Putting Evidence Into Practice:
Evidence-Based Interventions for Cancer and Cancer Treatment-Related Cognitive Impairment

Diane Von Ah, PhD, RN, Catherine Jansen, PhD, RN, AOCNS®,
Deborah Hutchinson Allen, MSN, RN, CNS, FNP-BC, AOCNP®,
Rosalina M. Schiavone, BSN, RN, OCN®, and Jennifer Wulff, MN, ARNP, AOCNP®

Cognitive impairment is a clinically complex symptom commonly experienced by cancer survivors. Although research in this area has grown, many questions remain regarding underlying mechanisms, trajectory, and specific interventions nurses can offer patients to prevent, treat, and manage cognitive impairment effectively. As part of the Oncology Nursing Society (ONS) Putting Evidence Into Practice (PEP) initiative, a comprehensive examination of the current literature was conducted to identify effective interventions for cognitive impairment in cancer survivors. The studies were categorized into nonpharmacologic interventions, including complementary and alternative therapies and cognitive training, and pharmacologic interventions, including psychostimulants and erythropoietin-stimulating agents. Using the ONS PEP Weight of Evidence Classification Schema, the levels of evidence for these interventions were consistent with the categories of *effectiveness not established* or *not recommended for practice*. Additional research is needed to identify effective preventive and treatment strategies for cognitive impairment in cancer survivors.

Cognitive impairment is a complex and distressing symptom related to cancer and its treatments. Although the actual prevalence of the symptom is not fully known, reports of cancer-related cognitive impairment prior to the initiation of therapy vary from 11%–35% of patients with breast cancer (Ahles & Saykin, 2007; Hermelink et al., 2007; Hurria et al., 2006; Jansen, Cooper, Dodd, & Miaskowski, 2011; Wefel, Lenzi, Theriault, Davis, & Meyers, 2004), 40% of patients with acute myeloid leukemia (Meyers, Albitar, & Estey, 2005), 46% of patients with testicular cancer (Wefel et al., 2011), 50%–80% of patients with brain tumors (Tucha, Smely, Preier, & Lange, 2000), and 70%–80% of patients with lung cancer (Meyers, Byrne, & Komaki, 1995). Cancer therapies

At a Glance

- Cancer and cancer treatment-related cognitive impairment significantly impact the functional ability and quality of life of cancer survivors.
- Evidence regarding the prevention, treatment, and management of cognitive impairment for cancer survivors is limited.
- Identifing the underlying physiologic mechanisms associated with cognitive impairment in patients with cancer may help the development of effective preventive and treatment strategies.

Diane Von Ah, PhD, RN, is an assistant professor and Robert Wood Johnson Foundation Nurse Faculty Scholar in Adult Health in the School of Nursing at Indiana University in Indianapolis; Catherine Jansen, PhD, RN, AOCNS®, is an oncology clinical nurse specialist in Patient Care Services at Kaiser Permanente in San Francisco, CA; Deborah Hutchinson Allen, MSN, RN, CNS, FNP-BC, AOCNP®, is an advanced practice nurse at Duke University Medical Center in Durham, NC, and a doctoral student at the University of North Carolina at Chapel Hill; Rosalina M. Schiavone, BSN, RN, OCN®, is a treatment nurse at Alta Bates Comprehensive Cancer Center in Berkeley, CA; and Jennifer Wulff, MN, ARNP, AOCNP®, is an advanced practice nurse in the Ben and Catherine Ivy Center for Advanced Brain Tumor Treatment at the Swedish Neuroscience Institute in Seattle, WA. The authors take full responsibility for the content of the article. The research effort was supported by the Robert Wood Johnson Foundation, Nurse Faculty Scholar Program grant #64194 (principal investigator: Von Ah). The content of this article has been reviewed by independent peer reviewers to ensure that it is balanced, objective, and free from commercial bias. No financial relationships relevant to the content of this article have been disclosed by the independent peer reviewers or editorial staff. Mention of specific products and opinions related to those products do not indicate or imply endorsement by the *Clinical Journal of Oncology Nursing* or the Oncology Nursing Society. (First submission January 2011. Revision submitted March 2011. Accepted for publication March 30, 2011.)
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such as surgery, radiation therapy, chemotherapy, hormonal therapy, and immunotherapy also have been associated with changes in cognitive functioning (Jansen, 2010). The type and severity of cognitive impairment, therefore, may vary depending on the location and stage of the cancer; the type, intensity, or combination of treatments; and the patient's progress in the disease trajectory.

