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The Benefits of Raloxifene Use in Postmenopausal Women with Alzheimers Disease

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Abstract

This qualitative systematic review aims to compile evidence to assess potential cognitive benefit with raloxifene use in postmenopausal women with Alzheimers disease. PubMed, EMBASE, and Cochrane Library databases were searched using the terms raloxifene, Evista, postmenopausal, Alzheimers, dementia, cognitive, and cognition. Reviewed studies were limited to human subjects written in the English language between 2002 and January 2017. Of 36 studies, only four articles were included in the assessment. The most reliable results come from the MORE trial which describes a dose-dependent (120 mg/day) reduction in cognitive impairment and lower risk of developing Alzheimers disease after three years of raloxifene use in postmenopausal women who were considered cognitively normal at baseline. The other three articles reviewed in this study showed no significant cognitive benefit associated with raloxifene treatment. However, all three of these studies showed high potential for bias based on this review of the cognitive assessment method, intervention, study duration, and population. Two of these three studies utilized a dose that was too low (60 mg/day) in cognitively normal women. The third study showing bias had the smallest total population (n=42) but it used an appropriate dose of 120 mg/day and it was the only study to include participants with an established diagnosis of Alzheimers disease. Based on the results of this database search and analysis, there appears to be insufficient available literature that includes an appropriate raloxifene dose, study duration, assessment method, and population. This suggests justification for future clinical trials to properly evaluate the potential cognitive benefit of raloxifene in postmenopausal women with Alzheimers disease.

1 Introduction

Centers for Disease Control (CDC) report Alzheimers disease (AD) as the 6th leading cause of death in all U.S. adults.(1) Death due to AD can be associated with late stage complications related to deterioration of normal bodily function, such as swallowing, walking, and controlling bladder or bowel.2 This loss of function and incapacitation can often lead to aspiration pneumonia, sepsis, hospital-acquired infections (hospitalization after falls, etc.), and even death. (1,2)

In order to prevent these life-threatening complications attributed to mental deterioration, it is necessary to slow the progression of the cognitive decline in Alzheimers patients. There are currently five FDA-approved drugs that function to treat cognitive symptoms (memory loss, confusion, trouble with thinking/reasoning, etc.) but there is no evidence of reduction in AD progression.1 Also, these current AD medications often exhibit adverse effects that limit long-term use. (2) Raloxifene (referred to as RAL in this study) is a selective estrogen receptor modulator (SERM) which is currently used to prevent osteoporosis in postmenopausal women. (3) Recent literature suggests raloxifene may provide significant cognitive benefit for patients with AD and reduce the rate of disease progression. (3-5)

The potential benefit in cognition is also supported on a molecular level through a complex network of pathways within the central nervous system. Decades of research show certain estrogenic compounds (such as

RAL) can improve cognition in older women due to estrogen-induced changes in neurotransmitters and blood flow. (4-7) However, clinical trials that evaluate RAL impact on cognition are very limited. Preliminary work for this study included an assessment of crystallography structures from a molecular visualization database (RCSB PDB). The assessment revealed novel isolated interactions with an inflammatory modulator (LTB4 12-hydroxydehydrogenase/15-oxo-prostaglandin 13-reductase) and cannabinoid receptor2. (8,9) This provides an additional link to support the potential for RAL to lower the rate of cognitive decline in patients with AD due to the central inflammation concept tied with disease progression. (10)

This study aims to assess the statistical power of published randomized clinical trials correlating the use of raloxifene with cognition and/or Alzheimers disease progression. The working hypothesis is that available literature showing a null effect will correlate with high risk of error due to aspects of the study design. This research aims to provide considerations for future clinical trial design pertaining to study duration, patient population, intervention, and cognitive assessment methods. This study also aims to justify further research on the ability for RAL to significantly reduce the cognitive impairment in postmenopausal women with AD.

