



# Treatment of Radiation-Induced Cognitive Decline in Adult Brain Tumor Patients

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## Opinion statement

Patients with either primary or metastatic brain tumors quite often have cognitive impairment. Maintaining cognitive function is important to brain tumor patients and a

decline in cognitive function is generally accompanied by a decline in functional independence and performance status. Cognitive decline can be a result of tumor progression, depression/anxiety, fatigue/sleep dysfunction, or the treatments they have received. It is our opinion that providers treating brain tumor patients should obtain pre-treatment and serial cognitive testing in their patients and offer mitigating and therapeutic interventions when appropriate. They should also support cognition-focused clinical trials.

## Introduction

Cognitive abilities in brain tumor patients can be affected by a myriad of factors: the tumor itself, depression and anxiety, fatigue, sleep dysfunction, pre-brain tumor cognitive baseline (premorbid functioning), pain, and brain tumor treatments themselves (surgery, chemotherapy, and radiation). Most often, attention, working memory, and information processing speed are affected but patients can present with a wide array of cognitive symptoms [1].

Radiation-induced cognitive decline (RICD) is considered a late effect of radiation therapy (RT) occurring in 30% or more of patients alive at 4 months after partial or whole brain irradiation. For those living over 6 months, that number may rise to 50% [2, 3]. Patients with RICD may be unable to continue

working and in severe cases may not be able to live independently. Memantine, donepezil, methylphenidate, and *Ginkgo biloba* have all been utilized as mitigating pharmacologic strategies with modest levels of success [4••, 5••, 6•, 7]. Neurocognitive rehabilitation has been explored as a non-pharmacologic intervention [8•]. Preventative strategies include using radiosurgery (SRS) when appropriate for patients with brain metastases or whole-brain RT with hippocampal avoidance. Cytoprotective agents under investigation include ramipril, fenofibrate, tamoxifen, indomethacin, and pioglitazone [9–14]. Here, we review the pathogenesis, diagnosis/classification, and management of RICD and discuss strategies used to minimize its risk.

## Pathogenesis

Microvascular damage, demyelination, direct damage to neurons and supportive brain parenchymal cells, stem-cell depletion, and changes in the brain microenvironment have all been reported as components of radiation-induced brain injury (RIBI), the histopathologic correlate of RICD [2, 15–38]. RIBI is characterized by multifocal white matter necrosis, neuro-inflammation with reactive microglia and astrocyte activation, and cerebrovascular injury. The cerebrovascular injury creates blood-brain-barrier disruption with perivascular edema, perivascular extracellular matrix accumulation, and haphazard microvascular proliferation. Recent evidence indicates chronic oxidative stress and persistent neuro-inflammation after RT plays a key role in RIBI [13, 39–51]. Inflammation-associated histologic findings include diffuse microglial activation, microglial aggregation at sites of necrosis, and mononuclear perivascular cuffing.

Initially, RICD was heavily attributed to depletion of neural stem cells in the subventricular zone of the hippocampus. More recently, there has been a growing

appreciation for a neuroanatomical target theory which suggests that different regions or substructures within the brain hold unique significance relative to cognitive function and may have differing thresholds for radiation damage [52•].

## Presentation and diagnosis

RICD is a clinical diagnosis and a diagnosis of exclusion. Disease progression, mental health comorbidity, severe fatigue, medication- or infection-induced delirium, and other forms of dementia such as Alzheimer's disease and vascular dementia must be ruled out.

The early-delayed effects of radiation manifest between 1- and 6-month post-RT and may be reversible. They are thought to be a consequence of transient demyelination. Late RICD occurs 6 months or later after RT and is considered progressive and irreversible. It is often characterized by problems with working memory, attention, executive function, cognitive flexibility, and processing speed. Radiographic evidence of white matter damage can support the diagnosis of RICD [53–60]. Hallmark radiographic changes include periventricular hyperintensities on T2-weighted magnetic resonance imaging (MRI) [61], increases in diffusivity, and decreases in fractional anisotropy on diffusion tensor MRI [62–64], and periventricular and subcortical low-density lesions detectable on computed tomography [65]. The degree of radiologically detectable white matter injury is correlated with the extent of cognitive decline.

Neuropsychological assessment is often the key to diagnosing and managing RICD. The Mini-Mental Status Exam (MMSE) was used in some older clinical trials reporting cognitive outcomes in treated brain tumor patients but was subsequently shown to have inadequate sensitivity compared to comprehensive neuropsychological testing [66]. Physicians should refer their patients to board-certified (or board-eligible) neuropsychologists who have experience working with brain tumor patients.

