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# Quality of life of irradiated brain tumor survivors treated with donepezil or placebo: Results of the WFU CCOP research base protocol 91105

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**Abstract**

**Background:** The health-related quality of life (HRQL) and fatigue of brain cancer survivors treated with donepezil or placebo for cognitive symptoms after radiation therapy were examined.

**Methods:** One hundred ninety-eight patients who completed >30 Gy fractionated whole or partial brain irradiation at least 6 months prior to enrollment were randomized to either placebo or donepezil (5 mg for 6 weeks followed by 10 mg for 18 weeks) in a phase 3 trial. A neurocognitive battery, the Functional Assessment of Cancer Therapy-Brain (FACT-Br) and the Functional Assessment of Chronic Illness Therapy (FACIT)-fatigue, was administered at baseline, 12 weeks, and 24 weeks.

**Results:** At 12 weeks, donepezil resulted in improvements in only emotional functioning ($P = .04$), with no significant effects at week 24. Associations by level of baseline cognitive symptoms (above or below the median score of the baseline FACT-Br "additional concerns/brain" subscale), indicated that participants with more baseline symptoms who received donepezil versus placebo, showed improvements in social ($P = .02$) and emotional well-being ($P = .038$), other concerns/brain ($P = .003$) and the FACT-Br total score ($P = .004$) at 12 weeks, but not 24 weeks. However, participants with fewer baseline symptoms randomized to donepezil versus placebo reported lower functional well-being at both 12 ($P = .015$) and 24 weeks ($P = .009$), and greater fatigue ($P = .02$) at 24 weeks.

**Conclusions:** The positive impact of donepezil on HRQL was greater in survivors reporting more baseline cognitive symptoms. Donepezil had significantly worse effects on fatigue and functional well-being among participants with fewer baseline symptoms. Future interventions with donepezil should target participants with more baseline cognitive complaints to achieve greater therapeutic impact and lessen potential side effects of treatment.

**Key words**

brain cancer | cognition | donepezil | quality of life | radiation

Declines in cognitive function are commonly reported among cancer patients and survivors. These changes may be a result of the cancer itself or a consequence of specific types of cancer treatments.[1] Chemotherapy[2,3] and radiotherapy[4–6] have been associated with cognitive declines, with the impact varying by the type of cancer, treatment site, stage of cancer, comorbidities, and age of the patient.[7] For some individuals, these changes dissipate over time, but for others, cognitive impairments are sustained, leading to declines in health-related quality of life (HRQL) and daily functioning.

Brain cancers pose particular challenges in the balance between effective treatment and the preservation of cognitive function. Many patients with primary brain tumors or brain metastases will receive whole or partial brain irradiation, as well as chemotherapy and/or surgery. Brain irradiation, particularly near the hippocampal region, has resulted in cognitive impairments, most particularly related to learning and memory.[4,5] Cognitive changes associated with irradiation occur in the majority of patients, with some of the more common HRQL impacts being pain, sleep disturbances, fatigue, mood changes, reduced physical functioning, and limitations in social and role functioning.[6,8–12] Depressive symptoms and fatigue, in particular, have been strongly associated with radiotherapy and decreased HRQL and cognitive functioning among brain tumor patients.[9,12–17] Interventions to alleviate these disease and treatment effects are major priorities in the care of patients with brain tumors and metastases.[7]

Prior studies have shown positive results for medications affecting neurotransmitters, including memantine and donepezil, for the treatment of cognitive symptoms in brain tumor patients and survivors.[18,19] Donepezil hydrochloride is a piperdine derivative that reversibly inhibits acetylcholine esterase (AChE); it is highly selective for AChE and well-tolerated.[20] Donepezil has demonstrated efficacy with moderate-to-severe Alzheimer's disease.[21,22] Donepezil has also improved cognitive functioning in patients with Parkinson's disease,[23] multiple sclerosis,[24] and traumatic brain injury,[25] as well as in healthy young adults.[26] In addition to the known direct effects on neuronal function, donepezil also increases cerebral perfusion in brain regions critical to cognitive processing.[27]