2   Methods

PubMed, EMBASE, and Cochrane Library databases were searched using the key terms raloxifene, Evista, postmenopausal, Alzheimers, dementia, cognitive, and cognition. Each search included a term for the drug of interest with different combinations of the terms: Alzheimers, dementia, cognitive, and cognition. Studies were limited to those with human subjects written in the English language after 2002 because the brand name drug (Evista) was approved by the U.S. FDA in 1997. Therefore, studies with clinically significant duration and sample size would not be published until 2002 at the earliest. Reference lists of qualifying articles were used to manually evaluate potential studies that were missed in the search process. The trials registry at www.clinicaltrials.gov was evaluated for completed and ongoing trial data. The search results and process for study selection is highlighted in Figure 1.

Studies were included if they were fully published randomized trials with at least one intervention as monotherapy with raloxifene, population of postmenopausal or menopausal women, and primary outcomes focused on cognition. Exclusion criteria included literature reviews, certain study designs (such as retrospective cohort, case series, case report, etc.), intervention with raloxifene as dual therapy, premenopausal status, and male participants. Data collection on studies that meet search criteria were analyzed for relevance based on study design, intervention, duration, patient population, and results. Quality of study evidence was assessed upon review of potential bias and/or conflict of interest, population size, cognitive assessment strategy, relevant confidence intervals, and p-values.

3   Results

The database search resulted in 36 studies and the manual search of reference lists did not identify additional studies for the review process. The initial screening for irrelevance led to exclusion of 27 studies with nine studies remaining for full-text review. Among the nine articles reviewed in full, there were five total studies excluded for being a literature review (3) or a duplicate study (2). The remaining four articles met all inclusion criteria and were thoroughly analyzed for this systematic review. (5,11-13) A visual representation of the study selection process and results of the search is provided in Figure 1.

A summary of the study design, intervention, duration, patient population, and results for each study included in this qualitative analysis is compiled in Table 1. The articles were arranged from top to bottom based on the relevance of each patient population as compared with the target population for this study (postmenopausal women with Alzheimers disease) and the designated intervention (RAL vs placebo). Only one study conducted by Henderson et al (11) had inclusion criteria of a current diagnosis of AD. The other three articles (5,12,13) reported patient populations that were women who were identified as having normal cognitive function upon enrollment ($\geq 95\%$ of subjects). The range for average participant age was 66
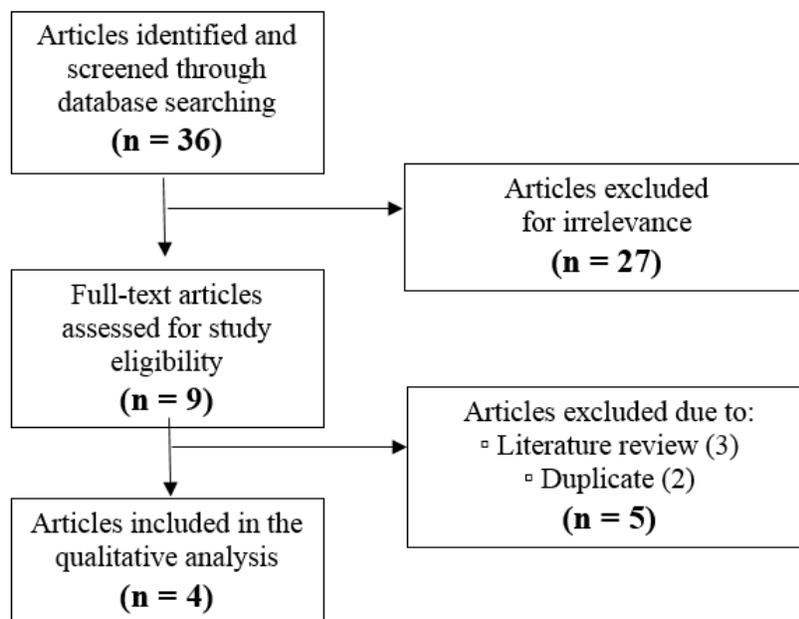
Figure 1: Study section flow diagram

to 76 years old across all four studies. Participants were classified as either high risk of breast cancer or current diagnosis of osteopenia or osteoporosis to ensure ethical use of RAL in consideration of the current FDA-approved indications.