## The value of neuropsychological evaluation

Ideally, neuropsychological assessment occurs at the time of initial diagnosis and before any treatments (including surgery) have been initiated. Cognitive evaluation prior to resection can predict patient outcomes [1] and can help determine whether a preoperative functional MRI, intraoperative language mapping, or transcranial magnetic stimulation may be useful [67]. After treatment with surgery, radiation, chemotherapy, or a combination of all three, serial neuropsychological evaluations following treatment can track treatment-related cognitive decline and can be an early indicator of tumor recurrence (even prior to radiographic progression) [68].

The neuropsychologic evaluation of brain tumor patients should be comprehensive in order to allow for consideration of all factors that may contribute to cognitive functioning (mood, fatigue, pain, and premorbid functioning). The report can be beneficial to patients and their families in a variety of ways. It may prompt the patient's physicians to offer them medications, cognitive rehabilitation, or home health [8•, 69]. A neuropsychologic assessment can also help

determine patient capacity for decision-making, recommendations for driving, care needs, and provide documentation for any necessary disability paperwork [1].

### Key neurocognitive tests and domains evaluated in a comprehensive evaluation

While most neurocognitive tests are marketed as assessing “language” or “memory,” multiple factors can contribute to a single score. For example, the Trail Making Test Part A (TMT-A) is commonly referred to as a test of attention but visual acuity, numeracy, and processing speed all contribute to performance on this test [70]. The Trail Making Test Part B (TMT-B) measures cognitive set-shifting (and is commonly appreciated as a measure of executive functioning) but also requires visual processing and motor speed.

The Digit Span (DS) test measures basic and complex attention (often referred to as working memory). This test is divided into three tasks: forward span, backward span, and numeric sequencing to provide a total score. To measure more complex working memory through the mental manipulation and sequencing of alpha-numeric information, the Letter-Number Sequencing (LNS) test can be used.

The Hopkins Verbal Learning Test-Revised (HVLTR) is used to measure multiple aspects of learning and memory. Containing 12 words that span three semantic categories, this test allows for the measurement of what is referred to as effortful encoding, delayed (free) recall, and yes/no recognition. This allows for the elucidation between overt forgetting and retrieval-based deficit. There are six alternate forms of the HVLTR which allows for repeated administration over short periods of time.

The Controlled Oral Word Association Test (COWAT) is a commonly appreciated measure of phonemic and semantic verbal fluency. Patients are asked to list words beginning with a specific letter of the alphabet and then those belonging to a specific category, which necessitates executive processing and linguistic fluency. The Boston Naming Test (BNT) is used to measure object naming and is exceptionally sensitive to language-dominant hemisphere disruption.

Other commonly used measures include those specifically designed to assess information processing speed such as the Coding and Symbol Search and those designed to assess verbal and visual abstract reasoning such as the Similarities and Matrix Reasoning which are both components of the Wechsler Adult Intelligence Scale, 4th edition (WAIS-IV).

A comparison of the patient’s raw and normalized scores over time can be completed using standard metrics that include a change of 1 standard deviation (SD) from baseline and/or normative data and reliable change indices (RCI) that allows for a correction of practice effects often seen in repeated examination.

## Estimating premorbid functioning, depression, fatigue, and quality of life

Premorbid functioning is assessed through a combination of considerations that includes single-word reading, and educational, occupational, and social demographic predictions, otherwise known as the Barona estimate.

Emotional and behavioral characteristics are measured via self-report questionnaires like the Beck Depression Inventory (BDI -2) and the Beck Anxiety Inventory (BAI). Fatigue is similarly measured via the Fatigue Severity Scale (FSS) and functional activities of daily living can be measured by the Barthel ADL (basic ADL) or the Functional Activities Questionnaire (FAQ; instrumental activities). Cancer-specific questionnaires that assess disease-related quality of life and cancer type-specific symptoms are also available in the public domain and include the FACT-Cog and the FACT-Br.