Cancer and cancer treatment-related cognitive impairment has been reported to significantly impact the functional ability and quality of life of cancer survivors (Fitch, Armstrong, & Tsang, 2008; Von Ah, Russell, Storniolo, & Carpenter, 2009). In recognition of those affects, the President's Cancer Panel (U.S. Department of Health and Human Services, 2004), National Cancer Institute Office of Cancer Survivorship (Hewitt, Greenfield, & Stovall, 2005), and the Oncology Nursing Society (ONS) (Berger et al., 2009) all have identified emerging chronic and latent effects of cancer and its treatment, including cognitive impairment, as a top research priority. Despite the priority, research in this area is relatively limited and, to date, no evidence-based guidelines for the prevention, treatment, or management of cognitive impairment have been established. Therefore, as part of ONS's Putting Evidence Into Practice (PEP) initiative, the current article comprehensively examines the current literature to identify effective interventions for the prevention, treatment, and management of cognitive impairment for cancer survivors.

Overview of Cognitive Function and Impairment for Cancer Survivors

Cognitive function is the information-handling aspect of human behavior, and involves the following cognitive processes: attention and concentration, executive function, information processing speed, language, visual-spatial skill, psychomotor ability, learning, and memory (Jansen, 2010). Because those processes are inter-related, difficulties in one may disrupt one or several other processes. Therefore, for the current review, cognitive impairment was defined as a decline in function in one or more of these cognitive processes. Cancer survivors commonly describe cognitive impairment in terms of symptoms, such as forgetfulness, memory lapses, difficulty with problem solving, inability to focus and concentrate, and mental slowness. Collectively, these symptoms have been termed chemo fog or chemobrain by patients with cancer (Hess & Insel, 2007); however, the underlying mechanism(s) for how cancer and its treatment impact cognitive functioning is not fully understood.

Ongoing research into the causes of cognitive impairment recently has begun to identify links between cancer, cancer treatment, and changes in cognitive functioning (Vardy, Wefel, Ahles, Tannock, & Schagen, 2008). Because of the complex and myriad physical and psychosocial dynamics associated with cancer and its treatment, isolating specific contributing causes is difficult. Potential underlying mechanisms of cognitive impairment in patients with cancer currently being explored include direct neurotoxic effects, oxidative stress, hormonal changes, immune dysregulation, cytokine release, clotting, and genetic predisposition (Ahles & Saykin, 2007; Dietrich, Han, Yang, Mayer-Pröschel, & Noble, 2006; Vardy et al., 2008). Other symptoms associated with cancer and its treatment, such as anemia, fatigue, sleep disturbance, anxiety, depression, and mood disturbance, also have been correlated with cognitive impairment (Hess & Insel, 2007; Jansen, Miaskowski, Dodd, Dowling, & Kramer, 2005; Von Ah et al., 2009). Risk factors for cognitive impairment are not limited to cancer, its treatment, and associated symptoms, as patient characteristics (e.g., age, educational level, intelligence), as well as other comorbidities or concomitant medications, may influence cognitive changes (Jansen, 2010).

Although the underlying mechanisms of cognitive impairment remain unclear, research exploring its impact has shown dramatic effects on the quality of life of cancer survivors (Ahles & Saykin, 2001; Cull et al., 1996; Mehnert et al., 2007; Reid-Arndt, 2006; Von Ah et al., 2009). In one survey of 471 cancer survivors, 62% stated that cognitive problems were disruptive to their functioning and relationships at home and at work (Hede, 2008). At work, cancer survivors with cognitive impairment have expressed feelings of being overwhelmed and having difficulties with making decisions and multitasking, and others have reported a lack of self-confidence in their overall work performance (Calvio, Peugeot, Bruns, Todd, & Feuerstein, 2010; Munir, Burrows, Yarker, Kalawsky, & Bains, 2010). Associations also have been found between cognitive impairment and poor physical, cognitive, and role functioning in breast cancer survivors who were five years post-treatment (Mehnert et al., 2007). Although cognitive impairment in cancer survivors may indeed appear subtle, the impact on survivors' quality of life, as well as their ability to function in occupational, social, and daily life activities, may be significant (Fitch et al., 2008).

