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Alcohol and Estrogen Replacement Therapy in Postmenopausal Women: Direct and Mediated Effects on Cognitive Component Processes

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Abstract

The literature remains contentious regarding the separate and combined effects of moderate drinking and ERT (Estrogen Replacement Therapy) on cognition. In the current study, the authors sought to disentangle the predictive utility of alcohol use, ERT and their interaction on the episodic and semantic memory stores of postmenopausal women. It was predicted that relationships between moderate drinking, ERT and cognition would be attenuated by demographic and health-related factors.

Postmenopausal women ($N=298$) completed a battery of cognitive tests designed to assess speed and accuracy of episodic and knowledge-based cognitive processing. Potentially confounding variables were categorized and tested as mediators in hierarchical regression analyses.

Moderate drinking was a weak predictor of episodic availability prior to removal of potential mediators. ERT use was a significant predictor of episodic and knowledge-based availability; no mediators were identified. Alcohol moderated ERT, as a combined alcohol/ERT variable was shown to be related to cognition. Neither moderate drinking nor ERT use was associated with cognitive speed.

These findings suggest that positive relationships between alcohol and cognition are likely mediated by other variables and should not be regarded as a benefit of drinking. Further, results support ERT as a predictor of knowledge-based and episodic availability, independent of mood stabilization or socioeconomic influences. Finally, alcohol and ERT appear to interact to impact both episodic and knowledge-based performance.

Keywords

alcohol; moderate drinking; estrogen replacement therapy; ERT; cognition

Introduction

Neuropsychological studies have long confirmed that people with alcoholism are frequently impaired on tests of learning, memory, visual spatial functioning, problem solving, and abstraction [1]. Although the cognitive consequences of chronic alcohol abuse are well established, the effects of moderate drinking are less well understood. Potential benefits associated with moderate alcohol consumption are of considerable interest, as about one-third of US women report regular drinking. Data on benefits and risks of moderate drinking are particularly compelling for postmenopausal women [2].

A separate body of research links estrogen replacement therapy (ERT) use in postmenopausal women to improvements in cognition [3,4]. However, those findings have been complicated by a recent lack of support for improved cognitive performance among ERT users [5,6].

Alcohol consumption has been identified as a potential confound in studies of ERT effects on cognition [7,8]. Our laboratory has hypothesized that cognitive effects of both alcohol and ERT may be mediated by unidentified biopsychosocial circumstances such as mental or physical health, demographic and/or socioeconomic influences. To this end, the current study was designed to determine whether moderate alcohol consumption and use of ERT affect cognitive processes among postmenopausal women. ERT was examined both with and without progestin, an additional hormone often prescribed in conjunction with estrogen to women whose uteri remain intact. Additionally, we proposed that certain variables such as age, level of education, health factors, and psychosocial functions may act as mediators within the alcohol and cognition, or within the ERT and cognition, relationships [9].

Method

This work was conducted at the University of Oklahoma Health Sciences Center (USA) and was approved by their Institutional Review Board.

Participants

Participants were healthy community volunteers recruited via print media, radio, and word-of-mouth. Three-hundred two postmenopausal women were successfully recruited. Four were eliminated from the analyses, one due to a large number of medical conditions that could compromise cognitive functioning, and three for excessive alcohol consumption. The ethnic/racial breakdown of the remaining 298 was as follows: 26 (9%) Black, 18 (6%) American Indian, 5 (2%) Latina, 3 (1%) Asian, and 246 (82%) Caucasian.

Individuals were recruited to represent the full spectrum of drinking styles. Divisions were constructed and named on the basis of logical descriptions of consumption patterns: teetotalers, low-moderate, mid-moderate, and high-moderate-to-at-risk drinkers. Teetotalers ($n = 85$) had a quantity-frequency index (QFI) [10] of 0.00 and were, in general, long-term abstainers. In low-moderate drinkers ($n = 76$) the QFI ranged from 0.01 to 0.09 (about one to three drinks, one or two times per month). Among mid-moderate drinkers ($n = 86$), the QFI ranged from 0.10 to 0.47 (about one to two drinks, once or twice per week). The QFI range for the high-moderate-to-at-risk drinkers ($n = 51$) was 0.48 to 1.68 (about one to three drinks, five to seven days per week).