Building on previous studies, we conducted a phase 3 randomized, placebo-controlled trial to determine whether 24 weeks of treatment with donepezil compared to placebo would improve overall cognitive functioning in adult brain tumor survivors who had completed a course of either partial or whole brain irradiation ≥6 months prior to enrollment. The primary results of this trial indicated that after 24 weeks of treatment, overall cognitive composite scores did not differ significantly between groups ($P$ = .48).[28] However, significant differences favoring donepezil were observed for memory (recognition, $P$ = .027; discrimination, $P$ = .007), and motor speed and dexterity ($P$ = .016). Significant interactions between pretreatment cognitive function and treatment were also found for the overall cognitive composite score ($P$ = .01), immediate recall ($P$ = .05), delayed recall ($P$ = .004), attention ($P$ = .01), visuomotor skills ($P$ = .02), and motor speed and dexterity ($P$ < .0001). Participants who had poorer cognitive performance at baseline benefitted more from donepezil than participants with better baseline cognitive performance.

This paper summarizes the impact of donepezil on the secondary outcomes of this trial, survivors' HRQL and fatigue.

## Materials and Methods

### Participants

Patients were recruited to the Wake Forest CCOP protocol 91105 between February 2008 and December 2011. Participants included nonpregnant, adult (≥18 years), primary or metastatic brain tumor survivors who had completed a course of fractionated partial or whole brain irradiation of ≥30 Gy at least 6 months prior to enrollment, and who had no imaging evidence of disease progression within the previous 3 months. Enrolled participants had a life expectancy greater than 6 months, with an Eastern Cooperative Oncology Group (ECOG) score between 0 and 2. Survivors could not be currently using cognition-enhancing medications, nor have any planned cancer treatments for the next 6 months.

Participants were enrolled at 2 academic medical centers (Wake Forest University Baptist Medical Center, Winston-Salem, NC and the M.D. Anderson Cancer Center, Houston, TX); 3 Cancer Trial Support Unit sites; and 21 Community Clinical Oncology Programs (CCOPs) affiliated with the NCI-approved Wake Forest CCOP Research Base (http://www.wakehealth.edu/cancer/researchbase). This protocol was approved by the institutional review board (IRB) at the Wake Forest University Medical School (IRB# 00000551). Participating CCOP member sites were required to obtain IRB approval at their home institutions prior to opening the trial at their respective sites. This trial is registered at the U.S. National Institutes of Health on ClinicalTrials.gov (identifier: NCT00369785).

Consented participants were randomized to a double-blind, placebo-controlled, phase 3 clinical trial in which eligible participants were assigned with equal probability to receive a single daily 5 mg dose of donepezil for 6 weeks, which was escalated to 10 mg/day for 18 weeks if well tolerated, or matching placebo. Only 3% of patients were not escalated to 10 mg/day. Drug and placebo were overencapsulated and distributed to the study sites by Biologics Inc., Raleigh, NC. Participants completed the outcome measures at baseline, and at 12 and 24 weeks, at which time active treatment was terminated. More detailed information about the main trial study procedures is available elsewhere.[28]

### Measures

The following measures were assessed:

#### *Demographic Characteristics*

Information was obtained from the participants on their age, race/ethnicity, marital status, educational attainment, and employment status at study baseline.

### *Clinical Characteristics*

Data on the participants' brain cancer, including tumor type (primary or metastatic) and location, sites of metastases, and specifics of radiation treatment, were completed by medical chart review at the participants' recruitment sites. Body mass index and ECOG performance status were assessed by clinic staff at baseline.

### *Functional Assessment of Cancer Therapy—Brain (FACT-Br)*

HRQL was assessed by the Functional Assessment of Cancer Therapy-Brain (FACT-Br) questionnaire, which has established reliability and validity.[29] This measure consists of 5 subscales: physical well-being (range: 0–28), social well-being (range: 0–28), emotional well-being (range: 0–24), functional well-being (range: 0–28), and the "additional concerns/brain" subscale (range: 0–76), consisting of symptoms related specifically to brain cancer and its treatment, predominantly cognitive symptoms. Individual scores are calculated for all subscales, as well as a total FACT-Br score comprised of items from all 5 subscales. Higher scores indicate better functioning on the total and all subscale scores.

