving endocrine therapy did have poorer performance on tests of verbal memory ($P=0.026$) and processing speed ($P=0.032$). Because ATAC trial participants were not divided by treatment arm in this analysis, it is challenging to interpret whether these effects are more prominent with anastrozole or tamoxifen.

Several studies of adjuvant therapy do specifically assess the role of anastrozole on cognitive function, albeit in relatively limited samples. Bender *et al* performed a cross-sectional study examining 31 patients who had received therapy with either anastrozole or tamoxifen for a minimum of 3 months.²⁸ Patients were between the ages of 21 and 65, and received evaluations of depression, anxiety, and fatigue in addition to cognitive function. In this small dataset, patients treated with anastrozole had poorer verbal and visual learning and memory in comparison to patients treated with tamoxifen. A separate prospective effort reported by Collins *et al* was designed to assess the cognitive effect of adjuvant hormonal therapy with either tamoxifen or anastrozole.²⁹ In this study, 31 women receiving tamoxifen and 14 women receiving anastrozole were assessed at the start of adjuvant therapy and at a 5–6 month interval. Cognitive testing scores using a standard battery were compared to scores obtained by a cohort of 28 healthy female volunteers. The results mirror that of the previously noted study--specifically, cognitive decline between the two time points of assessment was greater in patients receiving anastrozole as compared to patients receiving tamoxifen (39% v 64%). Notably, a lesser degree of cognitive decline was observed in healthy volunteers (7%) as compared to either population receiving endocrine therapy.

Exemestane

The effect of adjuvant exemestane on cognitive function has been assessed in the pivotal Tamoxifen and Exemestane Adjuvant Multinational (TEAM) trial.³⁰ In this study, postmenopausal females who had completed definitive local therapy for breast cancer were randomized to receive either 5 years of exemestane (25 mg oral daily), or 2.5 to 3 years of tamoxifen (20 mg oral daily) followed by 2 to 2.5 years of exemestane.³¹ An initial cognitive assessment was performed after breast surgery but before the initiation of endocrine therapy, and a second assessment was performed after one year of endocrine therapy. An extensive battery of 18 tests were used to examine 8 cognitive domains: (1) verbal memory, (2) visual memory, (3) information processing speed, (4) executive functioning, (5) manual motor speed, (6) verbal fluency, (7) reaction speed, and (8) working memory. Anxiety, fatigue and menopausal symptoms were also examined as potential confounders of cognitive performance. In total, 80 tamoxifen users and 99 exemestane users were included in this analysis, and results from this cohort were compared to results from

120 healthy controls. While exemestane users exhibited little difference from healthy controls in all cognitive domains, the results for tamoxifen users were striking. Tamoxifen users performed significantly worse as compared to healthy controls in tests of executive functioning ($P=0.01$) and verbal memory ($P=0.01$). Furthermore, patients receiving tamoxifen performed worse than patients receiving exemestane in tests of processing speed ($P=0.02$). While this TEAM substudy is again confounded by the brief duration of follow-up (and therefore no capture of latent effects), this dataset has a number of critical implications. Most importantly perhaps, the results of this study stand in sharp contrast to observations with anastrozole. It has been posited that exemestane (in contrast to anastrozole) has mildly androgenic properties, which may ultimately preserve cognition.^{32,33}

Letrozole

A recent report of cognitive testing paired with the Breast International Group (BIG) 1–98 study has produced results resembling that of the TEAM trial.³⁴ In BIG 1–98, 8,010 women were randomized to receive one of four arms: (1) tamoxifen alone for 5 years, (2) letrozole for 2 years followed by tamoxifen for 3 years, (3) tamoxifen for 2 years followed by letrozole for 3 years, or (4) letrozole alone for 5 years.³⁵ An assessment of cognitive function was performed at five years, and arms (1) and (2) who completed tamoxifen more recently were compared to arms (3) and (4) who completed letrozole more recently.³⁴ Patients who had recently completed letrozole received overall cognitive scores significantly higher than patients completing tamoxifen ($P=0.04$). This study differs from others cited herein in that only a single time point was assessed after a much more extensive period of therapy (5 years). Furthermore, it is challenging to discern the precise effects of letrozole and tamoxifen on cognition, given that endocrine switching arms were combined with single agent arms. Nonetheless, the general conclusion that cognition was better amongst letrozole treated patients once again stands in contrast to the data for anastrozole. While this is challenging to resolve, letrozole is thought to be a more potent inhibitor of aromatase than anastrozole (IC_{50} of 11.5 nM and 15 nM, respectively), perhaps leading to its distinct physiologic effects.³⁶

CONCLUSIONS

Though thousands of breast cancer patients have been enrolled on trials evaluating the efficacy of endocrine therapy, there is a relative paucity of data addressing cognitive changes with these agents.³⁷ Moreover, the available data have created a state of clinical equipoise. The amalgam of data from the MORE, BCPT and STAR trials suggest little cognitive deterioration with SERM therapy, while data from the TEAM and BIG 1–98 trials show a signal of cognitive deterioration with tamoxifen.^{16,18,21,31,34} With respect to AIs, a greater cognitive decline has been observed with anastrozole therapy as compared to tamoxifen therapy, while lesser decline has been seen with both exemestane and letrozole.^{24,25,27,29,31,34,38} Larger studies are clearly needed to validate these findings, rather than small case-control studies or limited subset analyses of large, randomized trials. Furthermore, to ensure uniform interpretation of the study findings, a standard cognitive assessment should be utilized though Table 1 illustrates a typical testing battery, most studies employ a distinct set of examinations. Also complicating the generalizability of study findings is the use of distinct schedules for cognitive assessment. A standard schedule should be devised, and adjuvant studies should include time points spanning beyond completion of endocrine therapy to characterize possible latent effects.

