The Effect of Short-Term Estradiol Therapy on Cognitive Function in Older Men Receiving Hormonal Suppression Therapy for Prostate Cancer

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See editorial comments by Dr. Sanjay Asthana on pp 316–318.

OBJECTIVES: To determine the effect of estrogen (E) alone (without the influence of testosterone (T)) on cognitive function in older men, using 17-β micronized estradiol versus placebo in older men rendered hypogonadal (low T and E) by treatment for prostate cancer.

DESIGN: Short-term double-blind, randomized, controlled trial.

SETTING: An outpatient General Clinical Research Center.

PARTICIPANTS: Twenty-seven community-dwelling men aged 65 and older receiving neoadjuvant or established therapy with luteinizing-hormone releasing-hormone agonists for treatment of prostate cancer enrolled in a short-term randomized, controlled trial of 17-β micronized estradiol versus placebo on the effect on biochemical markers of bone turnover.

MEASUREMENTS: Hormone levels, including E, T, and sex hormone–binding globulin; standardized neurocognitive tests, including measures of sustained attention, executive function, and memory; and questionnaires to assess subjects' perception of cognitive deficits and symptoms of depression.

RESULTS: There were no significant differences between patients receiving E or placebo on 15 of 17 neurocognitive measures and no significant differences in self-reported cognitive deficits or number of depressive symptoms.

CONCLUSION: Although studies have suggested that E replacement therapy may improve cognitive function, most notably memory performance in postmenopausal woman, there was no evidence in the present study that the addition of short-term E therapy was more beneficial than placebo in tests of cognitive performance in hypogonadal men. **J Am Geriatr Soc 52:269–273, 2004.**

Key words: estrogen; cognitive function; older men; estradiol

A number of studies have investigated the role of sex steroids and cognitive function in older men and women. The role of estrogen (E) in women has been looked at more closely, because animal models have indicated that E can increase acetylcholine activity, improve neuronal survival and dendritic sprouting, and protect neurons from cerebral ischemia.[1] Studies in postmenopausal women have examined the effect of E on cognition and memory and its potential for protection from dementia, but a recent meta-analysis[2] found inconsistent results. Ten studies in the same meta-analysis addressed the risk of the effect of E on development of dementia. Results ranged from the suggestion of a beneficial effect (a 29% lower risk of developing dementia in E users) to an increased risk of developing Alzheimer's disease. In sum, studies of E in women show an effect on cognition, but the specific benefits, risks, and long-term consequences are not yet understood.

Studies of the effect of endogenous gonadal steroids on cognition in older men are fairly limited in number. Most have focused on the role of the major male gonadal steroid, testosterone (T), and have suggested some correlations with specific tasks of cognitive function in younger[3–5] and older men;[6–10] studies of the role of E on cognitive function in men are even fewer. One intervention study in younger men evaluated the effect of T without E on cognitive function. Thirty men receiving relatively high-dose E preparations for transsexual reassignment were compared on a battery of cognitive tests with a transsexual control group not

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receiving E.[11] The E group scored higher on Paired Associate Learning (a verbal memory task) than the control group, but although E preparations used in this setting are known to increase E levels above the normal male physiological range and to decrease T levels to below the normal male physiological level, lack of measurement of hormone levels limited the study. In one other small longitudinal study, tests of cognitive function were compared in older men (N = 23) and in two groups of women (users and nonusers of E, N = 24 total) at two time points 18 months apart.[12] Men had higher E levels than women nonusers. On forward digit span, men had similar scores to women nonusers, and women using E had higher scores than women nonusers; both groups of women had higher scores than the men on verbal fluency tests. The men had higher T levels than either group of women. The authors suggested that E levels in older men and women may protect against some declines in memory tasks with aging.

