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Chemotherapy-related cognitive dysfunction and effects on quality of life in gynecologic cancer patients

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Abstract

Introduction—chemotherapy-related cognitive dysfunction (CRCD) is a growing problem due to rising cancer rates and increasing numbers of cancer survivors. upwards of 70% of ovarian cancer patients report cognitive-changes following treatment for their cancer.

Areas covered—the underlying mechanisms of CRCD are a subject of active research and debate. the initial insult may start with the diagnosis of cancer itself, both in the number of peripheral cytokines it produces but also in the psychological changes caused by stress and anxiety associated with the diagnosis. chemotherapy, in its ability to alter dna in the replication cycle, has been shown to damage neurons and their stem cell precursors.

Expert commentary—based on proposed mechanisms and advancements in other neuropsychological diseases, various pharmacologic and behavioral interventions have been demonstrated to show improvements in patient's quality of life and in their perceived cognitive abilities and memory. further research is necessary to be able to determine when and how these cognitive changes occur, and if their multiple potential biological underpinnings can synergize toward deleterious cognitive effects. future therapies will include prevention strategies to avert CRCD's effects on patients.

Keywords

Chemobrain; chemotherapy-related cognitive changes; gynecologic cancers; chemofog; cancer-related cognitive decline

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Declaration of interest

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1. Introduction

Modern therapeutics used in gynecologic cancer care has led to more women living long beyond their initial diagnoses and treatment periods [1]. While survivorship in this population is viewed as the final goal by both patients and physicians, many survivors now report a large array of treatment-related toxicities, which severely decrease their quality of life after cancer treatment is completed. The most affected quality-of-life domains in the surveillance period include changes in cognition (specifically learning and memory), genitourinary issues, sexual health, and psychological concerns of recurrence. Of significant concern to many of these women is chemotherapy-related cognitive dysfunction (CRCD) – in one study of ovarian cancer patients, nearly 70% reported cognitive dysfunction [2].

CRCD refers to what has been cited in some studies as chemobrain or chemofog. While it does infer to chemotherapy playing a role, as demonstrated in various *in vivo* and *in vitro* studies, it does not attribute all cognitive decline that women experience to chemotherapy alone. It does, however, recognize that chemotherapy does play a role in this decline that is still being further defined. CRCD can specifically affect survivors of gynecologic cancers because many are exposed to platinum-based therapy, specifically cisplatin, which has been shown to affect neurons both in *in vitro* and *in vivo* studies. Some of the mechanisms by which cisplatin effects hippocampal neurons include reducing dendritic branching and spine density as well as by causing mitochondrial DNA damage, the latter of which can lead to oxidative stress which is postulated to also play a role in this cognitive dysfunction [3,4]. The cognitive problems are also further worsened by the fact that some ovarian cancer patients, diagnosed before naturally occurring menopause, undergo oophorectomy which causes immediate surgically induced menopause [5].

There is sparse literature on CRCD, partly due to under-reporting. Clinicians seldom explore changes in cognition unless specifically raised by patients [6]. In gynecologic cancers, the most common neurological complaint is taxane-induced peripheral neuropathy [7]. However, other neurologic and psychiatric symptoms, less commonly reported, are still faced by many cancer survivors. These include, but are not limited to anxiety, depression, and fatigue – which also worsen the patient's ability to process and retain new information. Furthermore, age-related cognitive decline can be a confounding variable when evaluating patients for CRCD. The presence of new or concomitant neurologic and psychiatric disorders can also confound symptoms reported by the patient that may be attributed to new cognitive disorders that are not related to concurrent chemotherapy treatments. Another factor that contributes to the general paucity of data in this field is the lack of uniformity in testing for CRCD. Despite this, although various cognitive assessments exist to test for cognitive decline before, during, and after treatment; however, studies have cited that despite performing at average levels on these assessments they do not correlate with patient's own subjective experience while undergoing treatment of cancer. This limitation is thought to be due to lack of sensitivity of these assessments at detecting more subtle changes [8].

The objective of this review is to define CRCD, determine the scope of the problem, and discuss therapeutic interventions and prevention strategies for this significant quality-of-life issue in survivors of gynecologic cancers. In this undertaking, we recognize that quality of

life and cognition are two distinct entities and CRCD may affect quality of life. We caution that while some studies presented in this review report an increase in quality of life, they do not necessarily correlate with improvements in patient cognitive abilities. Although some of these studies did not demonstrate an improvement in that cognitive domain, the improvement in the patient-reported quality-of-life scales was deemed important enough to include highlighting their role on how patients subjectively feel with these interventions.