### *Fatigue*

The 13-item Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) scale assesses symptoms of fatigue over the past 7 days, with a score range of 0 to 52.[30] Higher scores indicate lower levels of fatigue. The FACIT-F has established reliability and validity.[30]

### *Cognitive function*

The cognitive function of the participants was measured by a battery of validated instruments. Verbal learning and memory were assessed with the *Hopkins Verbal Learning Test-Revised* (HVLT-R).[31] HVLT-R variables include learning [Total Recall (TR) = sum of 3 learning trials; score range: 0–36], memory [Delayed Recall (DR) = trial 4; score range: 0–12 and %Savings (%S) = [(DR/highest of last 2 learning trials) x 100]; score range ≥0], recognition memory [True Positives (TP); score range: 0–12], and discrimination [Discrimination (Discrim) = true positives minus false positives; score range: -12–12]. The modified *Rey-Osterreith Complex Figure* (mROCF)[32] assessed visuomotor skills (mROCF-Copy; score range 0–24), immediate figural recall (mROCF-IR; score range: 0–24) and delayed figural recall (mROCF-DR; score range 0–24). The *Trail Making Test-Parts A and B*[33] assessed attention (TMT-A) and executive function (TMT-B). Verbal fluency was assessed with the *Controlled Oral Word Association* test (COWA).[34] Concentration and working memory were measured with the *Digit Span* test (DS) [Forward (DSF; score range: 0–14), Backward (DSB; score range: 0–14), and DS-Total (DSF + DSB; score range 0–28)], a subtest of the Wechsler Adult Intelligence Scale-III.[35] Motor speed and dexterity were measured with the *Grooved Pegboard* (GP)[36] for the dominant hand (GP-D) and the nondominant hand (GP-ND).

A summary *Cognitive Composite* score (CC) was computed by standardizing (z-scores) 8 individual test scores representing the major cognitive domains (HVLT-TR, HVLT-DR, mROCF-DR, DS-Total, COWA, TMT-A, TMT-B, and GP-D) using the pretreatment overall means and standard deviations. The negative of the TMT-A, TMT-B, and GP-D standardized scores were used in calculating the composite scores. Additionally, log transformations were used on the TMT-A and TMT-B scores (prior to standardizing) due to skewness in the original distributions.

### *Depression*

The *Patient Health Questionnaire (PHQ-9)* was used to assess depressive symptoms. It is a self-report instrument for screening, diagnosing, and monitoring depressive symptoms.[37] It incorporates Diagnostic and Statistical Manual of the American Psychiatric Association diagnostic criteria (DSM-IV), and is comprised of 9 items, including a question on suicidal ideation. Scores range from 0 to 27, with higher scores indicating greater levels of depression. The PHQ-9 is also currently recommended by the American Society of Clinical Oncology as a screening and diagnostic tool for depressive symptoms among cancer patients.[38]

## Statistical Analyses

The primary objective of this randomized trial was to assess the effect of donepezil on global and domain-specific cognitive performance following 24 weeks of therapy. A secondary objective, which is the focus of this paper, was to assess the effect of donepezil on the HRQL (ie, FACT-Br total score and the "additional concerns/brain" subscale) and fatigue (FACIT-fatigue total score) of the participants. For completeness, we also assessed the effect of donepezil on the other FACT-Br subscales. All participants who provided any postrandomization HRQL or fatigue data were used in the analyses. Each outcome was assessed at the .05 level of significance. We did not adjust for multiple comparisons, given that these were secondary and exploratory analyses.

Patients enrolled in this trial were stratified by accruing site (academic vs CCOP sites) and type of radiation (whole vs partial), and assigned within strata to receive donepezil or a placebo with equal probability using variably sized permuted block randomization. The planned sample size of 200 was determined to provide sufficient power for detecting an effect of donepezil on the primary outcome (ie, the cognitive composite measure).[28] Power calculations done at that time indicated that we had greater than 80% power for detecting 10% or greater relative differences in the additional concerns/brain subscale and the overall FACT-Br score. A repeated measures mixed effects model was used to assess treatment differences in HRQL and to obtain least squares estimates of the measures over time. We included the following covariates in addition to the treatment indicator: the baseline value of the outcome being analyzed, strata, age (years), baseline composite cognitive score, baseline PHQ score, race (Non-Hispanic White vs other), gender, ECOG performance status, and education (≤high school, some college, ≥college). An unstructured covariance