About 55% used ERT. Three basic patterns of use were acceptable: daily ERT without progestin (ERT Only), daily ERT plus daily-use progestin (ERT+DPro), and daily ERT plus non-daily use progestin (e.g., progestin on days 15–25 of each month; ERT+NDPro). All participants were $\geq 80\%$ compliant with their ERT regime. In order to be included in the study, ERT had to have been used for at least one full year prior to study enrollment.

Procedure

Screening questions were asked about alcohol consumption patterns, demographics and health. Potential participants were excluded for known neurological disease, trauma, prolonged periods of unconsciousness, and medical illnesses. Additionally, volunteers were excluded for medical illnesses thought to compromise cognition. "Postmenopause" was defined as the absence of a menstrual period for at least one year. At the time of screening, the study was thoroughly explained and an IRB-approved consent form was signed. Individuals were paid 10 USD and, if eligible, scheduled for the study visit.

Study Visit

Participants arrived at 8:30 a.m. Breath alcohol concentration (BrAC) was measured with an Alco-Sensor (Intoximeters Inc.) and was equal to .000 in all cases. Approximately 20 ml of blood was drawn to measure plasma estradiol. Height, weight, and blood pressure were assessed. As part of a larger study, cognitive tests (detailed below) and several psychosocial measures were administered. Total scores from the Beck Depression Inventory II [11] and the Spielberger State Anxiety Inventory [12] as well as index scores assessing physical symptoms, global depression and depressed mood from the Moos Health and Daily Living scale (HDL) [13] were included as potential affective covariates. Additionally, two HDL health-related indices were included as potential health-functioning covariates: medical conditions and medication use.

Using a component-process model, tasks requiring memory based on specific situations and remote "how to" information were chosen to represent, respectively, episodic and knowledge-based memory stores [14]. Traditional definitions of availability and access, provided by Crowder [15] and further discussed within the context of the component process model [16] were conceptualized, respectively, as "correct responses" and "time to task completion." Four dependent variables (episodic availability, episodic access, knowledge availability, and knowledge access) were thus assessed across a variety of neuropsychological measures. Specific tests were chosen based on their ability to effectively represent the theoretical information stores [14,16] and their use within the literature for assessment of potential cognitive deficiencies and/or benefits associated with use of alcohol or ERT [17–26].

Measures Representing Episodic Memory

Tasks representing episodic memory and learning are linked to a specific context or situation [14]. To that end, the following tasks were chosen: *Continuous Performance Test* [27], *Digit Symbol*, *Digit Span* [28], *Logical Memory*, *Visual Reproduction* [29], and *California Verbal Learning Test* [30].

Measures Representing Knowledge Memory

Tasks representing knowledge memory require skills, logic, and problem-solving abilities that are not "tied to the unique context in which it was acquired" [14, p. 1184]. In line with this definition, the following tasks were chosen: *Verbal Fluency* [31], *Shipley Institute of Living* [32], *Block Design* [28], *Luria Verbal- Spatial Problem Solving Test* [26], *Category Test* [33], and *Wisconsin Card Sorting Test* [34].

Dependent variable scores from each of the tests described above were standardized to a mean of 50 and a standard deviation of 10 in order that all measures would be equally weighted. Episodic access, episodic availability, knowledge access and knowledge availability scores were computed by averaging the standardized scores of the respective dependent variables (e.g., total correct, response times) thus providing a composite score to better reflect the latent

construct of the underlying process. Individuals were paid an additional 50 USD at the end of their study visit participation.

Results

To verify that the composite scores were representative of an underlying construct, a confirmatory factor analysis was performed on the standardized scores. A two factor model was proposed, providing a good fit (Goodness of Fit Index = 0.92). Cronbach alpha reliability estimates for episodic and knowledge-based composite scores were 0.74 and 0.71, respectively.