Nurses in hospital, outpatient clinic, and homecare settings are in a prime position to identify and address cognitive impairment in cancer survivors. For that reason, nurses' access to the latest evidence regarding how to address this disruptive and potentially debilitating symptom is imperative. The specific aims of the current article are to (a) provide current evidence regarding the prevention, treatment, and management of cancer and cancer treatment-related cognitive impairment for cancer survivors; and (b) discuss the process and development of the Evidence-Based Interventions for Cancer and Cancer Treatment-Related Cognitive Impairment PEP content from ONS.

Methods

Development of the Process Team

The members of the Cognitive Impairment PEP team consisted of oncology nurses serving in a variety of roles, including three advanced practice nurses (one of whom was the project leader), a nurse researcher, two staff nurses, and two ONS staff members (a researcher and a librarian). The oncology nurse team members were selected by a competitive application process based on their expertise and/or interest in addressing cognitive impairment in cancer survivors. The overriding goal of the team was to critically examine and synthesize the literature on the prevention, treatment, and management of cognitive impairment in cancer survivors.

Search Strategy

An extensive review of the literature regarding cognitive impairment was conducted using ProQuest Nursing Basic, PubMed, CINAHL®, EMBASE, and Cochrane Collaboration. A computerized literature search was conducted using the consolidated problem, intervention, comparison and outcome (PICO) terms (Melnyk & Fineout-Overholt, 2010) (see Table 1). Database searches were performed by all members of the PEP team and pertinent empirical literature was posted to an ONS Web page repository for team review. Bimonthly conference calls among the team members were conducted to facilitate organization, establish guidelines, and coordinate group consensus for project deliverables.

The initial research studies reviewed were published from 2000–2010. Additional manual searches (e.g., bibliographies, reference lists) were conducted and, as a result, some earlier interventional trials were included in the review (Bruera, Miller, Macmillan, & Kuehn, 1992; Cimprich, 1993; Meyers, Weitzner, Valentine, & Levin, 1998). As described earlier, cognitive impairment was defined for the current review as a decline in function in one or more domains of cognitive function, including attention and concentration, executive function, information processing speed, language, visual-spatial skill, psychomotor ability, learning, and memory (Jansen, 2010). The studies selected for the review were limited to those empirical manuscripts that were in English and examined the prevention, treatment, or management of cognitive impairment in adult patients with cancer. Because of the specificity of cognitive and development issues in children, studies focusing on pediatric cognitive impairment were excluded. The final literature search for evidence related to interventions was performed in August 2010.

Critical Review of the Evidence

The Cognitive Impairment PEP team used a systematic approach to reviewing, critiquing, and assigning the level of evidence of the literature. The approach was similar to the process used by previous ONS PEP teams (Damron et al., 2009). The literature was divided into two categories, nonpharmacologic and pharmacologic interventions. Following an initial review of literature in those categories, the team further divided the literature as follows: nonpharmacologic interventions, including complementary and alternative therapies (e.g., vitamin E, exercise, natural restorative environmental interventions) and cognitive training programs; and pharmacologic research, including psychostimulant medications (e.g., dexmethylphenidate [D-MPH], methylphenidate [MPH], modafinil, donepezil) and erythropoietin-stimulating agents (ESAs). To ensure consistency among the team members regarding the review process, the nurse researcher conducted a sample review of one of the empirical journal articles. The critique and summary of each manuscript included the author(s), year of publication, characteristics of the intervention, sample, setting, study design, measures, results, conclusions, and limitations of each study. That important information was recorded in a summary table of the evidence developed by ONS. Next, the PEP team divided the workload to make sure a primary and secondary reviewer was assigned for each of the identified categories. After completion of the table of evidence, each group summarized the findings for their assigned areas and all material was reviewed by the entire team for consensus on the assignment of the level of evidence based on established criteria. The ONS PEP Weight of Evidence Classification Schema (Mitchell & Friese, 2010), based on the work of Ciliska, Cullum, and Marks (2001), Hadorn, Baker, Hodges, and Hicks (1996), Ropka and Spencer-Cisek (2001), and Rutledge, DePalma, and Cunningham (2004), was used as the framework to determine the levels of evidence.

