Published in final edited form as:

J Cancer Surviv. 2016 February ; 10(1): 176–184. doi:10.1007/s11764-015-0463-x.

A study of donepezil in female breast cancer survivors with self-reported cognitive dysfunction 1 to 5 years following adjuvant chemotherapy

J. A. Lawrence^{1,5}, L. Griffin¹, E. P. Balcueva², D. L. Groteluschen³, T. A. Samuel⁴, G. J. Lesser^{1,5}, M. J. Naughton¹, L. D. Case¹, E. G. Shaw¹, and S. R. Rapp¹

J. A. Lawrence: jalawren@wakehealth.edu

¹Wake Forest University School of Medicine, Winston-Salem, NC 27157, USA

²Michigan CCOP, St. Mary's of Michigan, Saginaw, MI 48602, USA

³St. Vincent CCOP, Green Bay Oncology, Green Bay, WI 54301, USA

⁴Medical College of Georgia MBCCOP, Augusta, GA 30912, USA

⁵Department of Hematology and Oncology, Wake Forest University School of Medicine, Medical Center Blvd., Winston-Salem, NC 27157, USA

Abstract

Purpose—Some breast cancer survivors report cognitive difficulties greater than 1 year after chemotherapy. Acetylcholinesterase inhibitors (AChEI) may improve cognitive impairment. We conducted a randomized, placebo-controlled, pilot study to assess the feasibility of using the AChEI, donepezil, to improve subjective and objective measures of cognitive function in breast cancer survivors.

Methods—Women who received adjuvant chemotherapy 1–5 years prior with current cognitive dysfunction symptoms were randomized to 5 mg of donepezil/day vs placebo for 6 weeks and if tolerated 10 mg/day for 18 weeks for a total of 24 weeks. A battery of validated measures of attention, memory, language, visuospatial skills, processing speed, executive function, and motor dexterity and speed was administered at baseline and at 24 and 36 weeks. Subjective cognitive function, fatigue, sleep, mood, and health-related quality of life were evaluated at baseline and at 12, 24, and 36 weeks.

Results—Sixty-two patients were enrolled, 76 % completed the study, self-reported compliance was 98 %, and toxicities were minimal. At the end of treatment, the donepezil group performed significantly better than the control group on two parameters of memory—the Hopkins Verbal Learning Test -Revised (HVLT-R) Total Recall ($p=0.033$) and HVLT-R Discrimination

Correspondence to: J. A. Lawrence, jalawren@wakehealth.edu.

Portions of these results were presented at 50th Annual Meeting of the American Society of Clinical Oncology, Chicago, IL, USA, May 29–June 2, 2014 (9516) and the 2014 International Cognition and Cancer Taskforce, Seattle, WA, USA, February 10–13, 2014 (22).

Conflict of interest There are no conflicts of interest to disclose.

($p=0.036$). There were no significant differences on other cognitive variables or in subjective cognitive function or quality of life.

Conclusion—Accrual to this feasibility trial was robust, retention was good, compliance was excellent, and toxicities were minimal.

Implications for Cancer Survivors—Randomized clinical trials in breast cancer survivors to improve cognitive dysfunction are feasible. A phase III trial testing the efficacy of donepezil is warranted given these pilot results.

Keywords

Cognitive dysfunction; Breast cancer survivors; Donepezil; Memory

Introduction

There are 13.7 million cancer survivors in the USA, and those affected by breast cancer make up 22 % of that group [1]. Women who receive adjuvant chemotherapy for breast cancer sometimes report a long-term consequence of cognitive dysfunction [2]. The reports of cognitive impairment are highest during chemotherapy and decline as time post-chemotherapy increases. However, for some, cognitive effects remain. Breast cancer survivors report long-term (>1 year post-chemotherapy) cognitive difficulties that began during chemotherapy [2–7]. Furthermore, there may be some patients who have no evidence of acute cognitive dysfunctions during chemotherapy but have delayed decline 1 year subsequent to chemotherapy [8]. The cognitive dysfunction is apparent across key domains, including concentration, memory, processing speed, and executive functions [9–11]. Accordingly, cognitive impairment associated with cancer and chemotherapy can adversely affect occupational performance, interpersonal relationships, and quality of life.

The specific mechanisms of chemotherapy or cancer-induced injury to the central nervous system remain unclear. Potential pathways of injury are direct (neurotoxicity), including impaired neurogenesis [10, 11]. Cognitive impairment could also be through indirect mechanisms such as treatment-induced metabolic and hormonal abnormalities, inflammatory cytokine activation, medical co-morbidities, fatigue, injury to other body organs, or micro-vessel disease [12, 13]. In brain imaging studies, changes in cerebral metabolism and blood flow have been noted [14] along with cerebral atrophy [15]. Furthermore, cognition may be affected secondarily through factors such as fatigue, sleep disturbance, anemia, and mood [16–19].