## Classification of patients with RICD

Although the cognitive effects from brain tumors and their treatment range from mild to severe, there is no accepted classification or phenotyping of cognitive impairment in brain tumor survivors. This stands in stark contrast to the literature on Alzheimer's disease (AD). The concept of mild cognitive impairment (MCI) as a syndrome prodromal to AD and related dementias was introduced over 20 years ago [71]. The National Institute on Aging (NIA) and the Alzheimer's Association (AA) have specified criteria for MCI, dementia, and AD. MCI is defined by the presence of a personal concern regarding a change in cognition and a measured deficit in at least one major cognitive domain with relative preservation of basic and instrumental functional abilities [72]. Additional criteria have been proposed for MCI subtypes that distinguish amnesic from non-amnesic cognitive deficits and single cognitive domain deficits from multi-domain deficits [73]. These criteria have become standard in research and clinical care and have undergone recent updates [74]. Standardized diagnostic criteria for MCI [72, 75] and AD [76–78] have helped to stimulate, organize, and focus research efforts on AD. Our group recently proposed applying slightly modified MCI NIA-AA criteria to cancer survivors with cognitive dysfunction [79–81]. We then retrospectively reviewed patients enrolled on our phase 3 randomized trial of donepezil versus placebo to estimate the prevalence of MCI in brain tumor survivors. We found that two-thirds of post-RT brain tumor survivors met NIA-AA criteria for MCI. Of patients meeting MCI criteria, the majority (58%) were subclassified as amnesic MCI-multiple domain which is the phenotype most commonly associated with AD. Applying this classification schema to patients with RICD does have limitations. In particular, it does not help discern between patients with transient/early decline and those with progressive/late decline. Classification of cognitive impairment in brain tumor patients could lead to improved treatments for RICD and thus should be a research priority for the field.

## Treatment options

Treatment options for RICD can be partitioned into pharmacologic or non-pharmacologic treatments. Pharmacologic treatment options include donepezil, memantine, methylphenidate, armodafinil, and ginkgo biloba. Non-pharmacologic treatments include cognitive rehabilitation and exercise programs.

## Donepezil

Donepezil is an acetyl-cholinesterase inhibitor indicated for mild to moderate Alzheimer's Dementia. A randomized, phase III, open-label, placebo-controlled trial enrolled irradiated brain tumor survivors (at least 6 months after RT) and evaluated cognition before treatment with donepezil or placebo and then after 24 weeks of medication [5••]. This study did not meet its pre-specified primary endpoint (a difference in a cognitive composite score between the treatment group and the placebo group). However, patients randomized to donepezil performed better on measures of verbal and working memory (HVLТ-DR and -IR) as well as a measure of motor speed and dexterity (Grooved Pegboard). There was also an interaction effect between pre-randomization (baseline) cognitive performance and treatment group—patients with poorer initial cognitive functioning benefited more from donepezil across multiple domains and in their cognitive composite scores. Similarly, the quality-of-life analysis of this study showed that patients with greater baseline concern about their cognitive function showed improved quality-of-life based on several scales (compared to placebo), whereas patients with better baseline quality-of-life had a slight decrease in their quality-of-life survey scores with donepezil (versus placebo) [82]. For this reason, donepezil continues to be used in the clinic for patients who have objective memory deficits (particularly if they have deficiencies on the HVLТ) or have at least moderate impairment relative to normative data in multiple domains and feel that their memory concerns are compromising their quality-of-life.

The starting dose of donepezil is 5 mg and after 4–6 weeks, this can be increased to 10 mg daily. Common side effects include headache, urgent and frequent bowel movements, anorexia, weight loss, insomnia, and vivid dreams. Care should be taken when prescribing this to patients with bradycardia, a prolonged QT interval, or severe COPD because increased cholinergic activity can worsen these conditions. Drug interactions or incompatibilities include non-steroidal anti-inflammatory drugs (NSAIDs), cardiac medications like beta-blockers or calcium-channel blockers, or cholinergic agents like pilocarpine.

## Methylphenidate

Methylphenidate is a stimulant approved for treatment of Attention-Deficit Hyperactivity Disorder (ADHD) and ADD. Some patients have greater difficulties in attention (versus memory) and in these patients, a trial of methylphenidate is a reasonable option but there is no data supporting its use as a prophylactic agent. There is data that methylphenidate can improve fatigue, attention, and cognition in children who received WBRT and in patients with chemotherapy-related fatigue [83, 84]. However, a randomized, open-label, placebo-controlled phase III trial of methylphenidate taken during brain RT and for 8 weeks after showed no difference in FACIT-F scores or cognitive measures [6•]. This study was hindered by a higher than expected drop-out rate which may have left it underpowered to detect a true difference.

The starting dose of immediate-release methylphenidate is 5 mg BID which can be increased by 5 to 10 mg increments per week for a maximum of 60 mg/day divided into two or three doses. Common side effects include increased heart rate, blood pressure, or palpitations; agitation, sweating, insomnia, emotionally lability, or psychosis; decreased appetite or weight loss; and decreased peripheral circulation.