**Table 1** Demographic and clinical characteristics by treatment group

| Characteristic | Donepezil No. (%) | Control No. (%) |
|---|---|---|
| **Total N** | 99 (100) | 99 (100) |
| ***Age, years*** | | |
| Median (range) | 56 (19–84) | 54 (19–81) |
| Age ≥ 50 | 58 (59) | 61 (62) |
| ***Sex*** | | |
| Female | 56 (57) | 50 (51) |
| Male | 43 (43) | 49 (49) |
| ***Race*** | | |
| Hispanic | 1 (1) | 0 (0) |
| Asian | 1 (1) | 0 (0) |
| African-American | 7 (7) | 9 (9) |
| Non-Hispanic White | 90 (91) | 90 (91) |
| ***Marital Status**** | | |
| Single | 12 (12) | 10 (10) |
| Married/Married-like | 66 (67) | 73 (74) |
| Separated/Divorced/ Widowed | 21 (21) | 15 (15) |
| ***Education**** | | |
| ≤ High school graduation | 29 (29) | 33 (34) |
| Vocational / Some college | 39 (39) | 40 (42) |
| College degree or higher | 31 (31) | 23 (24) |
| ***Income**** | | |
| < U.S. $20 K | 31 (36) | 34 (42) |
| U.S. $20–50 K | 31 (36) | 27 (33) |
| U.S. $50+ K | 24 (28) | 20 (25) |
| **Work Outside Home*** | 28 (28) | 31 (32) |
| ***Months since Diagnosis*** | | |
| Median (range) | 37.7 (7.3–298.4) | 39.9 (8.8–423.2) |
| ≥ 36 months from diagnosis | 51 (52) | 55 (56) |
| ***Body Mass Index*** | | |
| Median (range) | 27.2 (17.3–49.4) | 27.9 (18.4–41.1) |
| Underweight and normal, < 25 | 36 (36) | 28 (28) |
| Overweight, 25–29.9 | 31 (31) | 36 (36) |
| Obese, ≥ 30+ | 32 (32) | 35 (35) |
| ***ECOG Performance Status*** | | |
| 0 | 49 (49) | 45 (45) |
| 1 | 46 (46) | 48 (48) |
| 2 | 4 (4) | 6 (6) |
| ***Diagnosis*** | | |
| Primary brain tumor | 65 (66) | 65 (66) |
| Brain metastasis | 27 (27) | 26 (26) |
| PCI | 7 (7) | 8 (8) |
| ***Primary Tumor Type (N = 65/group)*** | | |
| Glioblastoma multiforme | 15 (23) | 8 (12) |
| Anaplastic astrocytoma | 4 (6) | 10 (15) |
| Anaplastic oligodendroglioma | 8 (12) | 8 (12) |
| Anaplastic oligoastrocytoma | 2 (3) | 1 (2) |
| Anaplastic ependymoma | 3 (5) | 1 (2) |
| Anaplastic mixed glioma | 0 (0) | 1 (2) |
| Low-grade astrocytoma | 5 (8) | 1 (2) |
| Low-grade oligodendroglioma | 5 (8) | 8 (12) |
| Low-grade oligoastrocytoma | 0 (0) | 1 (2) |
| Meningioma | 13 (20) | 9 (14) |
| Pilocycstic astrocytoma | 2 (3) | 4 (6) |
| Other | 8 (12) | 13 (20) |
| ***Metastasis Site (N = 34 per group)*** | | |
| Lung | 19 (57) | 21 (62) |
| Breast | 9 (27) | 7 (21) |
| Other / Unknown | 6 (18) | 6 (18) |
| ***Strata*** | | |
| 1—Whole brain, WFU | 10 (10) | 10 (10) |
| 2—Whole brain, CCOP | 30 (30) | 30 (30) |
| 3—Partial brain, WFU | 30 (30) | 30 (30) |
| 4—Partial brain, CCOP | 29 (29) | 29 (29) |

* Some missing data.

**Abbreviations:** CCOP, Community Clinical Oncology Program sites; ECOG, Eastern Cooperative Oncology Group; K, $1000; PCI, prophylactic cranial irradiation; WFU, Wake Forest University.

matrix was used to model the correlation in outcomes over time. Linear contrasts within the mixed models were used to assess the effect of donepezil at 12 and 24 weeks.