Neurotransmitter modulators have improved cognitive function in other cancer populations. Donepezil, a reversible acetylcholinesterase inhibitor used widely to treat symptoms associated with Alzheimer's disease and vascular dementia [20–23], directly affects neuronal function by increasing the bioavailability of acetylcholinesterase and increasing cerebral perfusion [24]. Shaw et al. performed a phase II open-label study and reported that irradiated brain tumor survivors who had completed a course of 30 Gy of brain irradiation 6 months prior to enrollment and were treated with 5 mg/day of donepezil for 6 weeks followed by 10 mg/day for 18 weeks showed improvement in cognitive symptoms, cognitive

functioning (attention/concentration, verbal and figural memory, and verbal fluency), mood, fatigue, and quality of life [25]. A recent phase III randomized, placebo-controlled trial of donepezil (5 mg/day×6 weeks followed by 10 mg/day× 18 weeks) in the same population of brain tumor late survivors revealed a modest benefit for memory and motor dexterity and speed. Among patients with the poorest pre-treatment cognitive performance, the effect was stronger [26]. Given the encouraging results with brain tumor patients and the significant burden of cognitive dysfunction in breast cancer survivors, we conducted a small randomized pilot study to evaluate the feasibility of using donepezil as a treatment for cancer-associated cognitive dysfunction in breast cancer survivors. To allow time for the recovery of cognitive function after receiving chemotherapy, we chose to study women 1–5 years post-chemotherapy who reported having significant cognitive symptoms.

Methods

Patient population

Women with a history of invasive breast cancer who completed adjuvant chemotherapy 1 to 5 years previously and who reported significant cognitive symptoms were eligible to enroll. Documentation of prior chemotherapy (>4 cycles of cytotoxic chemotherapy) was required. Women on hormonal therapy must have been on the same agent for at least 3 months with plans to continue it for the duration of the study. Prospective participants were pre-screened for self-reported cognitive problems with the FACT-Cognition (Version 3) [27]. Women were required to have self-reported cognitive problems. Women who scored 63 or higher on the FACT-Cog Perceived Cognitive Impairment sub-scale (indicating little dysfunction) were ineligible. Patients whose performance status was >60 (Karnofsky Scale) or 0–2 (ECOG score) were eligible. Women were excluded if they had ever been diagnosed with metastatic disease, dementia, or a cerebrovascular accident. The use of any non-study cognition-enhancing drugs was not allowed during study or up to 4 weeks prior to enrollment. Additional exclusion criteria included (1) ongoing ketoconazole or quinidine, (2) hypersensitivity to donepezil, (3) use of investigational medications within the prior 30 days, (4) traumatic brain injury, multiple sclerosis, or recent myocardial infarction, (5) history of schizophrenia, psychosis or substance abuse, (6) untreated current severe depression (treated depression was permitted if treatment was stable), (7) acute severe fatigue, chronic fatigue syndrome, or fibromyalgia, and (8) history of hepatic or renal dysfunction. The study (NCT 01466270) was approved by the Institutional Review Board (IRB) at Wake Forest University School of Medicine (Winston Salem, NC) (WFUSM) and by the IRBs at the participating sites. The study accrued patients at WFUSM and at 15 Community Clinical Oncology Programs (CCOPs) affiliated with the NCI-approved Wake Forest University CCOP Research Base.

Design and treatment

This was a randomized, double blind, placebo-controlled clinical trial in which eligible participants were stratified by menopausal status (pre- vs peri-/post-) and time since chemotherapy (12–36 months vs >36 months) and assigned with equal probability (using variably sized permuted block randomization) to receive 5 mg of donepezil/day for 6 weeks which was escalated to 10 mg/day for 18 weeks if well tolerated or matching placebo. Study

drug (donepezil, Aricept®) and placebo were distributed to the study sites by Biologics Inc., Raleigh, NC, USA. Treatment was discontinued at 24 weeks. Study measures were collected at baseline and at 12 weeks by mail and telephone (some measures), 24 weeks (end of treatment), and 36 weeks by centrally trained and certified examiners following a standardized testing protocol. Adherence was measured by self-reported pill diaries. Toxicity was assessed by study personnel at clinician encounters and by telephone at 12 weeks. Toxicity was graded by the Common Toxicity Criteria v4.03.

Measures

A battery of validated and standardized measures of attention, memory, language, visuomotor skills, processing speed, executive function, and motor dexterity and speed was completed by the participants at baseline and at 24 and 36 weeks. Verbal learning and memory were assessed with the Hopkins Verbal Learning Test-Revised (HVLT-R) [28]. HVLT consists of a 12-item word list which is read to subjects on three successive learning trials. Free recall scores are recorded for each learning trial. After a 20-min interval during which subjects complete other non-interfering tasks and questionnaires, they were asked to recall the target words. Lastly, a yes/no recognition task is then presented in which subjects were asked to identify all target words by responding “yes” and to reject 12 non-target words by responding “no” to minimize confounding by practice effects [28]. Test-retest reliability of the HVLT is quite good (0.74). HVLT-R variables included learning [total recall (TR)=sum of three learning trials; score range 0–36], memory [delayed recall (DR)=trial 4; score range 0–12], recognition [true positives (TP); score range 0–12], [discrimination index (Discrim)=true positives minus false positives; score range –12–12] and [%savings (%S)=[(DR/highest of learning trials 2 and 3) × 100]; score range 0]. The modified Rey–Osterreith Complex Figure (mROCF) [29] assessed visuo-motor skills (mROCF-Copy; score range 0–24), immediate recall (RF-IR; score range 0–24), and delayed recall (RF-DR; score range 0–24). The Trail Making Test—Parts A & B [30] assessed attention (TMT-A) and executive function set shifting (TMT-B). Verbal fluency was assessed with the Controlled Oral Word Association (COWA) [31]. Concentration and working memory were measured with the Digit Span (DS) test [forward (DSF); score range 0–16 and backward (DSB); score range 0–14], a subtest of the Wechsler Adult Intelligence Scale-III [32]; a DS-total score was the sum of DSF and DSB. Motor speed and dexterity were measured with the Grooved Pegboard [33] for the dominant hand and the non-dominant hand. For most tests, a higher score is better with the exception of when the score represents time and a lower score is better (Trail Making Test and Grooved Pegboard).