ANOVA was used to determine demographic and alcohol-use differences. Correlations were computed to identify possible confounders within the relationships of interest. Regression was used to evaluate the predictive potential of the independent variables on dependent variables. Stepwise regression was used, followed by linear regression to evaluate effects of confounders.

Demographic and drinking information is presented in Table 1. The groups did not differ with respect to QFI or age. Education level differed but a follow up Duncan's test was not significant ($df=294$, $\alpha=.05$). Years since menopause was significantly longer for the ERT Only group, likely because most had undergone surgical menopause, which tended to occur at a younger age. Likewise, duration of ERT use differed. Estradiol levels also differed, however when only the ERT-users were examined, Duncan's test did not reveal a significant difference ($df=147$, $\alpha = .05$). The groups did not differ with respect to race [Mantel-Haenszel $\chi^2(1, N=298) = 3.56$, $p = .06$].

Regarding potential confounds (see Table 2), demographic characteristics consistently correlated with episodic and knowledge availability scores. Diastolic blood pressure and body mass index were negatively correlated with episodic availability. As none of the health variables were correlated with knowledge availability, knowledge access, or episodic access measures, the health-related variables were used only in subsequent analyses of episodic availability processes. Affect measures were generally correlated with episodic availability, with some also related to knowledge availability.

Can moderate drinking practices be used to predict access and/or availability of episodic and knowledge-based information?

Alcohol variables were entered into a stepwise regression model. Maximum quantity was positively related to availability of episodic information ($B=.55$, Partial $R^2=.01$, $p=.04$). Moderate drinking was not predictive of performance within any of the other cognitive processes.

Do demographic, health, and/or affective functioning variables serve as mediators in the alcohol/cognition relationship?

Health, demographic, and affective variables that correlated with episodic availability were entered into the model followed by the alcohol maximum quantity variable. First, diastolic blood pressure and BMI were entered but maximum quantity continued to be predictive of episodic availability ($B=.53$, Partial $R^2=.01$, $p=.05$). Next, age and education were entered; alcohol no longer predicted episodic availability. Likewise, when the affective variables were entered first into the model, maximum quantity could no longer be used to predict performance. These data suggest that only the demographic and affective variables served as mediators to the relationship between alcohol and episodic availability.

Is ERT use predictive of these processes?

ERT use was positively related to availability of both episodic and knowledge-based information ($B=1.37$, Partial $R^2=.06$, $p=.0001$ and $B=1.28$, Partial $R^2=.05$, $p=.0002$, respectively). Progesterone use was not a significant predictor of access or availability within episodic or knowledge information stores.

Do demographic, health, and/or affective functioning variables serve as mediators in the ERT/cognition relationship?

Health variables were first entered into the model to determine whether they mediate the relationship between ERT and episodic availability. They did not; ERT use continued to predict episodic availability ($B=1.17$, Partial $R^2=.04$, $p=.0007$). The predictive relationship between the health variables and knowledge availability was not explored as knowledge availability was not associated with the health variables. When the demographic variables were first entered, ERT use continued to be related to episodic and knowledge-based performance ($B=1.13$, Partial $R^2=.04$, $p=.0006$ and $B=.85$, Partial $R^2=.02$, $p=.0082$, respectively). Finally, when the affective variables were first entered, ERT use continued to be positively related to episodic and knowledge availability ($B=1.30$, Partial $R^2=.05$, $p=.0001$ and $B=1.00$, Partial $R^2=.03$, $p=.0021$, respectively). These data suggest that none of the proposed variables mediate the ERT and episodic/knowledge-based processes.

Does alcohol serve to moderate the ERT/cognition relationship?

Moderation was tested by evaluating the interactive effects of alcohol and ERT (9). Utilizing total QFI, maximum and typical quantity, three alcohol/ERT combination variables were formed and entered into the model. The typical quantity/ERT variable emerged as a positive predictor of episodic and knowledge availability ($B=1.22$, Partial $R^2=.03$, $p=.0021$ and $B=1.40$, Partial $R^2=.04$, $p=.0006$, respectively), suggesting that alcohol moderates ERT's effect on cognition.