1.1. Defining the problem

Chemotherapy-related cognitive dysfunction (CRCD) refers to a patient's experience of the variety of cognitive changes that occur during or after chemotherapy administration [9]. These changes include problems with memory, word-finding difficulties, decreased executive function, task organization, and lower information processing speed. These cognitive domains are not typically assessed prior to treatment to understand where most patients' baselines lie. The inherent problems of assessing cognitive function before starting the cancer treatment includes both the time and logistics constraints to fully assess these symptoms before starting potentially curative treatment – as a full neuropsychological evaluation is both time and resource intensive and there is an inability to detect specific and discrete cognitive deficits using a short and easy-to-use instrument such as the standard mini-mental status examination (MMSE) [10]. Most gynecologic oncologists will fail to recognize that a neuropsychological problem may exist if the patient has no trouble comprehending the written consent for surgery or chemotherapy. The patient, herself, may fail to recognize whether the problem had a temporal relationship with the onset of chemotherapy initiation. However, assessing patient's baseline cognitive function before initiating chemotherapy is of utmost importance, as the patients who have had less cognitive reserve to begin with, are likely more susceptible to CRCD [11]. Furthermore, symptoms of CRCD may be subtle, despite interfering with daily life [12], and understanding their complete spectrum demands additional investment of time and expertise. Often times, even when the changes are not subtle, they fail to be apparent on neuropsychological testing batteries, which were formulated and tested, in other patient populations with degenerative neurologic conditions.

In a cross-sectional study in ovarian cancer patients examining cognition in patients with ovarian cancer, this population of cancer patients was noted to have significant impairment. Although the study was limited by its cross-sectional nature, without the ability of examining whether these deficits existed at baseline, it did demonstrate that women who received both chemotherapy and radiation had a trend to score lower than the other women with ovarian cancer that completed the cognitive assessments [13]. In a prospective longitudinal Gynecologic Oncology Group (GOG) study of ovarian cancer patients using online cognitive tests as well as validated questionnaires assessing quality of life, patient perceptions of their own cognitions, neuropathy scale, and an anxiety and depression survey, at baseline only a subset of patients had evidence of cognitive impairment in one domain of the online testing. Interestingly, impairments in at least one domain were seen in 25% of patients in this population during chemotherapy with only 17% impairment at 6-month follow up. While this suggests that chemotherapy plays a role in impairment, a causal link cannot be drawn from these conclusions [14].

One of the reasons why it is difficult to determine the scope of the problem caused by CRCD is because of its largely unknown mechanism. Additionally, some studies in cancer literature have demonstrated that cognitive impairments may exist at cancer diagnosis. One of the few studies exploring cognitive function in ovarian cancer patients noted that at baseline there were deficits in select types of cognitive skills – specifically in this study, deficits were noted in fine motor skills [15]. This study explored both quality-of-life questionnaires reporting patients' subjective experiences and also took into account neuropsychological evaluation. No consensus however has been developed on what cognitive tests – subjective or objective – to use to determine baseline or posttreatment cognitive impairments.

Assessments ranging from patient-reported questionnaires through online-based cognitive tests have been used in the studies reporting cancer and CRCD in the literature. The Cognitive Function Scale of the European Organization of Research and Treatment of Cancer Quality of Life Questionnaire C30, The Questionnaire of Experienced Deficits of Attention, Perceived Cognition Questionnaire, Patient Assessment of Own Functioning Scale, and the Cognitive Failures Questionnaire. Of the cognitive tests that have been employed the Cog State is an interactive, web-based cognitive test that allows for faster assessment of cognition and this has been validated specifically for clinical trials. Other formal cognitive tests that exist include Web-Based Cognitive Stability Test, the traditional Mini Mental Status Exam, Cognitive Drug Research Computerized Cognitive Assessment, California Verbal Learning Test-II, the Wechsler Memory Scale and Wechsler Adult Intelligence Scale. Without the proper training for administering these tests or evaluating the results, the clinical value is greatly diminished, therefore we recommend formal consultation with a neurologist when new cognitive changes are detected by the clinician or reported by the patient. Additionally, the role of neurological imaging is crucial – it is imperative in the setting of focal neurologic deficits or symptoms and should be considered in patients with vague complaints, biomarker evidence of recurrence and no clear site of disease recurrence on traditional imaging which typically looks at the base of the skull through the middle thigh.