Methylphenidate can lower seizure-thresholds so caution should be used in patients with a history of difficult-to-control seizures and is generally not prescribed for patients who are having break-through seizures on medications or. The use of methylphenidate is contraindicated for patients on Monoamine Oxidase Inhibitors (MAOIs). It should not be used in patients with glaucoma or a history of stroke, myocardial infarction, or tachycardia. Methylphenidate can cause anorexia and weight loss so do not prescribe it to patients who already have cancer-related anorexia.

### Armodafinil and modafinil

Armodafinil and its predecessor modafinil are wakefulness-promoting drugs primarily used in the treatment of narcolepsy. In a randomized, placebo-controlled phase II trial, patients with primary brain tumors receiving at least 45 Gy were randomized to armodafinil or placebo during RT and for 1 month after RT. Fatigue, quality-of-life, and cognitive performance were all evaluated [85]. While there was not a significant difference in fatigue scores between groups at 4 weeks after RT, patients with greater baseline fatigue (below the group median) appeared to derive a benefit with improved fatigue levels and higher quality-of-life ratings in those receiving armodafinil compared to placebo.

The starting dose for armodafinil is 150 mg taken once daily. In narcolepsy, doses up to 250 mg daily can be used. However, the phase II trial used 150 mg daily without any dose-escalation. Common side effects include headache, nausea, weight loss, tremor, or dizziness among others. The starting dose of modafinil is 100 mg and can be increased every 3–7 days up to 400 mg daily. Caution should be used in patients with cardiac disease, hepatic impairment, or a history of Tourette's syndrome.

### Cognitive rehabilitation

Cognitive rehabilitation has been shown in a randomized trial to improve subjective and objective neurocognitive performance [8•]. In this study, low-grade glioma survivors with stable disease were randomized to a cognitive rehabilitation program or a wait list. The program consisted of 7 weeks of rehabilitation (which consisted of 6, 2-h sessions with a trained neuropsychologist and a computer-based retraining program) and a booster session 3 months after completion of the rehabilitation program (a telephone call discussing important aspects of retraining). The training focused on compensation mechanisms for impaired attention, memory, and executive function. Immediately after treatment, patients who participated in the rehabilitation program reported improved cognitive functioning on questionnaires but did not perform better on objective measures of cognitive performance. However, after 6 months, the patients who underwent rehabilitation performed objectively better on measures of verbal memory and attention compared to control patients and reported less mental fatigue. This group is currently in the process of validating a computer-based rehabilitation program [86].

## Prevention

### Radiosurgery

Currently, the most effect strategy to prevent RICD is to limit the integral dose of RT to the brain. Stereotactic radiosurgery (SRS) is highly focused radiation

treatment given in a single dose and has supplanted WBRT in patients with a limited number of brain metastases because cognitive decline is less after SRS than after WBRT. In 2009, Chang et al. published the results of a randomized trial of SRS versus WBRT for patients with 1–3 brain metastases which showed less cognitive decline with SRS [87••]. At 4 months, only 24% of patients receiving SRS had declined in their HVLt-R score compared to 52% of patients in the WBRT arm. Overall survival was not different between the two arms. Subsequently, a N0574 (which randomized patients with 1–3 brain metastases to SRS alone or SRS + WBRT) showed a much higher incidence of cognitive decline in the group receiving WBRT than those receiving SRS alone [88••]. Then NCGTGN107C/CEC 3 offered confirmation that cognitive-deterioration-free survival is longer in patients receiving SRS compared to WBRT. In this phase III trial, 194 patients who had undergone resection for a brain metastasis < 5 cm were randomized to postoperative SRS to the surgical cavity or WBRT [89••]. At 6 months, 52% of patients receiving SRS had cognitive decline compared with 85% of the patients receiving WBRT. Again, there was no difference seen in survival between the two groups. This was a landmark trial and will likely serve as a benchmark and historical control study for some years to come.

### Hippocampal avoidance

The hippocampus has been recognized as a key anatomic location for memory for quite some time. After studies showed that metastases to the limbic circuit are rare, the concept of avoiding the hippocampus during WBRT to try to mitigate cognitive side effects evolved and was then tested in the multicenter phase II trial [14]. This trial (RTOG 0933) compared decline in HVLt-DR in patients treated with hippocampal avoidance to the decline in HVLt-DR in historical control patients. An initial report of a trial looking at WBRT plus memantine versus WBRT with hippocampal avoidance plus memantine (CC001) showed that time to cognitive decline was longer in the hippocampal avoidance arm [90••]. There are multiple additional clinical trials underway investigating the utility of hippocampal avoidance in patients with brain metastases from breast cancer, non-small-cell lung cancer, small-cell lung cancer, and glioblastoma.