Outside of SERMs and AIs, novel endocrine therapies should be evaluated for effects on cognitive function. Randomized trials of fulvestrant have led to incorporation of the agent into current clinical algorithms.^{3,39,40} As preclinical data implicate an inhibitory effect of fulvestrant on neuronal growth and development, the effect of this agent on cognitive

function should be explored.¹¹ Finally, in evaluating the effect of endocrine therapies on cognitive function, the effect of menopausal status should not be overlooked. Hermelink *et al* reported results from 101 breast cancer patients receiving neoadjuvant chemotherapy at a single institution.⁴¹ Post-chemotherapy treatments were heterogeneous, with patients receiving either no endocrine therapy, tamoxifen, or an AI, and a subgroup of patients developed chemotherapy-induced menopause. With cognitive function recorded at baseline, at the completion of chemotherapy, and one year thereafter, chemotherapy-induced menopause appeared to have favorable effects upon cognition, while therapy with AIs or tamoxifen had little impact.

As the data presented herein suggest, a great deal of further research is required to more fully comprehend the cognitive effects associated with endocrine therapy. Although endocrine therapies have inarguably had a significant positive impact on the treatment of breast cancer, the practitioner and patient must better understand the scope of toxicity to make informed therapeutic decisions.

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Figure 1. Schematic outlining preclinical data related to the effects of endocrine therapy on cognitive function. Estradiol appears to promote dendritic branching and further stimulates neuronal growth--the latter process is inhibited by fulvestrant. Estradiol also appears to increase serotonergic neurotransmission, which is abrogated by tamoxifen.

TABLE 1Tools used to assess cognitive function in the Multiple Outcomes of Raloxifene Evaluation (MORE) study.¹⁶

Clinical Tool	General Description
Short Blessed Test ⁴²	<ul style="list-style-type: none"> Assesses orientation, concentration, and memory Scored from 0–28 Lower scores indicate better performance
Trail Making Test (A) ⁴³	<ul style="list-style-type: none"> Assesses visuospatial scanning, motor speed, attention, and executive function Involves connecting a series of numbered circles Better performance indicated by a shorter completion time
Trail Making Test (B) ⁴³	<ul style="list-style-type: none"> Assesses visuospatial scanning, motor speed, attention, and executive function Involves connecting an alternating sequence of numbered and lettered circles Better performance indicated by a shorter completion time
Word List Memory Test ⁴⁴	<ul style="list-style-type: none"> Assesses learning and immediate/delayed memory Requires immediate recall of 10 standardized words Scoring (from 0–10) based on the number of words recalled
Word List Recall Test ⁴⁴	<ul style="list-style-type: none"> Assesses learning and immediate/delayed memory Requires recall of 10 standardized words after a period of 20 minutes Scoring (from 0–10) based on the number of words recalled
Word List Fluency Test ⁴⁵	<ul style="list-style-type: none"> Assesses verbal production, semantic memory and language Subjects name as many animals as possible in 60 seconds Scoring based on the number of animals named

Table 2

Overview of key studies assessing the effect of SERMs on cognition.

Study	Study Size/Randomization	Conclusion
MORE	N=7,478 Treatment Arms: <ul style="list-style-type: none"> • raloxifene • raloxifene • placebo 	<ul style="list-style-type: none"> • No overall effect on cognitive function • Lower risk of cognitive decline (when assessed by Word List Recall Test only) with raloxifene
CoSTAR	N=1,498 Treatment Arms: <ul style="list-style-type: none"> • tamoxifen • raloxifene 	<ul style="list-style-type: none"> • Cognitive testing similar in both groups
P-1	N=13,388 Treatment Arms: <ul style="list-style-type: none"> • tamoxifen • placebo 	<ul style="list-style-type: none"> • Little difference between groups in cognitive dysfunction

Table 3

Overview of key studies assessing the effect of AIs on cognition.

Study	Design	Conclusion
IBIS-II	N=227 Treatment Arms: <ul style="list-style-type: none"> • anastrozole • placebo 	<ul style="list-style-type: none"> • No differences in cognitive function
ATAC	N=94 (of 6,241) + 35 controls Treatment Arms: <ul style="list-style-type: none"> • anastrozole • tamoxifen 	<ul style="list-style-type: none"> • No difference between therapy groups and controls in working memory, attention and visual memory • Therapy groups poorer performance in verbal memory and processing speed
Bender <i>et al</i>	N=31 Treatment Arms: <ul style="list-style-type: none"> • anastrozole • tamoxifen 	<ul style="list-style-type: none"> • Anastrozole group poorer verbal and visual learning and memory than tamoxifen group
Collins <i>et al</i>	N=45 + 28 controls Treatment Arms: <ul style="list-style-type: none"> • anastrozole • tamoxifen 	<ul style="list-style-type: none"> • Anastrozole group greater cognitive decline than tamoxifen group • Healthy controls less cognitive decline than both therapy groups
TEAM	N=179 + 120 controls Treatment Arms: <ul style="list-style-type: none"> • exemestane • tamoxifen→exemestane 	<ul style="list-style-type: none"> • Exemestane group little difference from healthy controls in all cognitive domains • Tamoxifen group worse than healthy controls in executive function and verbal; worse than exemestane group in processing speed
BIG 1-98	N=8,010 Treatment Arms: <ul style="list-style-type: none"> • tamoxifen • letrozole→tamoxifen • tamoxifen→letrozole • letrozole 	<ul style="list-style-type: none"> • Latter 2 arms higher overall cognitive scores than first 2 arms