Table 1. Cognitive Impairment Search Terms for Computerized Databases Using PICO Schema

IDENTIFIER	SEARCH TERMS
Patient or problem	Patients with cancer who have cognitive impairment, cognitive deficits, or cognitive dysfunction: changes in attention, chemotherapy-related cognitive changes, concentration, delirium in advanced cancer, executive function, information processing speed, language, memory changes or dysfunction, motor skills, visual-spatial skills
Intervention	**Pharmacologic:** ACE inhibitors, d-methylphenidate, donepezil, erythropoietin, MAO inhibitors, modafinil, statins, stimulants **Nonpharmacologic:** acupuncture, complementary and alternative interventions, energy conservation and restorative activities, environmental interventions, exercise, ginseng, ginkgo biloba, herbals, meditation, memory and adaptation training, neuropsychiatric rehabilitation, vitamins, vitamin E
Comparison	Standard care
Outcome	Improvement in cognitive function: attention, concentration, executive function, information processing and speed, memory, motor skills, visual-spatial skills; energy conservation, improvement in energy or fatigue; improved ability to compensate for memory problems; improvement in quality of life; improvement in self-reported and cognitive test results

ACE—angiotensin-converting enzyme; MAO—monoamine oxidase; PICO—patient or problem, intervention, comparison, outcome

Note. Based on information from Melnyk & Fineout-Overholt, 2010.

Results

A total of 29 studies met the inclusion criteria and were included in the review. The studies were categorized and reviewed as described previously (see Figure 1). The literature has been synthesized and categorized based on the classification schema. Overall, the research to date regarding interventions for the prevention, treatment, and management of cognitive impairment is limited and, consequently, the levels of evidence for the various interventions reviewed were categorized as *effectiveness not established* or *not recommended for practice*.

Effectiveness Not Established

The level of evidence category *effectiveness not established* includes interventions for which insufficient data or data of

Nonpharmacologic Interventions

Complementary and alternative medicine

- **Vitamin E:** Chan et al., 2004; Jatoi et al., 2005[a]
- **Exercise:** Korstjens et al., 2006; Schwartz et al., 2002[a]
- **Natural restorative environmental:** Cimprich, 1993; Cimprich & Ronis, 2003

Cognitive training programs

- Ferguson et al., 2007; Gehring et al., 2009; Locke et al., 2008; McDougall, 2001; Poppelreuter et al., 2009; Sherer et al., 1997

Pharmacologic Interventions

Psychostimulants

- **Methylphenidate:** Bruera et al., 1992; Butler et al., 2007; Gagnon et al., 2005; Lower et al., 2009; Mar Fan et al., 2008; Meyers et al., 1998; Schwartz et al., 2002[a]
- **Modafinil:** Blackhall et al., 2009; Kohli et al., 2009; Lundorff et al., 2009
- **Donezepil:** Jatoi et al., 2005[a]; Shaw et al., 2006

Erythropoietin-stimulating agents

- Chang et al., 2004; Iconomou et al., 2008; Mancuso et al., 2006; Mar Fan et al., 2009; Massa et al., 2006; O'Shaughnessy, 2002; O'Shaughnessy et al., 2005

[a] Study has been listed in two intervention categories.

Figure 1. Research Addressing Cognitive Impairment Interventions in Cancer Survivors

inadequate quality to warrant a practice recommendation currently exists. Most of the studies reviewed were assigned this level of evidence primarily because of lack of sufficient testing (e.g., small samples, one-arm trials) of the interventions. Interventions identified in this category require further examination using well-designed randomized, controlled trials and adequate sample sizes to determine effectiveness.

Nonpharmacologic Interventions

Complementary and alternative medicine: Complementary and alternative medicine (CAM) incorporates various practices and products that are not considered part of conventional medicine. CAM interventions noted in the literature to address cognitive impairment in patients with cancer included the use of vitamin E (Chan, Cheung, Law, & Chan, 2004; Jatoi et al., 2005), exercise (Korstjens, Mesters, van der Peet, Gijsen, & van den Borne, 2006; Schwartz, Thompson, & Masood, 2002), and natural restorative environmental interventions (Cimprich, 1993; Cimprich & Ronis, 2003).