### Memantine

Memantine is an N-Methyl-D-Aspartate (NMDA) receptor antagonist approved for use in moderate to severe dementia. The NMDA receptor is a voltage-gated glutamate receptor that allow sodium and calcium influx into neurons when activated and holds special significance in synaptic plasticity. However, over-activation of the NMDA receptor has been linked to glucotoxicity (excitotoxic cell death).

A randomized, double-blind, placebo-controlled trial enrolled patients anticipated to receive WBRT for brain metastases. Patients received memantine or placebo during WBRT and after (for a total of 24 weeks) [4••]. The primary endpoint was patient performance on the HVLt-R-DR at 24 weeks. Similar to the donepezil trial, this study was a negative study (there was no statistical difference in HVLt-R-DR scores between memantine and placebo groups at 24 weeks). However, the study was underpowered as only 29% of patients enrolled completed the cognitive evaluation at 24 weeks. On secondary analysis, memantine did delay time to cognitive decline and was well-tolerated. Our

institutional practice is to discuss the use of memantine with patients who require WBRT but who are anticipated to have relatively long survival (e.g., patients with EGFR or ALK-mutated lung cancer or breast cancer with innumerable metastases which preclude the use of SRS). We do not routinely offer it for patients with uncontrolled systemic disease or poor performance status. For patients who have already received RT and have memory deficits that have not improved with donepezil, memantine is also a reasonable option.

The starting dose for memantine is 5 mg. After 1 week, it can be titrated to 5 mg twice daily (BID), then after another week, 10 mg in the morning and 5 mg in the evening (15 mg total) and then after another week, 10 mg BID. Common side effects include headaches, dizziness, drowsiness, confusion, irritability, and constipation. Caution should be used in patients with liver or kidney dysfunction. An abnormal urine pH can lead to decreased drug excretion and higher than anticipated blood levels of memantine.

### Investigational cytoprotective agents

Preclinical data suggests that angiotensin-converting enzyme (ACE) inhibitors such as ramipril taken during RT may protect against RICD by decreasing radiation-induced inflammation [9, 10]. There is an ongoing cooperative group trial investigating its ability to reduce RICD in patients with glioblastoma receiving chemoradiation. Similarly, there is preclinical data that peroxisomal proliferation-activated receptor (PPAR) agonists such as pioglitazone can protect against RICD by via transcriptional inhibition effect on the NF- $\kappa$ B pathway which is a key mediator of the pro-inflammatory cascade triggered by RT. There are emerging data that PPAR- $\gamma$  agonists can be neuroprotective in stroke, Alzheimer's disease and Parkinson's disease [91–95]. An initial safety study of pioglitazone in brain tumor patients has been completed [96] and there are plans for a cooperative group trial evaluating the efficacy of pioglitazone in the prevention of RICD.

## Developing a treatment plan for each patient

For patients with complaints of cognitive changes post-RT, it is imperative to elucidate from the patient and their caregivers whether depression or fatigue are significant issues. If depression and anxiety do not seem to be significant concerns, try to determine their cognitive concerns. Often, it is either short-term/working memory or attention. Review their medication list to see if there are any anti-cholinergic drugs (most often for urinary symptoms), sedating medications (especially things like opioids and gabapentin) which could be contributing to cognitive problems. If this is the case, evaluate how necessary these medications are for the patient and consider reducing or removing them. Progressive disease should be ruled out with imaging. Reversible causes of cognitive changes should be ruled out which generally involves checking B12/folate levels, TSH/free T4, morning cortisol, and testosterone levels (in men).

The next step is usually neuropsychological testing. For high-functioning patients who are working, we recommend comprehensive evaluation. For patients with a lower performance status, an abbreviated testing session with selected tests (see above) may be more appropriate and give you enough information to create a care plan.

Our strategy has been to first address depression and fatigue (see Fig. 1). If the patient acknowledges depression or severe fatigue and the neuropsychologist mentions these factors in their report, then consider starting your patient on anti-depressants. Usually, we start with a serotonin-uptake inhibitor (SSRI). In patients with both depression and severe fatigue, methylphenidate and an SSRI can be started synchronously with methylphenidate acting as a bridge since it can take 6 weeks for the clinical effect of SSRIs to become evident. Be cautious about using the dopamine-norepinephrine reuptake inhibitor bupropion in patients with a history of seizures. If fatigue (without depression) is a key factor, then consider armodafinil or modafinil. These medications should also be used cautiously if the patient has a history of seizures. For patients whose fatigue seems related to sleep dysfunction, it can be helpful to discuss sleep hygiene practices, rule out obstructive sleep apnea, and consider melatonin supplementation.