Subjective cognitive functioning and symptoms were evaluated with the Functional Assessment of Cancer Therapy—Cognition (Version 3) at baseline and at 12 (by mail and telephone), 24, and 36 weeks. The FACT-Cog (Version 3) is a validated self-report measure of perceived cognitive function and impact on quality of life over the prior 7 days [27, 34]. It consists of four subscales—Perceived Cognitive Impairments (PCI; range: 0–80), Perceived Cognitive Abilities (PCA; 0–36), Impact on Quality of Life (IQL; 0–16), and Comments from Others (CFO; 0–16). Higher subscale scores indicate better functioning. We enrolled only women with a FACT-Cog PCI score<63, a score that reflected moderate to severe problems [35, 36]. Fatigue was assessed with the FACIT-Fatigue Subscale and the PROMIS

7-item Fatigue Scale. Sleepiness was measured with the Epworth Sleepiness Scale, and mood was assessed with the Beck Depression Inventory and Beck Anxiety Inventory. Health-related quality of life (HRQL) was measured by the Rand-36 Health Survey [37–41]. All of the written questionnaires were administered at the four time points.

Analysis

Chi-square, Fisher exact, and Wilcoxon rank-sum tests were used to assess unadjusted group differences in categorical and continuous variables. Mixed effects repeated-measures analysis of covariance (RMANCOVA) was used to assess treatment differences in the cognitive function and HRQL measures and to obtain least squares (LS) estimates of the measures over time. Differences (donepezil minus placebo) in LS means are also provided, so for those outcomes for which higher scores reflect better performance, positive differences indicate a benefit for donepezil. An unstructured covariance matrix was used to model the correlation in outcomes over time. Models were fitted for each outcome which just included treatment group, time, strata, and the baseline level of the outcomes. A sample size of 60 participants was selected to provide reasonable estimates of retention ($\pm 16\%$ with 95 % confidence) and treatment group differences for the continuous outcomes (± 0.6 SDs with 95 % confidence assuming 20 % dropout). This study was not powered to detect treatment differences in any of the outcomes. In this paper, we present the results for the first 24 weeks, which was the period during which the participants received treatment.

Results

Patient characteristics

Sixty-two patients were enrolled between July 24, 2012 and January 24, 2013. The women enrolled had a median age of 56 years, were primarily white (90 %), were married (71 %), and had high school education or more (98 %) (Table 1). Most of the women were peri- or postmenopausal (95 %) and were on hormonal therapy (68 %), predominantly an aromatase inhibitor. Characteristics were similar for the two groups.

Accrual, retention, adherence, and toxicity

Sixty-two patients were accrued from 16 sites in 6 months for an accrual rate of ten patients per month. Forty-seven women (76 %) completed the 24-week treatment phase, 71 % of the women receiving donepezil and 81 % of the women receiving the control ($p=.374$). Of the six control patients who dropped out, two were due to sickness or toxicity, one refused, and three were lost to follow-up. Of the nine donepezil patients who dropped out, five were due to sickness or toxicity, three refused, and one was an MD decision. Self-reported adherence to the study drug while on therapy was 98 % for both arms. The common toxicities experienced by patients on both arms were mostly grade 1 or 2 with the exception of grade 3 insomnia reported in two patients in the donepezil arm and one case of grade 3 muscle cramps on the placebo arm.

Cognitive measures

The measures of objective and subjective cognitive function are summarized in Table 2. On average, our sample showed poorer performance compared to non-cancer comparison

groups on all cognitive measures except the mROCF (data not shown). However, the range of scores for each measure was broad and included some scores that were better than the mean for the comparators. There were no significant group differences for any cognitive parameter at baseline. Scores on most cognitive measures improved from baseline to week 24 for both groups perhaps due to test familiarity (practice effects) or statistical regression to the mean. Results of the mixed effects models are shown in Table 3. The donepezil group performed significantly better than the control group on two parameters of memory from the HVLT-R: total recall ($p=0.033$) and discrimination index ($p=0.036$). There were no other significant group differences after 24 weeks of treatment with donepezil.

We looked at sub-groups within our study to discern if there were differences by hormonal therapy. The women who were concurrently on hormonal therapy with an aromatase inhibitor performed worse on all the HVLT-R components compared to the larger group (not on hormonal therapy or tamoxifen) though not significantly so. Furthermore, this group declined in their performance on the HVLT-R over time. In contrast, all other groups improved over time, although modestly. Given the heterogeneity of our sample with respect to cognitive functioning at baseline, we performed an exploratory analysis of a treatment by baseline cognitive function interaction for all cognitive measures. A significant interaction effect was found for executive function (TMT B, $p=0.007$); those with lower baseline executive function randomized to the donepezil arm showed greater improvement in executive function at 24 weeks than the controls.