Assessment of quality revealed no potential conflict of interest in all four articles. Total study population (n) varied significantly among articles with a range of 42 to 5386 participants. Author assessment of cognitive outcomes was unique for each of the four articles. The strategies used to review changes in cognition as a result of raloxifene use included: ADAS-cog rating, cognitive screening in combination with brain scan and laboratory exams, and two different versions of a test battery designed to evaluate memory and learning. All four studies were randomized clinical trials and two of those studies (5,11) were also classified as double-blind placebo-controlled trials.

One study (5) from 2005 described a decrease in risk of developing AD and/or cognitive impairment after three years of treatment with 120 mg/day RAL (relative to placebo) for women with osteoporosis who were enrolled based on normal cognitive status. This 2005 trial noted a dose-dependent relationship where the treatment group that received 60 mg/day RAL showed no significant difference in cognition relative to placebo. (5) Three more recent studies (11-13) from 2015, 2009, and 2007 showed no significant difference in cognition between treatment groups after the use of RAL. The 2015 article (11) indicated no statistically significant difference in cognitive changes after one year of treatment with 120 mg/day RAL relative to placebo for women with late-onset mild to moderate AD. The 2009 study (12) showed no significant differences in the adjusted mean cognitive measures between cognitively normal women with increased risk of breast cancer who received either 60 mg/day RAL or 20 mg/day tamoxifen for two years. Finally, the 2007 article (13) showed no statistically significant difference in cognitive interactions after three months of treatment with either 60 mg/day RAL or 10 mg/day alendronate for women with osteoporosis and normal cognitive status upon enrollment.

Table 1. Results of Articles Selected for Review

Citation	Study Design and Intervention	Patient Population	Results
2015 [11] Henderson	Randomized, double-blind, placebo-controlled trial 120 mg/day RAL or placebo 12 month assessment of change between treatment groups in cognitive subscale rating (ADAS-cog)	(n = 42) Women, late-onset mild to moderate AD, postmenopausal Mean age of 76 years	No significant difference between RAL and placebo group in terms of change in ADAS-cog scores at 12 months (standardized difference 0.03; 95% CI=20.39-0.44; 2-tailed p= 0.89)
2005 [5] MORE Trial	Randomized, double-blind, placebo-controlled trial 120 mg/day RAL or 60 mg/day RAL or placebo 3-year assessment of participants who showed clinical signs of dementia *or* those who scored in the lowest 10th percentile on cognitive screenings. Participants then evaluated by blinded dementia specialist via brain scans and lab tests to assess etiology. Diagnosis completed by blinded adjudication committee	(n = 5386) Women, osteoporosis, normal cognitive status, postmenopausal Mean age 66 years	Compared to placebo, women taking 120 mg/day RAL had 33% lower risk of mild cognitive impairment (RR = 0.67; 95% CI=0.46–0.98), somewhat lower risks of Alzheimer's disease (RR=0.52; 95% CI=0.22–1.21) and lower risk of any cognitive impairment (RR=0.73; 95% CI=0.53–1.01) These risks were not significantly different in the group taking 60 mg/day RAL
2009 [12] Co-STAR Trial	Multicenter, randomized clinical trial 60 mg/day RAL or 20 mg/day tamoxifen Standardized 83-minute test battery (modeled after WHISCA exam) once annually for 2-3 years	(n = 1498) Women, no history of dementia or cognitive impairment, increased risk of breast cancer, postmenopausal Mean age of 70 years	No significant differences in adjusted mean cognitive measures between two treatment groups for all scheduled visits (baseline at time=0, then 1 and 2 year follow-ups)
2007 [13] Buckwalter	Randomized clinical trial 60 mg/day RAL or 10 mg/day alendronate 3-month neuropsychological exam (battery of widely used and well-standardized) evaluated relative to baseline cognitive measurement	(n = 70) Women, osteoporosis, no history of medical condition that impacts cognition, postmenopausal Mean age 67 years	RAL treatment group was superior in only one cognitive interaction item, otherwise, there were no statistically significant differences in cognitive interactions RAL group showed improved performance exclusively in Logical Memory II: Thematic recall (p=0.2) whereas alendronate group showed slight decline

Abbreviations: RAL = raloxifene; AD = Alzheimer's disease; RR = relative risk; CI = confidence interval; WHISCA = Women's Health Initiative Study of Cognitive Aging; ADAS-cog = Alzheimer's Disease Assessment Scale, cognitive subscale.