Do demographic, health, and/or affective variables mediate the alcohol/ERT and cognition relationship?

When the health variables were entered into the model, alcohol/ERT continued to be useful in predicting performance ($B=1.00$, Partial $R^2=.02$, $p=.0151$). When the demographic variables were entered, alcohol/ERT continued to predict episodic and knowledge availability performance ($B=.95$, Partial $R^2=.02$, $p=.0159$ and $B=.94$, Partial $R^2=.02$, $p=.0150$, respectively). When the affective variables were entered into the model, alcohol/ERT continued to relate to episodic and knowledge availability ($B=1.42$, Partial $R^2=.04$, $p=.0006$ and $B=1.33$, Partial $R^2=.04$, $p=.0007$, respectively). Thus none of the proposed variables mediate the alcohol/ERT and cognition relationship.

Discussion

Results from this study indicate that what may appear to be a positive association between maximum amount of alcohol consumed and episodic availability (i.e., attention, concentration, short-term memory, learning of new material) may reflect a masked relationship between cognition and other variables that correlate with alcohol use; in this case, demographic and affective functioning variables. Interestingly, health-related variables did not play a mediating role. While it should be interpreted with caution, it does support the premise that positive relationships between alcohol and cognitive functioning are likely mediated by unidentified variables and should not necessarily be regarded as a benefit of drinking. These findings are especially interesting in light of recent studies suggesting that moderate drinking may be beneficial to cognitive performance and/or prevent aging-related cognitive decline (35).

Compared to alcohol, ERT use had a stronger predictive relationship with both episodic and knowledge availability processes. No mediators were identified; none of the potentially confounding variables predicted cognitive performance better than ERT use. Our findings contribute important new information with regard to ERT's relationship to cognitive processes, specifically in terms of episodic and knowledge-based information stores. The current study supports ERT as a predictor of episodic and knowledge availability performance, independent of demographic, affect and health-related factors. Direct actions of estrogen on brain areas important for learning and memory, as well as for affective states are well established (36), but while many studies continue to show direct estrogenic effects on brain (3,37,38), others have reported little or no benefit of ERT on cognition (39,40). While the relationship between use of progestin and cognition has received little empirical attention (41), several studies have suggested that the addition of progestin to the ERT regimen may impact the estrogenic effect (42,43). In the current study, progestin use did not emerge as a viable predictor of cognitive performance. Possible reasons include duration of ERT (44), cognitive area being tested (45), and type of progestin (46,47).

As described by Barron and Kinney (9), alcohol and ERT appear to serve in a moderating capacity supporting previous findings of an alcohol/ERT relationship (7,8). Whether the relationship is biological or psychosocial, the phenomenon is worthy of continued investigation, as no health, demographic or affective-functioning variables were found to confound the relationship.

Neither alcohol nor ERT use was related to cognitive speed as measured by episodic and knowledge-based access scores. Although studies investigating response speed during *acute* administration of alcohol have demonstrated alcohol-related slowing (48,49), the current study of *chronic* moderate drinking reflected no significant variability across consumption patterns. It should be noted that the tests used were somewhat diverse in terms of speed demands. Studies designed to consider response time reflected by other tasks might obtain different results.

This study has several limitations. First, many of the partial R^2 values are quite small. This is particularly true of those associated with the alcohol effects. While the small R^2 values do not negate the existence of the effect, they do speak to the magnitude of the effect size. This is not surprising given that our participants were all relatively healthy, non-abusers, and that the consequences associated with moderate drinking are likely to be subtle.

Another limitation concerns our combining of test scores to create the four cognitive process scores. While combining scores does provide a stable performance measure with which to test the model, it has the potential to mask between-groups differences on individual test-scores. Further, it is possible that performance on some tests could be influenced by other cognitive issues such as processing and execution speed. If this study's focus was to assess performance within specific cognitive domains, this limitation would pose a justifiable concern. However, this study's purpose was, instead, to evaluate processes across domains. The current study represents an initial attempt to examine these complex relationships and clearly demonstrates value in the continuation of this research.