Because these studies appear to suggest variable results in sex steroid influence on cognitive function in men and women, making any definitive conclusions is presently premature. Because T is converted to E in many tissues, including the central nervous system, it could exert its influence directly or indirectly through conversion to E via the aromatase enzyme. Thus, studies that have not measured E levels have not taken this confounding factor into consideration. Furthermore, serum levels may not accurately reflect tissue levels. Given the inability to measure tissue levels of hormones in human subjects, one unique disease model in which to better understand the role of E on cognition in men is that of men undergoing hormonal suppression with luteinizing-hormone releasing-hormone agonist (LHRH-A) therapy for locally advanced prostate cancer. This therapy leads to hypogonadism, with low T and E levels. Treating these men with E is medically acceptable and allows one to test the effect of E alone on cognitive function. E levels can be raised to the normal male physiological range to determine the effects on cognitive function in the relative absence of T-mediated effects. It was hypothesized that the addition of E therapy to men rendered hypogonadal due to LHRH-A therapy would improve memory performance.

METHODS

Subjects

Volunteers were community-living men aged 65 and older from the greater Hartford, Connecticut, area. They were receiving treatment with LHRH-A after primary treatment for localized prostate cancer (established group) or were planning to receive neoadjuvant treatment with LHRH-A for Stage B or C prostate carcinoma (neoadjuvant group). Subjects were recruited using newspaper advertisements, contacts at senior citizen centers, and physician referral to participate in cognitive testing as part of a short-term study of bone turnover. Men in good health and free of any serious medical conditions (acute or chronic) and who were able to travel to the health center for outpatient visits and sign a written informed consent, which was approved by an institutional review board, were eligible for this study. Subjects with diagnosed cognitive impairment, bone metastases secondary to prostate carcinoma, chronic medical conditions such as renal or liver disease, diseases of bone metabolism, or taking medications known to cause bone loss or medications used to treat osteoporosis were excluded.

Protocol

This was a 9-week randomized, double-blind, placebo-controlled trial of 1 mg/d of micronized 17-β E versus placebo (PL). Micronized 17-β E was purchased from the manufacturer, and the University of Connecticut Health Center pharmacy compounded the E and PL pills in a capsule with lactose so that they appeared identical. All subjects were receiving depot LHRH-A therapy. Fourteen men were on established LHRH-A therapy (EST group) for a mean duration of 31 months (range of 1–99 months) and had clinical Stage T4 disease, and 13 were receiving neoadjuvant treatment (NEO group) before external beam radiation or seed implantation and had clinical Stage T2–3 disease. The EST and NEO groups were randomized independently so that approximately equal numbers of men were in the E and PL arm. Subjects in the EST group underwent hormone measurements and cognitive testing twice (Figure 1): at their baseline visit and 9 weeks after the intervention. The NEO group had hormone measurements and cognitive testing before initiation of therapy of LHRH-A treatment (screening visit); 3 weeks after the initial injection, designated their baseline (BL) visit; and 9 weeks after the intervention. Men who agreed to participate in the study underwent complete medical history and physical examination. All subjects in the EST and NEO groups were randomized at the BL visit to E (1 mg/d micronized E) or PL for 9 weeks. Four subjects had missing data; two were colorblind and could not be administered the Stroop Color and Word Test (Stroop), one was inadvertently not administered the Benton Visual Retention Test (BVRT), and one was not administered the recognition part of the Auditory Verbal Learning Test (AVLT). Thus, 23 subjects had complete data on the cognitive portion of the study and were entered into analysis (13 E, 10 PL).

Hormone Measurements

Sex-hormone measurements included E, total T, and sex hormone–binding globulin (SHBG). Endocrine Sciences (Calabasas Hills, CA) measured assays for total T, E, SHBG, follicle-stimulating hormone, and luteinizing hormone. T and E were measured using radioimmunoassay and SHBG using a competitive binding assay.