Quality of life measures

Quality of life measures are also summarized in Table 2. The quality of life scores overall were lower than what is found in women without cancer (data not shown). There were few significant differences between the donepezil and the placebo groups in the quality of life measures over the course of the study. There were no significant differences between the donepezil and placebo groups at week 24 for either the FACT-Cog total score or the four sub-scale scores ($p>0.05$). At 12 weeks, participants in the donepezil arm reported greater anxiety than those in the placebo arm ($p=0.049$), but there were no significant differences between the arms at 24 weeks ($p=0.205$). No group differences were observed in fatigue, sleep, or depression between the two groups of participants or on any subscale of the SF-36 at baseline and at 12 or 24 weeks. It is of note that the physical component score (PCS) and the mental component scores (MCS) of the SF-36 were poorer than what has been found in women without a history of cancer [13]. There were also no significant group differences in any of the HRQL measures when the analyses were stratified by time since completion of chemotherapy for breast cancer (<30 months, 30–60 months).

Discussion

This randomized, placebo-controlled clinical trial assessed the feasibility of using 5–10 mg/day of donepezil for 24 weeks to improve cognitive function in breast cancer survivors who self-reported moderate cognitive dysfunction 1 to 5 years following chemotherapy. Enrollment was rapid, retention was good, and the drug was well tolerated. Estimates of

variability and treatment differences for various cognitive function and quality of life outcomes are provided.

Although this study was not powered to detect differences in outcomes, there appears to be an indication that donepezil improved verbal memory in survivors who entered the study with poorer cognitive functioning. At completion of the intervention, there were modest but significant differences between the groups for verbal learning and memory, with better performance in the donepezil group compared to controls. Thus, our small clinical trial demonstrated that this treatment approach was feasible and potentially effective in breast cancer survivors following chemotherapy. This is the first clinical trial of an acetylcholine esterase inhibitor to demonstrate a benefit for objectively measured cognitive functioning [42, 43] in patients with chemotherapy-related cognitive dysfunction. Other agents that have been tested with some success have wake-promoting or stimulant properties [43].

Tamoxifen has been shown to be protective for cognitive performance tasks that are dependent on cholinergic pathways and hippocampal function [44]. Therefore, women on tamoxifen may be less likely to benefit from an acetyl-cholinesterase inhibitor such as donepezil. Most of the women on our study were on hormonal therapy with an aromatase inhibitor, and therefore we had insufficient number of women to evaluate that difference. When the subset of participants on hormonal therapy were examined separately, the improvement on HVLT-R—Total Recall score with donepezil persisted ($p=0.048$).

Although we enrolled only women who reported moderate to severe cognitive problems, their performance on the cognitive measures ranged from quite impaired to normal using non-cancer comparison groups. This incongruence was consistent with prior reports of discordance between self-reported symptoms and objective measures of cognitive dysfunction [9, 45–48]. The heterogeneity with respect to cognitive functioning at baseline may help to explain the overall modest treatment effects we observed with donepezil. When we examined the interactions between treatment and baseline cognitive functioning, a stronger treatment effect was found among women with poorer cognitive functioning at study entry.

Improvement in learning and memory may be critical to improving everyday problem solving for a breast cancer survivor. Memory performance, measured with the HVLT-R, was predictive of independent functioning over 5 years in a geriatric non-cancer cohort [49]. Although significant treatment group differences in memory tasks did occur, we did not find significant differences in HRQL among women on donepezil compared with women receiving placebo. Previous reports have shown greater improvement in HRQL in the first 1–3 years post-chemotherapy than in later years [50]. The mean time since chemotherapy in the present study was 30 months, and most study participants were <3 years post-treatment (65 % in donepezil, 65 % in placebo). The only significant difference in qualitative measures identified was that women taking donepezil reported higher anxiety at 12 weeks than the placebo group, but this effect was not present at 24 weeks. Anxiety is a potential side effect of donepezil, so this could have been related to the study drug. It is unclear why this difference occurred midway through the study treatment.

Limitations of the present study include the small sample size. This was designed to be a feasibility study, and it was not powered to adequately test donepezil's efficacy. A follow-up study is planned based on these results. The women were enrolled subsequent to completion of chemotherapy 1–5 years previously and therefore have late cognitive dysfunction. We do not know the trajectory of their impairment. It is presumed that among the women who enrolled in this study, there were women who suffered acute cognitive dysfunction and continued to decline in the subsequent years, and there are also women who had late cognitive dysfunction that may lead to chronicity. These two groups may differ in the mechanism of impairment. We assessed adherence using a self-report pill diary; we do not have more objective measures of adherence. We do not have data on the screened populations as we do not require participating sites to track and report screening information as these are busy clinical community sites and our protocols are time and labor intensive. It is a limitation of the study that we cannot characterize better the entire prospective participant population which constrains generalization. Strengths of the study include the use of a well-validated neurocognitive test battery that assessed multiple cognitive domains, inclusion of community-based clinical oncology sites, excellent participant adherence to study requirements, and overall retention.