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Table 1
Alcohol Use and Demographic Characteristics by ERT Group (Mean $\pm$ Std or Percent) and F (df), X^2 (df, N), and p-values

	No ERT <i>n</i> = 133	ERT-Only <i>n</i> = 64	ERT+DPro <i>n</i> = 88	ERT+NDPro <i>n</i> = 13	<i>F</i> (df)	<i>p</i>
QFI	0.20 $\pm$ 0.34	0.22 $\pm$ 0.29	0.27 $\pm$ 0.32	0.14 $\pm$ 0.24	1.10 (3,294)	.35
Age (yrs)	57.3 $\pm$ 5.00	56.0 $\pm$ 4.43	55.9 $\pm$ 4.20	55.2 $\pm$ 3.85	2.26 (3,294)	.08
Education (yrs)	14.4 $\pm$ 2.5	14.8 $\pm$ 2.4	15.6 $\pm$ 2.3	15.2 $\pm$ 2.5	4.63 (3,294)	.004
Menopause (yrs)	9.09 $\pm$ 7.13	13.29 $\pm$ 6.21	6.02 $\pm$ 4.39	5.78 $\pm$ 4.29	13.12 (3,241)	.001
ERT use (yrs)	0 $\pm$ 0	11.3 $\pm$ 6.6	5.3 $\pm$ 4.1	7.8 $\pm$ 4.8	24.03 (2,162)	.0001
Estradiol (pg/ml)	14.5 $\pm$ 10.5	118.5 $\pm$ 103.4	75.9 $\pm$ 71.2	105.6 $\pm$ 87.5	41.39 (3,269)	.0001
					X^2 (df,N)	<i>p</i>
Black	10.53%	9.38%	5.68%	7.69%	3.56 (1,298)	.06
American Indian	8.27%	4.69%	4.55%	0.00%		
Latina	2.26%	1.56%	1.14%	0.00%		
Asian	1.50%	0.00%	0.00%	7.69%		
White	77.44%	84.38%	88.64%	84.62%		

Table 2
Correlation Coefficients (Pearson *r*'s, *p*-values): Potential Confounders

Episodic Access			Episodic Availability			Knowledge Access			Knowledge Availability			N
	r	p	r	p	r	p	r	p	r	p		
Demographics:												
Age	.20***	0.0004	-.15*	0.01	.24***	<0.0001	-.13*	0.02			298	
Education	.03	0.62	.19***	0.0008	-.16**	0.0073	.38***	<0.0001			298	
Medical:												
Systolic BP	.07	0.23	-.08	0.19	.02	0.77	-.11	0.07			287	
Diastolic BP	.11	0.06	-.14*	0.02	-.08	0.17	-.09	0.12			288	
Body Mass Index	.05	0.44	-.13*	0.03	-.01	0.92	-.10	0.09			297	
HDL 3	.04	0.49	.01	0.93	-.02	0.72	.03	0.59			295	
HDL 13	.01	0.83	.01	0.87	-.06	0.29	-.03	0.59			295	
Affective:												
SSAI	-.05	0.36	-.21***	0.0003	.08	0.19	-.22***	0.0002			288	
HDL 2	.01	0.96	-.04	0.48	-.05	0.39	-.06	0.31			295	
BDI-II	.03	0.58	-.16**	0.006	.08	0.13	-.14**	0.01			294	
HDL 4	-.07	0.90	-.13*	0.03	.01	0.92	-.02	0.75			280	
HDL 5	-.05	0.40	-.13*	0.03	.03	0.58	-.02	0.75			286	

BP= Blood Pressure; HDL=Health and Daily Living index 2 (Physical Symptoms/somatic), 3 (Medical Conditions), 4 (Global Depression), 5 (Depressive Mood), and 13 (Medication Use); BDI-II=Beck Depression Inventory II; SSAI=Spielberger State Anxiety Inventory

13% (n=40) currently smoked. Daily nicotine estimates, collected as part of the larger study, did not correlate with any of the cognitive measures (all *r*'s ≤ .18, all *p*'s ≥ .28).

* *p* < 0.05

** *p* < 0.01

*** *p* < 0.001; exact *p*-values are included