1.2. Underlying mechanisms

The mechanism behind CRCD is unknown. Theories exist behind the various factors that may lead to its development. There is some thought that the diagnosis of cancer alone can cause cognitive changes by virtue of the cytokines released and stress-related changes [12]. This has been demonstrated in research on colon cancer and brain cancer [16,17]. Other factors that may be contributing to cognitive decline in this population include anxiety, depression, and menopause [18].

Physiologically, models have demonstrated that chemotherapy induces neurologic injury, even in the absence of cancer, both at the level of neurons as well as neural stem cell precursors [19,20]. To discern the variety of effects chemotherapy can have on the brain, researchers have studied the various regions of the brain that are responsible for learning and memory. The hippocampus, for instance, has an important role in memory. It has been shown that epigenetic changes in the hippocampus and prefrontal cortex, by means of histone acetylation, have caused decreases in neural progenitor cell proliferation [21]. *In*

vitro, hippocampal neurons demonstrate dramatic effects when encountering cisplatin, a common therapy in gynecologic cancers. Not only do they show decreased dendritic spine density but also irreversible excitatory synapse damage [4]. Discussion regarding the effects of chemotherapy on anatomic regions of the brain cannot continue without understanding the role of growth factors such as brain-derived neutrophic factor (BDNF). Low BDNF levels have been associated with cisplatin treatment as well as with cognitive decline in other neuropsychological diseases [4,22–25]. Polymorphisms of BDNF have demonstrated decreased activation in the region of the hippocampus on functional MRI [26].

Another plausible location of where chemotherapy may be exerting detrimental effects is the frontal cortex. Imaging studies, again as above, have shown changes in this area associated with chemotherapy. However, these alterations could not attribute a cause-and-effect mechanism suggesting that chemotherapy is inducing changes in the frontal cortex. A small imaging study of breast cancer patients, remote from receiving chemotherapy (at least 5–10 years prior to the study) used FDG PET CT scans to look at metabolic changes in various regions of the brain and noted decreased metabolism in the frontal cortex, basal ganglia, and cerebellum [27].

Increased cytokine production is a known effect of having cancer and its subsequent treatment. The role of cytokines in causing CRCD have been explored as well, with the specific cytokines implicated including IL-1, IL-6, IL-8, MCP-1, and TNF-α [28]. In patients diagnosed with cancer, cytokines can increase both with the diagnosis itself but also with chemotherapeutic intervention, and higher cytokine levels can be detected in the hippocampal structures [29]. The cytokine production surge is not uniform and varies among individuals even diagnosed with the same types of cancers receiving the same adjuvant therapies [12,30,31]. The direct results of chemotherapeutic regimens causing disruptions of the blood–brain barrier (BBB) and escalations in the peripheral production of cytokines (likely caused by stress and cellular injury) are profound alterations on the neuronal survival and plasticity [3,32]. Oxidative stress and mitochondrial damage are other proposed mechanisms by which neuronal and neural stem cell damage occurs ultimately leading to CRCD [4]. Last, epigenetic changes may cause chronic problems due to upregulation of DNA-altering genes that lead to a cascade of long-lasting neurocognitive changes [12]. All these theories are important due to the fact that the mechanisms behind the neuronal changes can become valuable targets for pharmacologic interventions. Some interventions already exist; others will include novel strategies that have yet to be discovered. Studies examining the underlying mechanisms that may be contributing to CRCD as well as highlights from studies specifically in a gynecologic cancer population are displayed in Table 1.

2. Methodology

In exploring the literature to query studies that have been done on this topic, we looked at clinical trials, case series, and literary reviews from 1995 to 2017. Search terms used to garner results including ‘chemobrain, chemotherapy-induced cognitive changes, or chemofog.’ With the added term of gynecologic cancer, the search was extremely limited likely demonstrating the lack of research specifically in this population. Because of the limited amount of clinical trials, the filter of clinical trials was removed and more specific

filter criteria were placed in the database. These included the addition of filters looking specifically at imaging-related changes, studies that tested pretreatment cognition and last pharmacologic and behavioral interventions. It was in using that search criteria as well as in reviewing published work through gynecologic and neurologic literature addressing CRCD that the studies presented in this review were selected. Summaries of the various studies are seen in Tables 1 and 2 but are also included in context below..