Conclusions

Complaints of cognitive dysfunction related to cancer and its treatments are common. To date, few effective treatments have been identified. This study suggests that breast cancer survivors experiencing cognitive problems several years following completion of chemotherapy may be helped by treatment with donepezil. Moreover, if treatment is targeted for survivors with greater cognitive deficits, the benefit may be greater. Other treatments, both pharmacological and non-pharmacological, are needed for this large and growing patient population.

Acknowledgments

The Wake Forest Community Clinical Oncology Program Research Base is funded by NCI/DCP grant 2U10CA081851.

References

1. de Moor JS, et al. Cancer survivors in the United States: prevalence across the survivorship trajectory and implications for care. *Cancer Epidemiol Biomarkers Prev.* 2013; 22(4):561–70. [PubMed: 23535024]
2. Castellon SA, et al. Neurocognitive performance in breast cancer survivors exposed to adjuvant chemotherapy and tamoxifen. *J Clin Exp Neuropsychol.* 2004; 26(7):955–69. [PubMed: 15742545]
3. Ahles TA, et al. Neuropsychologic impact of standard-dose systemic chemotherapy in long-term survivors of breast cancer and lymphoma. *J Clin Oncol.* 2002; 20(2):485–93. [PubMed: 11786578]
4. Kreukels BP, et al. Persistent neurocognitive problems after adjuvant chemotherapy for breast cancer. *Clin Breast Cancer.* 2008; 8(1):80–7. [PubMed: 18501062]
5. Schagen SB, et al. Cognitive deficits after postoperative adjuvant chemotherapy for breast carcinoma. *Cancer.* 1999; 85(3):640–50. [PubMed: 10091737]
6. Wefel JS, et al. The cognitive sequelae of standard-dose adjuvant chemotherapy in women with breast carcinoma: results of a prospective, randomized, longitudinal trial. *Cancer.* 2004; 100(11): 2292–9. [PubMed: 15160331]

7. Moleski M. Neuropsychological, neuroanatomical, and neurophysiological consequences of CNS chemotherapy for acute lymphoblastic leukemia. *Arch Clin Neuropsychol*. 2000; 15(7):603–30. [PubMed: 14590198]
8. Wefel JS, et al. Acute and late onset cognitive dysfunction associated with chemotherapy in women with breast cancer. *Cancer*. 2010; 116(14):3348–56. [PubMed: 20564075]
9. van Dam FS, et al. Impairment of cognitive function in women receiving adjuvant treatment for high-risk breast cancer: high-dose versus standard-dose chemotherapy. *J Natl Cancer Inst*. 1998; 90(3):210–8. [PubMed: 9462678]
10. Schagen SB, et al. Change in cognitive function after chemotherapy: a prospective longitudinal study in breast cancer patients. *J Natl Cancer Inst*. 2006; 98(23):1742–5. [PubMed: 17148777]
11. Christie LA, et al. Impaired cognitive function and hippocampal neurogenesis following cancer chemotherapy. *Clin Cancer Res*. 2012; 18(7):1954–65. [PubMed: 22338017]
12. Wefel JS, Witgert ME, Meyers CA. Neuropsychological sequelae of non-central nervous system cancer and cancer therapy. *Neuropsychol Rev*. 2008; 18(2):121–31. [PubMed: 18415683]
13. Koppelmans V, et al. Prevalence of cerebral small-vessel disease in long-term breast cancer survivors exposed to both adjuvant radio-therapy and chemotherapy. *J Clin Oncol*. 2015; 33(6): 588–93. [PubMed: 25559803]
14. Silverman DH, et al. Altered frontocortical, cerebellar, and basal ganglia activity in adjuvant-treated breast cancer survivors 5–10 years after chemotherapy. *Breast Cancer Res Treat*. 2007; 103(3):303–11. [PubMed: 17009108]
15. Inagaki M, et al. Smaller regional volumes of brain gray and white matter demonstrated in breast cancer survivors exposed to adjuvant chemotherapy. *Cancer*. 2007; 109(1):146–56. [PubMed: 17131349]
16. Goldstein D, et al. Fatigue states after cancer treatment occur both in association with, and independent of, mood disorder: a longitudinal study. *BMC Cancer*. 2006; 6:240. [PubMed: 17026776]
17. Jacobsen PB, et al. Fatigue in women receiving adjuvant chemotherapy for breast cancer: characteristics, course, and correlates. *J Pain Symptom Manag*. 1999; 18(4):233–42.
18. Jacobsen PB, et al. Fatigue after treatment for early stage breast cancer: a controlled comparison. *Cancer*. 2007; 110(8):1851–9. [PubMed: 17847016]
19. Broeckel JA, et al. Characteristics and correlates of fatigue after adjuvant chemotherapy for breast cancer. *J Clin Oncol*. 1998; 16(5):1689–96. [PubMed: 9586880]
20. Birks J, Harvey RJ. Donepezil for dementia due to Alzheimer's disease. *Cochrane Database Syst Rev*. 2003; (3):Cd001190. Review. [PubMed: 12917900]
21. Evans JG, Wilcock G, Birks J. Evidence-based pharmacotherapy of Alzheimer's disease. *Int J Neuropsychopharmacol*. 2004; 7(3):351–69. [PubMed: 15228642]
22. Malouf R, Birks J. Donepezil for vascular cognitive impairment. *Cochrane Database Syst Rev*. 2004; (1):Cd004395. Review. [PubMed: 14974068]
23. Petersen RC, et al. Practice parameter: early detection of dementia: mild cognitive impairment (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. 2001; 56(9):1133–42. [PubMed: 11342677]
24. Ceravolo R, et al. Cerebral perfusional effects of cholinesterase inhibitors in Alzheimer disease. *Clin Neuropharmacol*. 2004; 27(4):166–70. [PubMed: 15319702]
25. Shaw EG, et al. Phase II study of donepezil in irradiated brain tumor patients: effect on cognitive function, mood, and quality of life. *J Clin Oncol*. 2006; 24(9):1415–20. [PubMed: 16549835]
26. Rapp SR, et al. Donepezil for irradiated brain tumor services: a phase III randomized, placebo-controlled clinical trial. *J Clin Oncol*. 2014; 33(15):1653–9. [PubMed: 25897156]
27. Vardy J, et al. Assessing cognitive function in cancer patients. *Support Care Cancer*. 2006; 14(11): 1111–8. [PubMed: 16538498]
28. Brandt J. The Hopkins of Verbal Learning Test: development of a new memory test with six equivalent forms. *Clin Neurophysiol*. 1991; 5(2):125–42.