## Results

Study participants were predominantly in their 50s and 60s, Non-Hispanic White, and married or partnered (Table 1). More females were recruited than males, and the majority had achieved some posthigh school education. Most participants had ECOG scores of 0 to 1, 66% had primary brain tumors, 27% had brain metastases, and 8% received prophylactic cranial irradiation. The median time since diagnosis was 38 months (range: 7–423 months). There were no significant differences between the treatment and placebo groups on any demographic or clinical characteristic at baseline.

Study retention was 79% at 12 weeks and 74% at 24 weeks, and did not differ between groups ($P = .75$). Of the 46 people who did not complete all 24 weeks of treatment, the reasons for study dropout were: asked to be dropped from the study following initiation (n = 15), toxicity (n = 10), disease progression (n = 8), physician decision (n = 5), patient deaths (n = 3), and "other" (n = 11). Self-reported adherence to treatment (mean percent ideal dose), based on pill diaries fashioned in the image of monthly calendars, was 92% for participants receiving donepezil and 91% for those

receiving placebo ($P$ = .73) while on therapy. Clinical staff at the recruiting sites worked with individual patients who were having trouble with pill adherence, as identified by the monthly pill diaries or self-report. Donepezil was well-tolerated. The most common toxicity reported was fatigue (58% donepezil, 67% placebo; $P$ = .24), but only diarrhea was significantly different between groups (donepezil 25%, placebo 9%; $P$ = .005). Of the 153 patients who returned diaries and stayed in the study longer than 6 weeks, only 4 (3%) did not have their dose of donepezil escalated to 10 mg/day.

Means were calculated for the FACT-Br total score and all subscales and the FACIT-Fatigue by treatment arm and assessment point (Table 2). Higher scores indicate better functioning. In general, functioning was moderately high with baseline means for the total sample of 22.4 (social), 19.5 (functional), 18.7 (emotional), 22.0 (physical well-being), 50.5 (additional concerns/brain subscale), and 132.5 (total FACT-Br). None of the baseline HRQL measures differed significantly between arms.

Mixed effects regression analysis was used to assess changes in quality of life scores by treatment arm from baseline to 12 and 24 months after adjustment for baseline characteristics (Table 3). The covariates included treatment group assignment, baseline outcome measure, baseline cognitive composite score, baseline PHQ score, randomization strata, age, sex, race, ECOG performance status, and education. For the total sample, only the social well-being scale differed significantly between groups at 12 weeks ($P$ = .04). Participants who received donepezil reported higher emotional well-being than those who received placebo. However, there were no significant differences on any scale/subscale score at 24 weeks.