2.1. Chemobrain in other cancer types and the potential effects of maintenance therapy

Although this discussion is mostly in the setting of gynecologic cancers, research in CRCD has been done and varies between cancer groups. For example, in research on recurrent glioblastoma, cognitive function tended to decline throughout the course of treatment. Patients treated for hematologic malignancies, patients receiving full-intensity high-dose stem-cell transplant HD-SCT were at higher risk, especially in women compared to men. This change was attributed to shortened telomere length [33]. The experience in colorectal cancer is quite unique in that cognitive dysfunction was seen through the course of their treatment regardless of whether they received chemotherapy [17]. This suggests the presence of cancer may in and of itself predispose individuals to cognitive decline regardless of their adjuvant therapies. Last, childhood cancers present a specific dilemma because of their administration of chemotherapy during a time when neural development is very high. In a study of Acute Lymphoblastic Leukemia, nonverbal learning was affected by chemotherapy, specifically in girls [34].

Patients with gynecologic malignancies, specifically recurrent ovarian and advanced cervical cancer are being treated with bevacizumab (Avastin), a monoclonal antibody that inhibits vascular endothelial growth factor A [35,36]. Data showing its benefits and its good safety profile has made it a valuable option for many patients. Besides its use in these gynecologic cancers, bevacizumab is commonly used as adjuvant or maintenance therapy in other cancers. MRI imaging studies in patients receiving it for malignant gliomas have shown significant and progressive hippocampal atrophy, potentially more severe than in patients with Alzheimer’s disease, specifically during the point in their treatment where they were only receiving bevacizumab. This was quite profound considering they demonstrated no statistically significant change during their chemoradiation and adjuvant temozolomide and these changes were only seen with bevacizumab alone [37]. No similar study in gynecologic cancer patients on bevacizumab has been done.

3. Interventions

3.1. Pharmacologic interventions

Many interventions have been proposed and trialed however few have provided substantive results. However, there have been a few behavioral and pharmacologic interventions specifically targeting the various proposed mechanisms and demonstrating interesting results. Most of these therapies have been drawn from research on other neuropsychological diseases where different interventions have been shown to be useful.

Donepezil, a reversible acetylcholinesterase inhibitor, which has been used to treat Alzheimer's disease, has also been shown to improve multiple areas of cognition in brain tumor patients. This open-label, phase II study also found that not only did it improve cognition but also quality of life and mood [38]. There has also been considerable research with Modafinil, a centrally acting drug that has been used for narcolepsy, major depressive disorder, and obstructive sleep apnea [38]. In breast cancer patients, it has been shown to improve cognitive performance and attention [43]. These have been shown in phase III randomized controlled trials, both open label and blinded. Similar results have been shown with the use of methylphenidate in brain cancer patients and children with brain tumors or acute lymphocytic leukemia [44]. New pharmacologic agents already in the clinical practice for other conditions – such as HDAC inhibitors and S-adenosyl methionine (SAM) – may prove to be novel therapies to prevent epigenetic changes in the genome leading to chemotherapy [45]. Determining the timing of these future therapies in order to prevent CRCD without decreasing the efficacy of the cancer drugs is of utmost importance [46]. These and several other studies showing similar results are summarized in Table 2.

3.2. Behavioral interventions

Behavioral interventions such as relaxation were shown to improve quality of life but not to improve cognition. Studies in breast cancer patients have shown that cognitive-behavioral therapy improved patient's quality-of-life scores, although data regarding how its benefit on cognition and cognitive complaints has not been consistent among studies [47,60]. Occupational and speech therapy have demonstrated important roles however, mostly in the rehabilitative state, not in preventing future deficits [48–51]. Internationally, research on both short- and long-term yoga practices has demonstrated beneficial results in breast cancer patients treated with chemotherapy during treatment and months after treatment has completed [52–58]. These yoga studies show promising results in randomized-controlled trials [57]. Additionally, acupuncture has demonstrated positive effects on both memory and brain structures in Alzheimer Disease Patients, which were quantified using functional MRI [54], and could be trialed in the future for the CRCD patients. The pharmacologic and behavioral interventions have been summarized in Table 2.