4 Discussion and Conclusions

The database search revealed four articles that focused outcomes on cognitive function after use of RAL for variable study duration. Three of four studies highlighted in Table 1 indicate no significant difference in cognition after a treatment period with RAL. (11-13) However, it is important to review validity in terms of the study power and assess the trial design, population, duration, intervention, cognitive assessment method, and overall potential for error.

The most recent study by Henderson et al (11) (published in December 2015) was the only article to analyze the same population as the target in this study (women with current diagnosis of AD) and it was designed as a randomized, double-blind, placebo-controlled trial. The authors concluded there was no significant change in cognition between treatment groups (120 mg/day RAL versus placebo). (11) However, after analysis of the study design and results it seems to have multiple factors contributing to possible type II error. First, it carries the potential for small study bias with the total number of subjects enrolled in the trial (n=42).

Next, it is critical to consider the assessment tool utilized by Hendersons research team (ADAS-cog) and review the reliability of that examination process. The ADAS-cog exam was conducted by a trained technician who is not a medical expert. This assessment tool has been scrutinized in recent years due to the potential for variability among raters of the ADAS-cog exam. (14,15) One study by Schafer et al (14) even focused on quantifying the error that may occur with individuals who administer the ADAS-cog test. Schafer found 80.6% of highly experienced raters made at least one scoring error and 18% of all raters in the study made over 3 errors in scoring the ADAS-cog. (14)

The content and arrangement of the ADAS-cog exam is noted in numerous recent publications to demonstrate a low sensitivity and no capacity to detect changes in cognition over time. (14-16) It is suggested that the low sensitivity primarily stems from the floor or ceiling effect (depending on AD stage) that occurs with most items on the exam. (16) A study completed by Grochowalski et al (16) in 2016 showed the ADAS-cog exam had no reliability in measurements of cognitive change in one year for AD patients. This conclusion was reached after determination of the ADAS-cog change relative to baseline and comparison with results from two highly sensitive cognitive exams plus brain scan imaging. (16) Therefore, the limitations of ADAS-cog noted in Grochowalskis research is important to consider when assessing reliability in results reported by Hendersons one year trial.

The second study included in this systematic review, also known as the Co-STAR trial, (12) reported no difference between treatment groups with cognitively normal women who received either 60 mg/day RAL or 20 mg/day tamoxifen. The lack of placebo group and consideration of similarities in drug intervention (same drug class selective estrogen receptor modulator or SERM) suggests the Co-STAR trial results should not impact the conclusion of this study since tamoxifen may facilitate the same physiological process for cognitive improvement. The cognitive exam process (83-minute test battery administered by certified individuals) in the Co-STAR trial also holds the same potential for inter-rater error and low sensitivity as noted in the previous discussion regarding ADAS-cog exam reliability. (12)

The third article by Buckwalter et al (13) showed no significant difference after treatment with 60 mg/day RAL versus 10 mg/day alendronate for women who were classified as cognitively normal at the baseline. However, similarly to the Co-STAR trial, Buckwalters study design showed a high potential for error due to the selected cognitive assessment (trained technician rating responses to a unique cognitive test battery), study duration (3 months), and lack of placebo-control group. (13) Buckwalters study also had possible small study bias with the total number of participants (n=70) and used a RAL dose that was too low (60 mg/day) to impart cognitive benefit as indicated in the MORE trial that was published two years prior to Buckwalters work. (5,13)