Cognitive Testing

Cognitive tests were selected to measure sustained and divided attention, executive functioning, and memory. All subjects had the full battery of tests at each testing time point. Tests included the Rey Auditory Verbal Learning Test (RAVLT),[13] BVRT,[14] the Trail Making Test (TMT),[15] the Stroop,[16] and the Controlled Oral Word Association Test.[17] To minimize potential practice effects, alternate forms were used for the RAVLT and BVRT[17] but not for tests of sustained attention and executive functioning. The Cognitive Failures Questionnaire[18] and Beck Depression Inventory[19] were also administered to assess each patient's

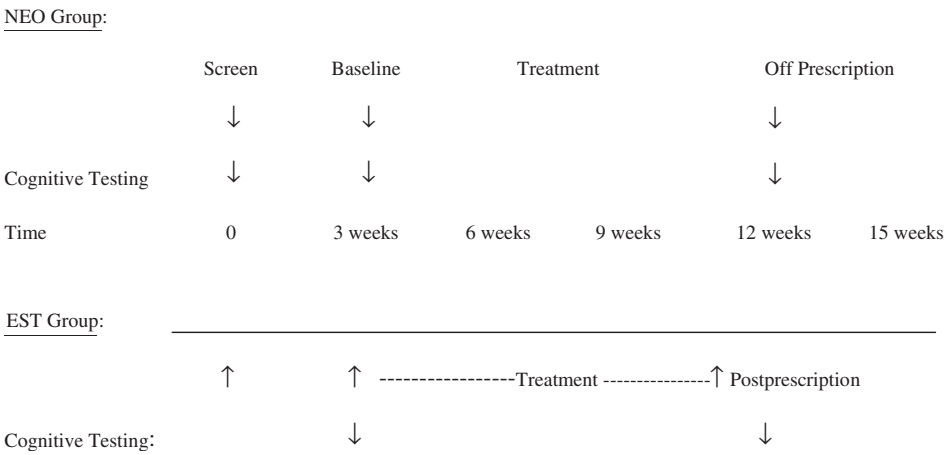

Figure 1. Study design. The figure represents the timeline of treatment for the two groups. EST = the group on established luteinizing-hormone releasing-hormone agonist therapy at initiation of study; NEO = the group receiving neoadjuvant therapy at initiation of study.

perceived cognitive deficits and symptoms of depression, respectively.

In the NEO group, cognitive testing was performed at baseline; at the 3-week visit, when T and E levels were at a nadir; and at the 12-week visit, so that the effect of E alone versus placebo could be evaluated. In the EST group, cognitive testing was performed at the 3-week visit and at the 12-week visit. All tests were administered according to standardized published procedures. The total testing time was approximately 60 minutes.

The data were coded according to group assignment (E vs PL) and baseline or follow-up visit. Basic demographic information, Folstein Mini-Mental State Examination (MMSE) scores, and baseline body mass index (BMI) and prostate-specific antigen levels are listed in Table 1 along with the results of a one-way analysis of variance (ANOVA) comparing study group characteristics.

Statistical Analysis

A series of repeated measures ANOVA models were conducted to examine changes in hormone levels over time. The between-subjects design factors in these models were treatment group (E or PL) and entry group (the NEO or EST group), and the within-subject factor was time. All of the subjects in both groups were assessed at baseline (Time 1) and again 9 weeks later (Time 2). Cognitive function data were analyzed as a repeated measures multivariate analysis of variance (MANOVA) with treatment group (E or PL) as the between-group factor and visit (baseline or follow-up) as the within-group factor. Neuropsychological test measures of memory function and attention/executive function were dependent measures. Scores from the Beck Depression Inventory and a questionnaire measuring subjective ratings of cognitive problems were also included as dependent measures. Because the effects of E may be domain specific to individual neuropsychological tests, these were also analyzed separately using a univariate repeated measures ANOVA with treatment group (E or PL) as the between-group factor and visit (baseline or follow-up) as the within-group factor.

RESULTS

Sample characteristics are reported in Table 1. One-way ANOVA shows no significant difference between the groups due to age, education, MMSE score, or the effect of LHRH-A therapy. Hormone levels are shown in Table 2. At baseline, there was no difference in hormone levels between the E and PL groups. The PL group had a higher level of T at baseline, although the difference was not significant. After 9 weeks of E treatment, there was a significant difference in E levels between the E and PL groups. SHBG was also higher in the E group, as would be expected.