29. Saxton, J.; Becker, JT.; Wisniewski, SR. The ROCF and dementia. In: Knight, JA.; Kaplan, E., editors. *The handbook of Rey–Osterrieth complex figure usage: clinical and research applications*. Lutz, FL: Psychological Assessment Resources; 2003. p. 659–82.
30. Reitan RM. Validity of the trail making test as an indicator of organic brain damage. *Percept Mot Skills*. 1958; 8(3):271–6.
31. Ruff RM, et al. Benton Controlled Oral Word Association Test: reliability and updated norms. *Arch Clin Neuropsychol*. 1996; 11(4):329–38. [PubMed: 14588937]
32. Weschler, D. *Wechsler Adult Intelligence Scale-III (WAIS-III)*. New York: Psychological Corporation/Harcourt, Inc; 1996.
33. Matthews, CG.; Klove, H. *Instruction manual for the adult neuropsychological test battery*. Madison: University of Wisconsin Medical School; 1970.
34. Wagner LI, et al. Measuring patient self-reported cognitive function: development of the functional assessment of cancer therapy-cognitive function instrument. *J Support Oncol*. 2009; 7(6):W32–9.
35. Berger AM, et al. Cancer-related fatigue. *J Natl Compr Cancer Netw*. 2010; 8(8):904–31.
36. Wagner LI, et al. Patient-reported outcomes in phase II cancer clinical trials: lessons learned and future directions. *J Clin Oncol*. 2007; 25(32):5058–62. [PubMed: 17991921]
37. Cella D, et al. Fatigue in cancer patients compared with fatigue in the general United States population. *Cancer*. 2002; 94(2):528–38. [PubMed: 11900238]
38. Reeve BB, et al. Psychometric evaluation and calibration of health-related quality of life item banks: plans for the Patient-Reported Outcomes Measurement Information System (PROMIS). *Med Care*. 2007; 45(5 Suppl 1):S22–31. [PubMed: 17443115]
39. Johns MW. A new method for measuring daytime sleepiness: the Epworth Sleepiness Scale. *Sleep*. 1991; 14(6):540–5. [PubMed: 1798888]
40. Beck SL, et al. Symptom experiences and quality of life of rural and urban older adult cancer survivors. *Cancer Nurs*. 2009; 32(5):359–69. [PubMed: 19661799]
41. Hays RD, Sherbourne CD, Mazel RM. The RAND 36-Item Health Survey 1.0. *Health Econ*. 1993; 2(3):217–27. [PubMed: 8275167]
42. Mar Fan HG, et al. A randomised, placebo-controlled, double-blind trial of the effects of d-methylphenidate on fatigue and cognitive dysfunction in women undergoing adjuvant chemotherapy for breast cancer. *Support Care Cancer*. 2008; 16(6):577–83. [PubMed: 17972110]
43. Kohli S, et al. The effect of modafinil on cognitive function in breast cancer survivors. *Cancer*. 2009; 115(12):2605–16. [PubMed: 19309747]
44. Newhouse P, et al. Tamoxifen improves cholinergically modulated cognitive performance in postmenopausal women. *Neuropsychopharmacology*. 2013; 38(13):2632–43. [PubMed: 23867982]
45. Bernstein LJ, Catton PA, Tannock IF. Intra-individual variability in women with breast cancer. *J Int Neuropsychol Soc*. 2014; 20(4):380–90. [PubMed: 24621519]
46. Shilling V, Jenkins V. Self-reported cognitive problems in women receiving adjuvant therapy for breast cancer. *Eur J Oncol Nurs*. 2007; 11(1):6–15. [PubMed: 16844416]
47. Schagen SB, et al. Late effects of adjuvant chemotherapy on cognitive function: a follow-up study in breast cancer patients. *Ann Oncol*. 2002; 13(9):1387–97. [PubMed: 12196364]
48. Shilling V, et al. The effects of adjuvant chemotherapy on cognition in women with breast cancer—preliminary results of an observational longitudinal study. *Breast*. 2005; 14(2):142–50. [PubMed: 15767184]
49. Gross AL, et al. Word list memory predicts everyday function and problem-solving in the elderly: results from the ACTIVE cognitive intervention trial. *Neuropsychol Dev Cogn B Aging Neuropsychol Cogn*. 2011; 18(2):129–46. [PubMed: 21069610]
50. Hwang SY, Chang SJ, Park BW. Does chemotherapy really affect the quality of life of women with breast cancer? *J Breast Cancer*. 2013; 16(2):229–35. [PubMed: 23843858]