**Table 2** Summary of FACT-Br total and subscale scores and FACIT-Fatigue scores by treatment arm and assessment point

| | | Study Arm | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Donepezil | | | | | | Control | | | | | |
| | | N | Mean | SD | Median | Min | Max | N | Mean | SD | Median | Min | Max |
| **Social Subscale* (range: 0–28)** | **Time 0** | 99 | 21.6 | 5.5 | 23.0 | 6.0 | 28.0 | 98 | 22.7 | 4.7 | 24.0 | 4.0 | 28.0 |
| | **12** | 78 | 22.8 | 4.9 | 24.0 | 7.0 | 28.0 | 79 | 22.2 | 5.6 | 24.0 | 0.0 | 28.0 |
| | **24** | 72 | 22.8 | 6.1 | 25.0 | 2.0 | 28.0 | 73 | 22.5 | 5.1 | 24.0 | 6.0 | 28.0 |
| **Emotional Subscale (range: 0–24)** | **Time 0** | 98 | 18.8 | 4.1 | 19.0 | 6.0 | 24.0 | 98 | 18.6 | 4.4 | 19.0 | 4.0 | 24.0 |
| | **12** | 78 | 19.4 | 3.6 | 20.0 | 10.0 | 24.0 | 79 | 18.3 | 4.7 | 19.0 | 4.0 | 24.0 |
| | **24** | 72 | 19.3 | 4.2 | 20.0 | 3.0 | 24.0 | 73 | 19.2 | 3.9 | 20.0 | 7.0 | 24.0 |
| **Physical Subscale (range: 0–28)** | **Time 0** | 99 | 22.3 | 4.6 | 23.0 | 10.0 | 28.0 | 98 | 21.2 | 5.2 | 22.6 | 5.0 | 28.0 |
| | **12** | 78 | 22.9 | 4.6 | 23.2 | 9.0 | 28.0 | 79 | 21.9 | 5.0 | 23.0 | 5.0 | 28.0 |
| | **24** | 72 | 23.0 | 4.7 | 24.0 | 4.0 | 28.0 | 73 | 22.0 | 4.9 | 23.0 | 7.0 | 28.0 |
| **Functional Subscale (range: 0–28)** | **Time 0** | 98 | 19.2 | 5.8 | 20.0 | 4.0 | 28.0 | 98 | 19.3 | 6.0 | 20.0 | 3.0 | 28.0 |
| | **12** | 78 | 19.5 | 5.8 | 21.0 | 4.0 | 28.0 | 79 | 19.2 | 5.9 | 19.0 | 3.0 | 28.0 |
| | **24** | 72 | 20.1 | 5.6 | 20.0 | 7.0 | 28.0 | 72 | 19.8 | 6.2 | 20.0 | 4.0 | 28.0 |
| **Additional Concerns (range: 0–78)** | **Time 0** | 99 | 50.5 | 11.4 | 51.0 | 26.0 | 73.0 | 98 | 50.5 | 11.3 | 51.5 | 22.2 | 74.0 |
| | **12** | 78 | 53.9 | 11.2 | 53.0 | 23.0 | 74.0 | 79 | 51.9 | 13.2 | 52.0 | 22.0 | 75.0 |
| | **24** | 72 | 54.8 | 11.9 | 55.5 | 30.0 | 75.0 | 72 | 53.3 | 11.9 | 54.8 | 24.0 | 75.0 |
| **FACT-Br Total Score** (range: 0–184)** | **Time 0** | 98 | 132.5 | 24.8 | 134.5 | 72.0 | 177.0 | 98 | 132.4 | 24.2 | 131.0 | 68.0 | 178.8 |
| | **12** | 78 | 138.4 | 24.5 | 144.0 | 66.0 | 182.0 | 79 | 133.5 | 28.5 | 135.2 | 49.2 | 180.0 |
| | **24** | 72 | 140.0 | 27.1 | 143.0 | 69.0 | 179.0 | 72 | 137.0 | 26.4 | 141.9 | 66.0 | 180.0 |
| **FACIT-Fatigue (range: 0–52)** | **Time 0** | 99 | 35.2 | 11.1 | 36.0 | 6.0 | 52.0 | 98 | 33.4 | 11.3 | 34.0 | 5.0 | 52.0 |
| | **12** | 78 | 37.7 | 10.3 | 40.0 | 9.8 | 52.0 | 79 | 35.7 | 11.0 | 38.0 | 8.0 | 52.0 |
| | **24** | 72 | 38.8 | 11.0 | 41.0 | 7.0 | 52.0 | 72 | 37.6 | 10.8 | 41.0 | 6.0 | 52.0 |

* Higher scores indicate better functioning for all subscale and total scores
** FACT-Br: total score of the social, emotional, physical, functional and brain subscale scores

**Table 3** Mixed model estimates at 12 and 24 weeks, overall and by the median split of the baseline FACT-Br additional concerns/brain subscale score: adjusted for trial-related factors and demographic and clinical characteristics*