Table 1. Baseline Characteristics of Study Subjects

	Estrogen Group (n = 13)	Placebo (n = 10)	
Characteristic	Mean ± Standard Error		*P*-value
Age	70.0 ± 2.07	70.7 ± 2.63	ns
Education, years	15.9 ± 0.63	15.9 ± 1.04	ns
Mini-Mental State Examination score	29.3 ± 0.31	29.3 ± 0.34	ns
Body mass index, kg/m^2	27.8 ± 1.2	27.7 ± 1.3	ns
Prostate-specific antigen, ng/mL	7.4 ± 2.8	7.1 ± 2.8	ns

NS = not significant.

Table 2. Baseline and 9-Week Hormone Levels

	Estrogen Group		Placebo		
	Baseline	9 Weeks	Baseline	9 Weeks	
Hormone*	Mean ± Standard Error				*P*-value†
Estrogen, pg/mL (5–50)	5.6 ± 0.8	55.3 ± 44.1	5.6 ± 1.0	5.9 ± 0.8	.002
Testosterone, ng/mL (2.8–8.8)	0.57 ± 0.21	0.48 ± 0.17	1.8 ± 0.74	1.7 ± 0.61	ns
Sex hormone binding globulin, nmol/L (9–111)	285 ± 34	343 ± 56	216 ± 51	184 ± 39	.04

* Values in parentheses are normal male values.
† Comparison between estrogen and placebo groups at 9 weeks.

Mean scores for the neuropsychological test measurements are presented in Table 3. Using MANOVA, neither the main effect of group ($F_{3,19} = 3.159$, *ns*) nor that of visit ($F_{3,19} = 0.706$, *ns*) was significantly different. The group-by-visit multivariate interaction was also nonsignificant ($F_{3,19} = 0.753$, *ns*), but univariate ANOVA revealed improved performances between baseline and follow-up visit on the long-delay recall on the RAVLT ($F_{1,21} = 4.214$, $P = .053$) and Stroop T-score ($F_{1,21} = 5.555$, $P = .028$), suggesting that all patients benefited from practice on these measures. There were also two significant group-by-visit interactions. E subjects showed a significant reduction in time to complete TMT Part A on their follow-up visit, compared with PL subjects ($F_{1,21} = 4.667$, $P = .042$) and improved performance on the Stroop ($F_{1,21} = 4.547$, $P = .045$). There were no differences between patients receiving E or PL on any of the other measures, including memory, or on any of the self-reported symptom questionnaires.

Although not shown, the data from the NEO group at baseline and 3 weeks after the first LHRH-A injection were analyzed to test the effect of acute gonadal steroid deficiency on cognitive function. No changes were found of performance measures on any of the cognitive tests that were performed.

DISCUSSION

This study has shown that short-term treatment with low-dose E, which achieved physiological male estrogen levels, did not improve cognitive function in men who were rendered hypogonadal due to androgen deprivation therapy for prostate cancer. One other study evaluated the effect of LHRH-A (E and T deficiency) for 6 months on cognitive