Table 1

Patient characteristics

Characteristic	Placebo N (%)	Donepezil N (%)
Total	31 (100)	31 (100)
Age		
Median (range)	55.8 (41–78)	55.8 (39–79)
Age 60	11 (35)	13 (42)
BMI		
Underweight–normal (<25 kg/m ²)	6 (19)	2 (6)
Overweight (25–30 kg/m ²)	12 (39)	12 (39)
Obese (>30 kg/m ²)	13 (42)	17 (55)
Strata		
Premenopausal, 12–36 months post-treatment	1 (3)	1 (3)
Premenopausal, 36–60 months post-treatment	1 (3)	0 (0)
Peri/Post, 12–36 months post-treatment	19 (61)	19 (61)
Peri/Post, 36–60 months post-treatment	10 (32)	11 (35)
Race/ethnicity		
Black	1 (3)	4 (13)
White	29 (94)	27 (87)
Other/multiple	1 (3)	0 (0)
ECOG performance status		
0	22 (71)	20 (65)
1	8 (26)	11 (35)
2	1 (3)	0 (0)
Health insurance		
Medicare	7 (23)	9 (29)
Medicaid	1 (3)	1 (3)
Private	25 (81)	26 (84)
None	2 (6)	0 (0)
Hormonal therapy	20 (65)	22 (71)
Tamoxifen	6 (19)	7 (23)
Prior taxane	10 (32)	12 (39)

N number, *BMI* body mass index, *Peri* peri-menopausal, *Post* post-menopausal

Table 2
Summary statistics for neurocognitive and HRQOL outcomes at 0, 12, and 24 weeks

	Week	Placebo			Donepezil		
		N	Mean	SD	N	Mean	SD
HVLT—Total Recall	0	30	23.5	5.8	30	24.9	6.8
	24	25	23.1	6.7	21	27.0	5.1
HVLT—Delayed Recall	0	30	8.1	2.9	30	9.0	2.9
	24	25	8.1	3.0	21	9.0	2.7
HVLT—Recognition	0	29	10.9	1.7	30	11.2	1.3
	24	25	11.0	1.4	21	11.6	1.0
HVLT—Discrimination Index	0	29	10.3	2.0	30	10.6	1.7
	24	25	9.9	2.3	21	11.1	1.2
HVLT—%Savings	0	30	85.0	22.1	30	87.6	23.0
	24	25	88.6	21.6	21	86.0	20.0
ROCF—Delayed Recall	0	30	17.1	4.1	30	16.3	4.8
	24	25	18.5	4.2	21	18.4	4.0
ROCF—Copy	0	30	21.6	2.8	30	21.6	2.7
	24	25	21.2	2.9	21	22.1	2.0
ROCF—Immediate Recall	0	30	17.3	4.2	30	16.7	4.7
	24	25	18.7	4.3	21	19.7	3.4
Trail Making—Part A Time	0	30	32.3	14.4	30	35.1	18.0
	24	25	30.2	10.0	21	30.7	12.5
Trail Making—Part B Time	0	30	86.3	50.3	30	87.2	50.2
	24	25	69.6	28.1	21	74.8	40.1
COWA—Total Words	0	30	36.0	9.9	30	34.0	9.6
	24	25	38.2	11.8	21	36.9	10.2
Digit Span—Forward	0	30	10.6	2.6	30	9.9	2.4
	24	25	11.1	2.6	21	10.5	2.4
Digit Span—Backward	0	30	6.2	1.9	30	5.9	2.6
	24	25	6.7	2.1	21	6.8	2.4
Digit Span—Total	0	30	16.7	3.6	30	15.8	4.5