| Outcome | *Overall* | | | *Greater Symptoms* | | | *Fewer Symptoms* | | |
|---|---|---|---|---|---|---|---|---|---|
| | **Donepezil** | **Control** | | **Donepezil** | **Control** | | **Donepezil** | **Control** | |
| | LSM (SE) | LSM (SE) | *P* value | LSM (SE) | LSM (SE) | *P* value | LSM (SE) | LSM (SE) | *P* value |
| **Social** | | | | | | | | | |
| 12 weeks | 23.1 (0.41) | 22.0 (0.41) | .055 | 22.5 (0.68) | 20.1 (0.70) | **.020** | 23.5 (0.49) | 24.0 (0.48) | .480 |
| 24 weeks | 23.1 (0.42) | 22.2 (0.42) | .143 | 21.5 (0.65) | 20.7 (0.68) | .416 | 24.4 (0.51) | 23.8 (0.49) | .407 |
| **Emotional** | | | | | | | | | |
| 12 weeks | 19.4 (0.29) | 18.5 (0.29) | **.040** | 17.8 (0.44) | 16.4 (0.45) | **.038** | 21.0 (0.38) | 20.6 (0.38) | .476 |
| 24 weeks | 19.4 (0.30) | 19.4 (0.30) | .947 | 17.8 (0.49) | 17.6 (0.50) | .715 | 20.9 (0.34) | 21.3 (0.33) | .511 |
| **Physical** | | | | | | | | | |
| 12 weeks | 22.5 (0.33) | 22.5 (0.33) | .981 | 20.6 (0.51) | 20.7 (0.54) | .911 | 24.3 (0.43) | 24.4 (0.42) | .944 |
| 24 weeks | 22.4 (0.37) | 22.5 (0.38) | .865 | 20.6 (0.63) | 20.3 (0.66) | .740 | 24.2 (0.38) | 24.8 (0.37) | .263 |
| **Functional** | | | | | | | | | |
| 12 weeks | 19.4 (0.42) | 19.6 (0.42) | .811 | 17.7 (0.63) | 16.3 (0.65) | .125 | 21.0 (0.56) | 23.1 (0.55) | **.015** |
| 24 weeks | 19.8 (0.42) | 19.9 (0.43) | .935 | 17.6 (0.60) | 16.0 (0.62) | .062 | 21.8 (0.54) | 23.9 (0.53) | **.009** |
| **Brain** | | | | | | | | | |
| 12 weeks | 53.9 (0.76) | 52.2 (0.76) | .115 | 47.7 (1.04) | 43.0 (1.08) | **.003** | 60.2 (1.08) | 61.3 (1.06) | .483 |
| 24 weeks | 54.8 (0.75) | 53.1 (0.76) | .117 | 47.4 (1.07) | 44.8 (1.13) | .105 | 62.4 (1.14) | 61.6 (1.11) | .621 |
| **FACT-Br** | | | | | | | | | |
| 12 weeks | 138.5 (1.47) | 135.0 (1.47) | .094 | 126.5 (2.18) | 117.0 (2.25) | **.004** | 150.1 (1.89) | 153.5 (1.85) | .218 |
| 24 weeks | 139.8 (1.48) | 137.4 (1.49) | .270 | 125.2 (2.19) | 120.0 (2.27) | .108 | 153.6 (2.08) | 155.4 (2.01) | .558 |
| **FACIT-F** | | | | | | | | | |
| 12 weeks | 37.2 (0.70) | 36.8 (0.71) | .647 | 33.5 (1.10) | 30.6 (1.15) | .085 | 40.7 (0.85) | 43.1 (0.84) | .057 |
| 24 weeks | 37.8 (0.76) | 38.4 (0.77) | .588 | 34.0 (1.23) | 32.9 (1.29) | .527 | 41.2 (0.87) | 44.2 (0.84) | **.020** |

*Adjusted for strata, age, sex, Eastern Cooperative Oncology Group (ECOG) Performance Status, education, baseline cognitive composite score, and baseline Patient Health Questionnaire (PHQ)—9 score.
**Abbreviations:** FACT-Br, Functional Assessment of Cancer Therapy-Brain; FACT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; LSM, least squares mean

Given that the main trial results differed by the reported level of the participants' baseline brain/cognitive symptom levels, analyses were also repeated, stratified by scores below and above the median score of the baseline Fact-Br additional concerns/brain subscale. These results indicated that participants with greater baseline symptoms who received donepezil reported significantly better social ($P = .02$) and emotional well-being ($P = .038$), lower additional concerns/brain symptoms ($P = .003$), and better FACT-Br total scores ($P = .004$) than controls at 12 weeks, but not at 24 weeks. However, among those who had fewer reported baseline symptoms on the additional concerns/brain subscale (ie, those with scores above the median of that subscale), those receiving donepezil reported poorer functional well-being at 12 ($P = .015$) and 24 weeks ($P = .009$), and greater fatigue ($P = .02$) at 24 weeks than placebo participants.