Table 3. Results of Cognitive Testing

	Estrogen (n = 13)		Placebo (n = 10)		
	Baseline	Time 2	Baseline	Time 2	
Variable	Mean ± Standard error				Time × Group *P*-value
RAVLT total score	40.1 ± 7.54	40.7 ± 9.48	39.9 ± 8.58	39.8 ± 6.66	.796
RAVLT short delay recall score	7.5 ± 2.15	7.3 ± 2.14	6.4 ± 2.80	6.6 ± 2.46	.530
RAVLT long delay recall score	6.1 ± 2.33	6.9 ± 3.01	5.7 ± 3.09	7.1 ± 2.13	.618
RAVLT recognition hits	12.2 ± 3.06	12.4 ± 1.98	10.3 ± 2.69	10.4 ± 2.88	.673
RAVLT recognition false positives	2.9 ± 3.62	2.7 ± 3.07	3.6 ± 3.05	3.1 ± 3.30	.959
Benton visual recognition total	5.8 ± 1.91	5.8 ± 2.13	5.9 ± 2.26	5.9 ± 2.15	.928
Benton visual recognition errors	6.8 ± 3.95	6.8 ± 5.05	5.9 ± 4.11	6.0 ± 3.57	.882
Digit span–number forward	7.9 ± 2.10	7.6 ± 2.14	7.6 ± 2.22	7.4 ± 1.71	.843
Digit span–number backward	6.1 ± 1.50	6.3 ± 1.25	6.0 ± 2.75	6.4 ± 2.55	.703
Trail-Making Test–Part A seconds	37.2 ± 15.67	34.6 ± 13.73	37.6 ± 10.06	40.4 ± 8.26	.042
Trail-Making Test–Part B seconds	81.4 ± 37.04	81.1 ± 44.34	95.7 ± 46.70	97.4 ± 43.59	.856
Stroop–Word Reading T-score	50.9 ± 8.65	50.7 ± 7.48	50.3 ± 6.88	50.1 ± 5.30	.991
Stroop–Color Reading T-score	42.8 ± 5.47	43.5 ± 5.87	39.7 ± 9.23	39.3 ± 7.76	.552
Stroop–Color/Word T-score	50.7 ± 8.57	56.7 ± 9.81	48.8 ± 10.87	49.1 ± 9.97	.045
Stroop–Interference T-score	52.9 ± 7.44	57.1 ± 7.85	53.2 ± 7.16	54.3 ± 5.50	.345
Verbal Fluency–total words	47.4 ± 13.87	47.7 ± 14.17	49.2 ± 8.08	44.5 ± 7.78	.067
Categorical Fluency–total words	19.5 ± 3.91	20.0 ± 4.62	17.0 ± 4.90	17.1 ± 4.20	.822
Beck Depression Inventory score	6.3 ± 4.11	6.2 ± 5.36	6.1 ± 3.73	5.3 ± 4.03	.582
Cognitive failures questionnaire	31.5 ± 13.36	30.1 ± 14.79	30.4 ± 9.86	32.6 ± 7.23	.246

Values are mean ± standard deviation.
RAVLT = Rey Auditory Verbal Learning Test.

function in older men and found some decline in two of 12 tests of attention and memory.[20] To the authors' knowledge the current study is the first interventional study to evaluate the effect of E versus PL on cognitive function in older men without the influence of testosterone. This study is unique in that it evaluated the contribution of E-mediated improvements to cognitive function in men while controlling for T, a confounder in previous studies.

The results suggest that there are few immediately observable improvements to cognitive function in hypogonadal men related to E. Only two of 17 neurocognitive measures showed improvement in a direction consistent with a facilitating effect of E on cognitive function. It is difficult to explain the slight improvement in the estrogen group on the TMT Part A and the Stroop trial. Both tests involve sustained attention and speed of information processing. The TMT involves several other cognitive processes, including visual scanning, attention, and motor speed, thus making it difficult to establish which component is due to E administration. Nevertheless, there were other tests in the battery requiring similar skills, and there were no differences on these measures (i.e., TMT Part B, verbal fluency, and the other Stroop subtests), including the interference measure. Moreover, whereas the literature suggests possible memory benefits from E, there was no reason to expect improvement on these measures. It is also noteworthy that both group means remained in the normal range. The observations that the improvement, although statistically significant, depicted change within the normal range expected on that test, and that it was a test not previously associated with improved cognitive function due to E in men or women, further weakened this finding. However, the sample size ($n = 23$) may not have provided sufficient statistical power to conclude that improvements do not occur. At this point it seems prudent not to overinterpret these data, but future studies should consider the potential benefits of E in cognitive domains other than memory.

Several other factors may have affected the study. Subjects all had high cognitive function at baseline (mean MMSE score = 29); thus, it is possible that a ceiling effect was observed. Furthermore, although short-term studies of E treatment have reliably elicited improvement in women, the study duration (9 weeks) may have been insufficient to observe similar changes in men because of differences in neurophysiology. If future studies find a similar effect on tasks that tap attention and cognitive control, a more focused investigation of how sex steroids influence attention function in men may be warranted.