	Week	Placebo			Donepezil				
		N	Mean	SD	Correlation ^a	N	Mean	SD	Correlation ^a
Grooved Pegboard—Dominant Hand (s)	24	25	17.8	4.1	0.82	21	17.3	4.5	0.87
	0	30	86.2	17.0		30	91.6	30.6	
Grooved Pegboard—Non-Dominant Hand (s)	24	25	78.4	15.7	0.85	21	81.4	38.9	0.91
	0	30	92.9	21.0		30	97.4	42.1	
FACT Cog—Perceived Cognitive Impairments	24	25	89.0	19.9	0.75	21	92.9	37.2	0.87
	0	31	26.6	13.6		31	28.3	14.0	
FACT Cog—Impact on QOL	12	27	46.5	12.4	0.60	23	46.2	15.9	0.50
	24	25	42.0	16.2	0.66	22	45.3	15.0	0.29
FACT Cog—Comments from Others	0	30	7.9	4.5		30	8.8	4.2	
	12	27	11.8	4.0	0.63	23	11.4	4.8	0.63
FACT Cog—Perceived Cognitive Abilities	24	25	11.6	4.5	0.73	20	12.1	3.9	0.53
	0	30	11.0	3.9		30	11.8	3.5	
FACT Cog—Total	12	26	14.2	2.8	0.75	23	14.3	2.3	0.69
	24	25	13.2	4.5	0.74	22	14.0	2.3	0.44
SF 36—Physical Component	0	30	11.3	4.8		30	13.7	4.0	
	12	27	14.2	6.0	0.53	23	16.6	6.1	0.62
SF 36—Mental Component	24	25	14.5	6.6	0.54	22	18.3	5.9	0.39
	0	31	55.8	22.2		31	61.5	19.6	
FACT Cog—Fatigue	12	27	86.1	23.0	0.66	23	88.5	25.6	0.59
	24	25	81.4	29.0	0.75	22	88.7	24.2	0.41
FACT Cog—Total	0	30	38.2	12.2		30	41.9	12.9	
	12	26	41.8	13.3	0.83	23	44.8	11.2	0.82
FACT Cog—Total	24	25	43.5	13.0	0.77	21	46.3	12.6	0.78
	0	30	43.5	11.4		30	47.4	11.6	
FACT Cog—Total	12	26	45.9	12.6	0.70	23	48.1	11.7	0.62
	24	25	49.7	11.4	0.85	21	51.5	10.1	0.68
FACT Cog—Total	0	30	28.5	14.0		30	32.2	12.8	
	12	27	34.2	13.1	0.79	23	35.1	12.6	0.60
FACT Cog—Total	24	25	36.8	13.0	0.90	22	39.0	11.7	0.69
	0	30	20.5	4.9		30	19.0	5.1	

	Week	Placebo			Donepezil		
		N	Mean	SD	N	Mean	SD
							Correlation ^a
Sleep	12	27	17.6	5.5	23	18.2	5.3
	24	25	17.0	4.8	22	16.9	4.7
	0	30	9.5	5.9	30	9.3	5.0
Beck Depression	12	26	8.3	4.4	23	8.7	5.1
	24	24	7.3	4.7	22	8.8	5.7
	0	30	12.4	8.7	30	11.0	5.9
Beck Anxiety Index	12	27	11.4	9.4	23	8.6	6.0
	24	25	9.4	7.8	22	8.5	6.5
	0	28	15.8	13.6	29	11.4	7.5
	12	27	11.9	12.1	23	11.1	7.9
	24	25	11.2	12.1	22	8.9	8.4

*HVLT*Hopkins Verbal Learning Test Revised, *COWA* Controlled Oral Word Association, *ROCF-m* Rey-Osterrieth Complex Figure-Modified

^aPearson correlation with baseline

Table 3

Estimated means and treatment effects for cognitive outcomes at 24 weeks based on a repeated measures mixed effects model

	Placebo LS mean (SE)	Donepezil LS mean (SE)	Difference in LS means (95 % CI)
HVLT—Total Recall	22.9 (1.22)	25.7 (1.34)	2.78 (0.23, 5.34) *
HVLT—Delayed Recall	8.3 (0.55)	8.8 (0.60)	0.44 (−0.70, 1.57)
HVLT—Recognition	11.1 (0.31)	11.3 (0.34)	0.22 (−0.39, 0.84)
HVLT—Discrimination	10.2 (0.37)	11.1 (0.41)	0.89 (0.06, 1.71) *
HVLT—%Savings	93.2 (4.94)	91.4 (5.47)	−1.78 (−12.40, 8.82)
ROCF—Copy	21.6 (0.66)	22.4 (0.73)	0.72 (−0.64, 2.08)
ROCF—Immediate Recall	18.3 (0.83)	19.0 (0.92)	0.72 (−1.08, 2.53)
ROCF—Delayed Recall	18.3 (0.85)	18.2 (0.94)	−0.19 (−2.04, 1.66)
Trail Making—Part A Time	28.9 (2.37)	28.0 (2.62)	−0.94 (−5.72, 3.83)
Trail Making—Part B Time	70.4 (6.71)	77.1 (7.44)	6.66 (−7.62, 20.94)
COWA—Total Words	37.9 (2.26)	38.9 (2.55)	0.96 (−3.46, 5.37)
Digit Span—Forward	10.8 (0.43)	11.1 (0.47)	0.30 (−0.54, 1.14)
Digit Span—Backward	7.1 (0.46)	7.0 (0.51)	−0.10 (−0.96, 0.76)
Digit Span—Total	18.0 (0.71)	18.2 (0.79)	0.22 (−1.21, 1.64)
Grooved Pegboard—Dominant Hand (s)	80.0 (3.57)	79.4 (3.93)	−0.58 (−9.12, 7.97)
Grooved Pegboard—Non-Dominant Hand (s)	86.5 (5.19)	92.4 (5.78)	5.83 (−4.75, 16.41)

HVLT Hopkins Verbal Learning Test Revised, *COWA* Controlled Oral Word Association, *TMT-A*, *TMT-B* Trail Making Test A and B, *ROCF-m* Rey–Osterrieth Complex Figure-Modified, *DST* Digit Span Test, *GP* Grooved Pegboard

* p -value<0.05