Vitamin E: Alpha-tocopherol (vitamin E) is a fat-soluble antioxidant. Because one proposed mechanism for cancer treatment-induced (e.g., radiation therapy, chemotherapy) cognitive impairment is oxidative stress (Ahles & Saykin, 2007), vitamin E has been suggested as a potential intervention to prevent the production of reactive oxygen. Only two studies examined the effect of vitamin E on cognitive function (Chan et al., 2004; Jatoi et al., 2005). Chan et al. (2004) demonstrated improvements in some domains of cognition (i.e., executive function, verbal memory, and visual memory) for patients who received 1,000 international units (IU) of vitamin E twice daily over one year. Jatoi et al.'s (2005) randomized, double-blinded placebo-controlled study attempted to evaluate the effect of vitamin E 1,000 IU daily in combination with donezepil 5 mg daily on cognition. However, the study ended early because of poor accrual and, therefore, failed to demonstrate a significant effect of vitamin E on cognitive impairment. Because of the lack of well-designed studies with adequate sample sizes, the effectiveness of vitamin E as an intervention for preventing or treating cancer or cancer treatment-related cognitive impairment has not been established. In addition, since the completion of those initial studies to examine the impact of vitamin E on cognitive functioning in cancer survivors, two meta-analyses have been conducted that suggest that doses of vitamin E of 400 IU per day or more are associated with a higher mortality risk (Bjelakovic, Nikolova, Gluud, Simonetti, & Gluud, 2007; Miller et al., 2005). Although additional research into these mechanisms is warranted (Bjelakovic et al., 2007), recommendations exist that high-dose vitamin E as discussed in this review should be avoided (Miller et al., 2005).

Exercise: Exercise has been defined as physical activity that is planned or structured and involves repetitive bodily movement to improve or maintain cardiorespiratory endurance, muscular strength, muscular endurance, flexibility, and body composition (Centers for Disease Control and Prevention, 2011). Two studies examined the impact of exercise on cognitive function as a secondary outcome (Korstjens et al., 2006; Schwartz et al., 2002). The physical exercise interventions used in those studies were not well described, but generally consisted of implementing a structured program including therapist instruction, recommendations, and goals for activities.

Korstjens et al. (2006) evaluated the effects of a 12-week rehabilitation program that combined exercise with a psychoeducational program on various aspects of quality of life, including cognition. Physical exercise sessions overseen by a physiotherapist occurred twice weekly for two hours and included aqua aerobics, group sports, or individual endurance and strength training. The psychoeducational component included seven two-hour sessions focused on coping with cancer. Improvements in global cognitive function were reported based on two items on the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core-30. Similarly, Schwartz et al. (2002) reported improvements in visual attention, motor speed, and cognitive flexibility when combining a 15-minute aerobic exercise program four days a week with methylphenidate 20 mg daily for four months. Although some improvements were reported in cognitive function in these studies, the difference in definition and delivery of the exercise intervention programs, small sample sizes, and study designs (combined multiple interventions) make determining the effect of an exercise intervention on cognitive impairment difficult. Additional studies aimed at examining the singular effect of exercise on cognitive function using objective cognitive measures are needed to fully understand whether the intervention is effective for cognitive impairment.

Natural restorative environmental interventions: Attention-restoring theory identifies that the environment may influence one's ability to concentrate and capacity to direct attention (Cimprich & Ronis, 2003); therefore, natural restorative environmental interventions may replenish psychological reserves and improve cognitive functioning. In fact, multiple studies involving healthy college students have demonstrated that students with access to nature scored better on measures of attentional fatigue than those without (Kaplan, 2001; Kuo & Sullivan, 2001; Tennessen & Cimprich, 1995). Two studies

were found that evaluated the impact of natural restorative environmental intervention on cognitive function in patients with cancer (Cimprich, 1993; Cimprich & Ronis, 2003).

Cimprich (1993) examined the impact of a natural restorative environmental intervention (walking in nature or gardening for 20–30 minutes three times a week) in 32 patients with breast cancer and assessed their level of attention at 3, 18, 60, and 90 days after surgery. Significant and sustained improvement in attentional fatigue scores were noted across all four time periods. Similarly, in a follow-up randomized, controlled trial of 157 patients with breast cancer, Cimprich and Ronis (2003) demonstrated that those who engaged in the natural restorative environmental intervention (home-based program involving 120 minutes of exposure to the natural environment per week) had greater recovery of capacity to direct their attention from pretreatment as compared with the nonintervention group, even after controlling for age, education, attention scores prior to surgery, other health problems, distress, and extent of the surgery. Overall, these two natural restorative intervention studies have been shown to improve the capacity to direct attention in patients with breast cancer prior to adjuvant therapy. Additional longitudinal research is needed to understand its sustainability throughout the treatment trajectory, as well as to test it in other cancer populations.