If depression and fatigue do not appear to be significant factors then try to discern from the report whether measures of working memory (such as the HVLТ), measures of attention (DS and TMT-A), or measures of executive function (COWA and TMT-B) are below normative data. For patients with complaints of short-term memory problems and corresponding low scores on HVLТ-IR and HVLТ-DR, a trial of donepezil or memantine may be appropriate. For patients who complain of attentional difficulties and with deficiencies on DS and TMT-A, a trial of methylphenidate may be appropriate. If you have not prescribed these medications previously, we would advise using a program that

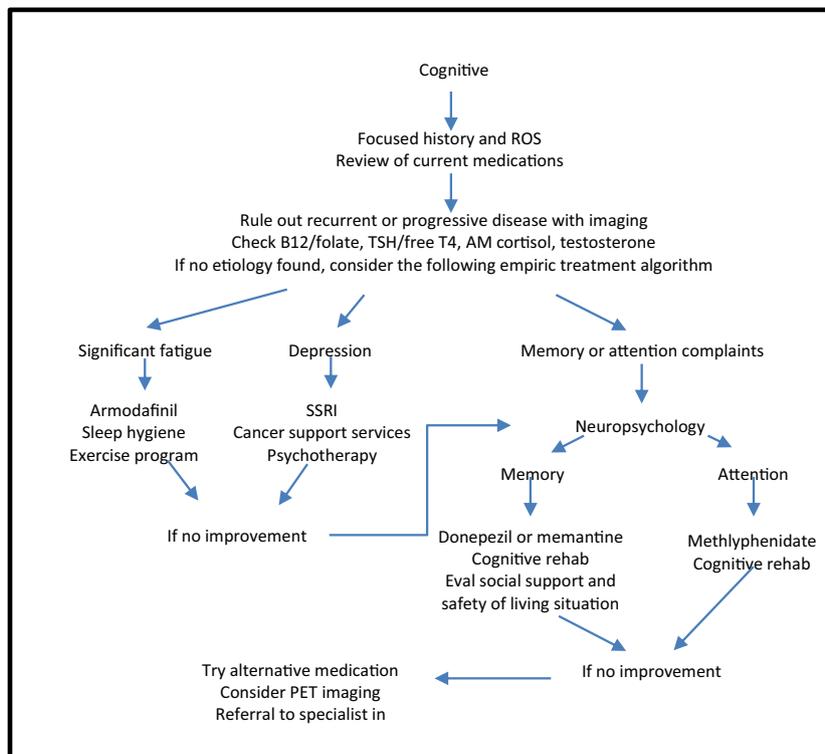


Fig. 1. Treatment algorithm for brain tumor patients with cognitive decline.

checks for drug interactions to confirm that none of the patients' existing medications present a contraindication to the use of the medication you are prescribing.

## Compliance with Ethical Standards

### Conflict of Interest

Christina K. Cramer has received speaker's honoraria from Monteris Medical, and is also a member of teaching faculty for an on-site SBRT training course to which Elekta refers customers and for which Elekta reimburses the department.

Tiffany L. Cummings declares that she has no conflict of interest.

Rachel N. Andrews declares that she has no conflict of interest.

Michael Chan has received speaker's honoraria from Monteris Medical, and is also a member of teaching faculty for an on-site SBRT training course to which Elekta refers customers and for which Elekta reimburses the department. Roy Strowd declares that he has no conflict of interest.

Stephen R. Rapp declares that he has no conflict of interest.

Edward G. Shaw declares that he has no conflict of interest.

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### Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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randomization (baseline) cognitive performance and treatment group—patients with poorer initial cognitive functioning benefited more from donepezil. For this reason, donepezil continues to be used in the clinic.

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This was a randomized, open-label, placebo-controlled phase III trial of methylphenidate taken during brain RT and for 8 weeks after, showed no difference fatigue or cognition between patients taking methylphenidate and those taking placebo. This study was hindered by a higher than expected dropout rate which may have left it underpowered to detect a true difference. There are other smaller studies to support the use of methylphenidate in treating cancer-related fatigue which is why methylphenidate is still used clinically.

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