## Discussion

This paper assessed the HRQL impact of a daily dose of donepezil or placebo on the cognitive function of adult brain tumor survivors who had been treated with brain irradiation. The main trial results showed that a daily dose of donepezil over 24 weeks could provide benefit to survivors with greater baseline cognitive symptoms.

Results of the HRQL analyses mirrored the results of the main trial to some extent. Among the patient group as a whole, after 12 weeks of treatment, only emotional well-being showed significant improvement among patients receiving donepezil versus placebo. There were also no significant differences between treatment arms at 24 weeks on any HRQL domain or fatigue. However, when participants were dichotomized by their baseline additional concerns/brain subscale scores, patients with scores below the median (ie, more reported baseline cognitive/brain symptoms) showed significant improvement in social and emotional well-being, reduced additional concerns/brain symptoms, and higher Fact-Br total scores at 12 weeks, but not at 24 weeks. Thus, in addition to its impact on improving cognitive function, donepezil had HRQL benefits among those with higher reported cognitive/brain symptoms at baseline. From the study results, the greatest effects occurred during the first 12 weeks of

donepezil treatment and lessened or remained steady over the last 12 weeks of the study.

What was unexpected was that among patients with fewer reported baseline cognitive or brain complaints, those randomized to donepezil reported significantly poorer postrandomization functional well-being at both 12 and 24 weeks, and greater fatigue at 24 weeks. This has not been reported in any prior studies of donepezil in this patient population. It is unclear why patients with fewer baseline symptoms may be detrimentally affected by donepezil. All medications produce some side effects, and it is generally agreed upon that patients should not be prescribed any medication for which there is not a clear indication of benefit. These results suggest that some minimum level of cognitive symptoms needs to be experienced by patients before donepezil is warranted. Patients were enrolled in this trial regardless of their level of baseline cognitive complaints.

Two prior trials of donepezil in brain tumor survivors also found improvements in patients' HRQL over 24 weeks of donepezil treatment. A phase 2 pilot study by Shaw et al[19] reported improvements in social and emotional well-being, and brain-related symptoms, as measured by the FACT-Br, but no change in functional well-being. Correa et al[39] in a small, non-placebo-controlled pilot study, reported significant improvements in social well-being after treatment with donepezil, and a borderline significant improvement in functional well-being.

This study found no significant impact of donepezil on fatigue, except in those participants with fewer reported cognitive symptoms at baseline. Among these participants, donepezil was actually associated with a post-treatment increase in reported fatigue at 24weeks. A prior phase 3 randomized, double-blind, placebo-controlled trial also examined the use of donepezil for the treatment of cancer fatigue.[40] That trial, however, showed no benefit or detriment of the use of donepezil versus placebo for fatigue among a mixed population of cancer patients, primarily breast, gastrointestinal, gynecologic, and lung. In general, improvements in fatigue have been shown in prior studies using stimulants, such as modafinil and methylphenidate, for the treatment of cognitive function and brain symptoms in brain tumor patients.[41,42]

The results of this study were limited by several factors. The choice of the dose of donepezil and duration of treatment were made based on studies with Alzheimer's disease patients, using current standard of care. Greater benefits in cognitive function, with resultant impacts on HRQL, might have occurred with a higher dose of donepezil or longer treatment duration. In a recent international study, donepezil 23 mg/d was associated with significantly greater cognitive benefits than donepezil 10 mg/d in patients with moderate-to-severe Alzheimer's disease.[43] Future research is needed to determine the optimal dosing of donepezil in brain tumor survivors. In addition, multiple comparisons may have led to one or more spurious significant findings. Strengths of this study include its large sample size, compared to previous trials, high levels of adherence and retention, multiple assessments of well-validated cognitive and HRQL measures, and a geographically diverse sample of participants.

In conclusion, in this trial the treatment impact of donepezil on HRQL was greater among survivors with more cognitive/brain symptoms at baseline, with significant improvements reported in social and emotional well-being, brain/cognitive symptoms, and total FACT-Br scores. However, donepezil had a significantly negative effect on functional well-being and fatigue among participants who had fewer cognitive/brain symptoms at baseline, as compared to those receiving placebo. Future interventions with donepezil would benefit from a focus on participants with higher baseline cognitive symptoms to achieve greater therapeutic impact and lessen potential side effects of treatment.

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