Cognitive training programs: Cognitive training programs have been defined as "any intervention aimed at improving, maintaining or restoring mental function through the repeated and structured practice of tasks which pose an inherent problem or mental challenge" (Sitzer, Twamley, & Jeste, 2006, p. 75). A total of six intervention studies tested cognitive training programs aimed to improve cognitive function during (Locke et al., 2008) or after completion of cancer-related treatments (Ferguson et al., 2007; Gehring et al., 2009; McDougall, 2001; Poppelreuter, Weis, & Bartsch, 2009; Sherer, Meyers, & Bergloff, 1997). Three studies focused on cancer survivors with primary brain tumors (Gehring et al., 2009; Locke et al., 2008; Sherer et al., 1997). Two studies targeted women with breast cancer (Ferguson et al., 2007; Poppelreuter et al., 2009). The final study examined a small subset of community-dwelling older adults who were diagnosed with cancer (McDougall, 2001). The cognitive training programs reviewed used a variety of methods (e.g., in-person group sessions with trained personnel, individual sessions, computer training programs), but all of them offered concurrent psychoeducational training directed to incorporate compensatory skills into daily function.

Cognitive training interventions were targeted to improve specific cognitive domains (i.e., memory and attention). Improvement in cognitive function (e.g., attention, executive function, psychomotor function, verbal memory) was found in two studies (Ferguson et al., 2007; Gehring et al., 2009). McDougall (2001) also reported improvements in memory, but that was based on a subjective measure. In contrast, other studies (Locke et al., 2008; Poppelreuter et al., 2009; Sherer et al., 1997) did not report any significant changes. Studies evaluating cognitive training programs varied in design, personnel, duration, and post-training follow-up, and most were limited by small sample sizes or lack of a comparison group to establish effectiveness; therefore, additional studies are warranted before cognitive training programs can be determined as effective and recommended for incorporation into practice.

Pharmacologic Interventions

Psychostimulants: The majority of intervention studies have focused on pharmacologic approaches to address cognitive impairment in cancer survivors. These studies predominately have evaluated D-MPH or MPH; however, a few additional studies have tested modafinil and donezepil. Although all of these medications fall into the category of psychostimulant medications, the evidence for each medication was reviewed separately.

Dexmethylphenidate and methylphenidate: D-MPH and MPH (Focalin®, Ritalin®) are stimulants used primarily in the treatment of attention deficit hyperactivity disorder for children. Seven studies were found that examined the use of D-MPH or MPH in the treatment of cognitive impairment in patients with cancer (Bruera et al., 1992; Butler et al., 2007; Gagnon, Low, & Schreier, 2005; Lower et al., 2009; Mar Fan et al., 2008; Meyers et al., 1998; Schwartz et al., 2002). Three small studies, using a starting daily dose of 10 mg in patients with advanced cancer, demonstrated an improvement in alertness and various cognitive domains, including attention, memory, executive functioning, and psychomotor function (Bruera et al., 1992; Gagnon et al., 2005; Meyers et al., 1998). As noted earlier, Schwartz et al. (2002) combined MPH 20 mg daily with an exercise program and reported some improvements in cognitive function. In contrast, three studies did not demonstrate any improvement in cognition (Butler et al., 2007; Lower et al., 2009; Mar Fan et al., 2008). Overall, studies evaluating the impact of MPH on cognitive function in cancer survivors produced mixed results and were limited significantly by small sample sizes, failure to recruit participants, and high attrition rates.