In conclusion, studies evaluating the isolated effects of T versus E on cognitive function in older men are limited in number, use a wide range of cognitive testing measurements, and have varying subject-inclusion criteria (eugonadal to hypogonadal). The present results suggest that sex steroid effects on male cognitive function may not be strongly related to E, but if the effect of E is subtle, it may emerge with a larger group of subjects. Future larger and longer studies using the present model and perhaps animal models will be required to adequately assess the individual role of T and E on cognitive function in the older male population.

REFERENCES

1. Yaffe K, Grady D, Pressman A et al. Serum estrogen levels, cognitive performance, and risk of cognitive decline in older community women. J Am Geriatr Soc 1998;46:816–821.
2. Yaffe K, Sawaya G, Lieberburg I et al. Estrogen therapy in postmenopausal women. Effects on cognitive function and dementia. JAMA 1998;279:688–695.
3. Kampen D, Sherwin BB. Estradiol is related to visual memory in healthy young men. Behav Neurosci 1996;110:613–617.
4. Errico AL, Parsons OA, Kling OR et al. Investigation of the role of sex hormones in alcoholics' visuospatial deficits. Neuropsychologia 1992;30:417–426.
5. Christiansen K. Sex hormone-related variations of cognitive performance in Kung San hunter-gatherers of Namibia. Neuropsychobiology 1993;27:97–107.
6. Yaffe K, Lui LY, Zmuda J et al. Sex hormones and cognitive function in older men. J Am Geriatr Soc 2002;50:707–712.
7. Barrett-Connor E, Kritz-Silverstein D. Gender differences in cognitive function with age: The Rancho Bernardo Study. J Am Geriatr Soc 1999;47:159–164.
8. Moffat SD, Zonderman AB, Metter EJ et al. Longitudinal assessment of serum free testosterone concentration predicts memory performance and cognitive status in elderly men. J Clin Endocrinol Metab 2002;87:5001–5007.
9. Cherrier MM, Asthana S, Plymate S et al. Testosterone supplementation improves spatial and verbal memory in older men. Neurology 2001;10:80–88.
10. Kenny AM, Bellantonio S, Gruman CA et al. Effects of transdermal testosterone on cognitive function and health perception in older men with low bioavailable testosterone levels. J Gerontol A Biol Sci Med Sci 2002;57A:M321–M325.
11. Miles C, Green R, Sanders G et al. Estrogen and memory in a transsexual population. Horm Behav 1998;34:199–208.
12. Carlson LE, Sherwin BB. Higher levels of plasma estradiol and testosterone in healthy elderly men compared with age-matched women may protect aspects of explicit memory. Menopause 2000;7:168–177.
13. Spreen O, Strauss E. Memory. In: Spreen O, Strauss E, eds. A Compendium of Neuropsychological Tests, 2nd Ed. New York: Oxford University Press, 1999, pp 260–422.
14. Sivan AB. Benton Visual Retention Test Manual, 5th Ed. San Antonio, TX: The Psychological Corporation, 1992.
15. Spreen O, Strauss E. Executive Functions. In: Spreen O, Strauss E, eds. A Compendium of Neuropsychological Tests, 2nd Ed. New York: Oxford University Press, 1999, pp 171–231.
16. Golden CJ. Stroop Color and Word Test: A manual for clinical and experimental uses. Wood Dale, IL: Stoelting Company, 1978.
17. Spreen O, Strauss E. Language Tests. In: Spreen O, Strauss E, eds. A Compendium of Neuropsychological Tests, 2nd Ed. New York: Oxford University Press, 1998, pp 423–480.
18. Broadbent DE, Cooper PF, FitzGerald P et al. The cognitive failures questionnaire (CFQ) and its correlates. Br J Clin Psychol 1982;21:1–16.
19. Beck AT, Steer RA. Beck Depression Inventory Manual. San Antonio, TX: The Psychological Corporation, 1987.
20. Green HJ, Pakenham KI, Headley J et al. Altered cognitive function in men treated for prostate cancer with luteinizing hormone-releasing hormone analogues and cyproterone acetate: A randomized controlled trial. BJU Int 2002;90:427–432.

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