The MORE trial (5) was the only article to report a reduced risk of cognitive impairment in the treatment group that received 120 mg/day RAL relative to placebo. However, the MORE researchers reported no significant cognitive benefit was observed with participants who received 60 mg/day RAL versus the placebo group. (5) This suggests that future studies to evaluate potential cognitive benefit of RAL should use a minimum daily dose of 120 mg due to that documented dose-dependent relationship with potential cognitive benefit. Analysis of the design and potential for error revealed that the MORE trial results show significantly

higher reliability, validity, and overall power when compared with the other three articles that were reviewed in this research. The study population was over 100 times larger in the MORE trial (n = 5386) when compared with the highly relevant study by Henderson. (5,11) The MORE trial was also nearly four times the population included in the second largest trial (Co-STAR) that was reviewed in this research.

Quality of the results reported in the MORE trial also relates to the cognitive assessment strategy and evaluation technique. This trial was unique because it utilized medical experts to conduct the cognitive assessment and collect data (brain scan, vitals, etc.). Blinded dementia specialists then reviewed results to determine etiology of the proposed dementia or AD. (5) Finally, diagnosis of AD and evaluation of the cognitive impairment was completed by a blinded adjudication committee. The use of a committee allowed drastic reduction in the potential error that was present for the other three studies based on inter-rater variability. Additionally, the MORE trial had the longest duration where primary outcomes were measured at 3 years. (5) Despite the fact that the trial did not completely match this studys target population of patients with dementia or AD (MORE participants were described at baseline as being cognitively normal), in-depth analysis of the MORE trial showed significantly higher reliability in results due to the selected method for cognitive assessment, duration, population size, and placebo-controlled study design. This reliability suggests benefit in future research to further assess the use of RAL to reduce the progression of cognitive impairment in women with AD.

One critical component to consider with all four studies involves the chemistry of oral RAL administration. Due to the molecular structure of RAL, there is poor penetration of the blood-brain-barrier which prevents extensive activity within the CNS. This physiological factor may contribute to the results reported by the MORE trial where there was a dose-dependent effect for RAL in terms of cognitive benefit. The MORE trial showed no significant difference in cognition when treated with 60 mg/day RAL but the group taking 120 mg/day RAL had significant cognitive benefit. (5) This suggests that the higher dose may be necessary to achieve concentrations that allow adequate penetration of the blood-brain-barrier to impart cognitive benefit. This physiological aspect of oral RAL administration was not included in any discussion for each of the four articles reviewed in this study. (5,11-13) Consideration of this molecular aspect is important to review because it shows the potential for very significant cognitive benefit if RAL were delivered in a way that could effectively penetrate the blood-brain-barrier.

In conclusion, this research indicates there is a significant lack of evidence to strongly support either benefit or lack of benefit in cognition with the use of RAL in postmenopausal women with AD. Only one study, the MORE trial, presented with a high level of reliability and power in results showing cognitive benefit in the group treated with 120 mg/day RAL. However, the MORE trial participants were classified at baseline (t=0) as cognitively normal so results cannot be extrapolated to patients who have AD. Therefore, it is not clear whether high-dose RAL could decrease the progression of cognitive impairment for patients with a current AD diagnosis. The study by Henderson et al (11) was the only article to include a population with an established diagnosis of AD but analysis of the study design suggests very high potential for bias and lack of reliability in results. The other two studies, Co-STAR (12) and Buckwalter et al, (13) used a dose that is too low (60 mg/day RAL) to produce cognitive benefit and did not include a placebo-control which severely limits the application of results. In consideration of the evidence presented in this systematic review, it seems that future research is critical to assess the potential for RAL to provide cognitive benefit in a clinical setting for patients with AD.

This research aims to provide considerations for future clinical trial design pertaining to study duration, patient population, intervention, and cognitive assessment methods. Additionally, this research hopes to stimulate future studies in medicinal chemistry that aims to improve RAL delivery into the CNS for use in biological studies to determine if there is significant cognitive benefit. The results from this study ultimately aim to justify further investigation of RAL cognitive benefits in postmenopausal women with AD.

5   Acknowledgement

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