Modafinil: Modafinil (Provigil®) is a psychostimulant used in the treatment of patients with narcolepsy. A review of the literature revealed three small studies investigating the use of modafinil in patients with cancer (Blackhall, Petroni, Shu, Baum, & Farace, 2009; Kohli et al., 2009; Lundorff, Jønsson, & Sjøgren, 2009). Similar to studies of D-MPH and MPH, the results of these studies were inconsistent. Lundorff et al. (2009) evaluated a one-time dose of modafinil 200 mg in 28 patients with advanced cancer and reported improvements in attention and psychomotor speed, but not in working memory. Kohli et al. (2009) evaluated modafinil 200 mg daily for four weeks in 68 women with breast cancer and found improvement in speed of memory and episodic memory, but not in working memory. In contrast, Blackhall et al. (2009) examined modafinil starting with initial doses of 100 mg daily for two weeks, then escalating to 200 mg of modafinil daily in 27 patients with cancer of all stages and did not find improvement in cognitive functioning. Because of the mixed results and small sample sizes, effectiveness of this medication has not been established.

Donezepil: Donezepil (Aricept®), an acetylcholinesterase inhibitor, is used to treat mild-to-moderate Alzheimer's dementia. Two studies have examined the effect of donezepil on cognitive impairment in patients with cancer (Jatoi et al., 2005; Shaw et al., 2006). Shaw et al. (2006) reported that patients with brain tumors experienced improved cognitive functioning and mood. However, those results were confounded by improvements related to treatment, including a reduction in tumor size, fatigue, and radiation-induced brain injury. Jatoi et al.'s (2005) randomized,

double-blinded placebo-controlled study attempted to evaluate the effect of donezepil 5 mg daily in combination with vitamin E 1,000 IU daily on cognition. As the study was closed early because of poor accrual, the information was insufficient to formulate any conclusions.

In summary, studies evaluating psychostimulants, including D-MPH, MPH, modafinil, and donezepil, have not provided the level of evidence to sufficiently establish their effectiveness in the treatment of cancer-related cognitive impairment. Additional randomized, controlled trials are needed to establish effectiveness before they can be recommended for use to address cognitive impairment in cancer survivors.

Not Recommended for Practice

Interventions deemed *not recommended for practice* are those in which the evidence clearly demonstrates the intervention is ineffective or harmful, or the cost or burden necessary for the intervention exceeds anticipated benefit.

Pharmacologic Interventions

Erythropoietin-stimulating agents: Erythropoietin is a naturally occurring glycoprotein that stimulates the production of red blood cells (by stem cells in the bone marrow) and is produced primarily by the kidneys. Although the underlying pathogenesis of cancer, and cancer treatment-related cognitive impairment, is still unknown, one proposed mechanism is anemia. Anemia has been associated with insufficient brain oxygenation resulting in decreased attention and concentration, memory, and executive functioning (Lezak, Howieson, & Loring, 2004). Anemia may be a direct result of tumor involvement in the bone marrow or bones, or from cancer treatments such as radiation therapy to areas of actively producing marrow, chemotherapy, or any combination of these (Jansen, 2010). For those reasons, the use of erythropoietin or ESAs to promote red blood cell production has been suggested as a potential intervention for cognitive impairment.

Although anemia may indeed be a potential mechanism of cancer and cancer treatment-related cognitive impairment, insufficient evidence exists for the use of ESAs in the prevention and management of cognitive impairment in patients with cancer. Several studies have investigated the use of ESAs for patients with cancer undergoing chemotherapy (Chang, Couture, Young, Lau, & Lee McWatters, 2004; Iconomou et al., 2008; Mancuso, Migliorino, De Santis, Saponiero, & De Marinis, 2006; Mar Fan et al., 2009; Massa, Madeddu, Lusso, Gramignano, & Mantovani, 2006; O'Shaughnessy, 2002; O'Shaughnessy et al., 2005). Conclusions from those studies were inconsistent, ranging from no protective or therapeutic benefit (Iconomou et al., 2008; Mancuso et al., 2006; Mar Fan et al., 2009; O'Shaughnessy, 2002; O'Shaughnessy et al., 2005), to significant improvements in cognitive functioning (Chang et al., 2004; Massa et al., 2006).

Overall, the results of the studies are limited by small sample sizes, lack of baseline measurement for cognitive function, absence of a control group, using tests that may lack sensitivity (e.g., Mini Mental State Examination [Meyers & Wefel, 2003]) or tests known to have pronounced practice effects with repeated testing (e.g., High Sensitivity Cognitive Screen [Vardy et al., 2006]), lack of objective measurements, and variability in the dose and duration of erythropoietin use. In addition to those limitations, additional investigation is not warranted, and erythropoietin is not recommended for practice, because of the U.S. Food and Drug Administration's (FDA's) black box warning regarding the increased risk of serious cardiovascular and thrombovascular events, as well as its potential to shorten overall survival in patients with cancer (FDA, 2010).

Implications for Nursing Practice

The comprehensive review of the literature conducted as part of the Cognitive Impairment PEP team revealed that research to date has focused predominately on nonpharmacologic (e.g., vitamin E [Chan et al, 2004; Jatoi et al., 2005], exercise [Korstjens et al., 2006; Schwartz et al., 2002], natural restorative environmental intervention [Cimprich, 1993; Cimprich & Ronis, 2003], and cognitive training [Ferguson et al., 2007; Gehring et al., 2009; McDougall, 2001; Poppelreuter et al., 2009; Sherer et al., 1997]) and pharmacologic interventions, including psychostimulants (e.g., D-MPH or MPH [Bruera et al., 1992; Butler et al., 2007; Lower et al., 2009; Mar Fan et al., 2008; Meyers et al., 1998], modafinil [Blackhall et al., 2009; Kohli et al., 2009; Lundroff et al., 2009], and donezepil [Jatoi et al., 2005; Shaw et al., 2006]) or ESAs (Chang et al., 2004; Iconomou et al., 2008; Mancuso et al., 2006; Mar Fan et al., 2009; Massa et al., 2006; O'Shaughnessy, 2002; O'Shaughnessy et al., 2005). Nonpharmacologic intervention studies testing the efficacy of vitamin E, exercise, natural restorative environmental interventions, and cognitive training programs were relatively few in number and limited by poor study designs (lack of comparison groups) and small sample sizes. Although the number of pharmacologic intervention studies was greater, additional testing is necessary to establish their effectiveness. ESAs, however, are no longer a viable option, with recent warnings regarding their routine use in patients with cancer because of increased risk of tumor growth, decreased survival, and increased cardiovascular side effects (FDA, 2010). Research on psychostimulants has been equivocal and limited by small and underpowered studies (Blackhall et al., 2009; Bruera et al., 1992; Butler et al., 2007; Jatoi et al., 2005; Kohli et al., 2009; Lower et al., 2009; Lundroff et al., 2009; Mar Fan et al., 2008; Meyers et al., 1998; Shaw et al., 2006), with early stopping from failure to reach accrual goals (Jatoi et al., 2005; Mar Fan et al., 2008) or high dropout (Blackhall et al., 2009), suggesting the medications were not acceptable to patients with cancer. Overall, research aimed at preventing, treating, and managing cognitive impairment has been limited.

More research is needed to develop and refine evidenced-based treatment options for patients with cancer. To accomplish that goal, nurse scientists will need to continue to seek out the underlying physiologic mechanisms associated with cognitive impairment and explore potential genetic polymorphisms that may predispose patients to incur cognitive impairment after cancer and its treatment. In addition, large randomized, controlled trials are needed to test novel treatments, including but not limited to pharmacologic interventions, psychological counseling, dietary interventions, restorative environmental interventions,

cognitive programs, or cognitive-behavioral interventions. In summary, although research in the area of cancer and treatment-related cognitive impairment has grown, additional research is needed to improve treatment options for patients.

Conclusions

Cognitive impairment is a complex clinical symptom incurred by a significant number of cancer survivors. Nurses need to be aware of the current interventional research to address this potentially debilitating problem. Although the current evidence regarding effective interventions to address cognitive impairment is limited, the Evidence-Based Interventions for Cancer and Cancer-Treatment Related Cognitive Impairment PEP content developed as part of this initiative will serve as a foundation for nurses to understand the current state of the science regarding interventions to prevent, treat, and manage cognitive impairment in cancer survivors (Allen et al., 2011). However, the work of this team will not stop here. The ONS PEP guidelines regarding cognitive impairment will be updated every six months and will summarize the latest research in this area. Therefore, these guidelines will continue to serve as a valuable resource for oncology nurses caring for patients with cancer and cancer treatment-related cognitive impairment.

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Author Contact: Diane Von Ah, PhD, RN, can be reached at dvonah@iupui.edu, with copy to editor at CJONEditor@ons.org.

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