Addressing CRCD would not only improve the quality of life in many cancer survivors, but would also increase their compliance with their cancer therapy. These studies, in addition to our own clinical experience, suggest that CRCD has tremendous quality-of-life implications in survivors of gynecologic cancers. This review also demonstrates that, not only is research in this field limited but it also underrepresents women diagnosed with gynecologic cancers [59]. Future research with models specifically examining this population is warranted.

4. Conclusion

This review has attempted to bring light to a condition that still does not have a definitive, scientifically proven etiology, and for which treatment options are very limited. CRCD may have many different causes. It can affect patients with certain cancers more than others. In the gynecologic population it is extremely important to address CRCD, as is potentially becoming more common and severe due to the use of neurotoxic drugs such as cisplatin and

other platinum-based compounds, to the advancing age of the population affected, and to the surgical menopause induced by life-saving cancer surgery. Studies specifically in ovarian cancer patients demonstrate that although there is an element of cognitive dysfunction, which is seen in this population at baseline, it can be precipitated by cancer-related treatment especially in an aging population [61]. As seen in the literature presented in this review, some cognitive dysfunction does exist at baseline in ovarian cancer patients. Although the term sometimes used by patients and even cited in some studies is chemobrain or chemofog, this misnomer seems to attribute all cognitive dysfunction experienced by a patient to chemotherapy. However, the term we have chosen to use in this review was CRCD because of the potential role that active chemotherapy does play in cognitive decline.

5. Expert commentary

Bringing light to this subject, we sought to examine why there are weaknesses in clinical management of CRCD and what they can be attributed to. Initial management of patients from diagnosis onwards focuses heavily on the cancer itself and the treatments necessary to cure it. Clinical management is focused on that because, in a sense, it has to in order to maximize a patient's time and energy and a physician's resources. Adding a neurocognitive assessment, even in its simplest form, can shift the focus away from assessing signs or symptoms of the cancer itself. This limits a provider from determining if cognitive deficits exist at baseline or even if there has been a marked change from baseline (a patient's state prior to her cancer diagnosis) to the patient's current state since learning she has a new cancer diagnosis. Its subtle changes on neurocognitive assessments also make diagnosing cancer-related cognitive decline difficult to quantify and compare. Ultimately when CRCD is noted, another weakness in its management is attributing it as a real entity related to cancer-treatment and not just age-related decline and potentially delaying treatment. Furthermore, without completely consistent results among both pharmacologic and behavioral interventions, even when CRCD is caught early and treatment is sought, it is difficult to prescribe a perfect regiment for each patient.

The major areas of growth in this field appear in two realms – the laboratory and the bedside. The laboratory seeks to find the underlying mechanisms of CRCD both *in vitro* and animal models. It attempts to delineate when, in the whole process, does CRCD occur and how much of a role the actual 'cancer' plays in all of it. When these can be determined, attempting to test currently available, FDA-approved therapies may be the next frontier in getting therapies from the lab to the patient in a safe and quick manner. With much focus placed on new therapies focused on the therapeutic roles of cytotoxic therapies, immunotherapies, and checkpoint inhibitors, basic science research has been lacking in finding the mechanisms behind some of the quality-of-life issues, like CRCD, patients exhibit. Continued assessment of patients' quality-of-life concerns and dedication to research specifically examining the biologic underpinnings of these concerns will bring us close to finding the mechanism behind CRCD and eventually cure or even prevent it.

Although various mechanisms have been proposed and presented in this review, a very exciting new realm of research examines how epigenetic changes may be causing neurotoxicity and symptoms of CRCD. This brings in histone deacetylase (HDAC)

inhibitors to play as potential therapeutic interventions. This is an area of exciting research that may prove to be an exciting frontier in this field.

Given as the current research on interventions for CRCD, this treatment-related toxicity will not have one easy solution. It will most probably require multiple levels of involvement through the continuum of care, including early recognition by the practitioners administering the chemotherapy, and a multi-disciplinary management teams (including neurologists and neuropsychologists) which will focus on addressing patient's concerns and actively promoting treatments that will potentially prevent or undo the harm that chemotherapy-may cause, while maintaining the patients on life-saving therapies and improving the quality of patient's survival.

6. Five-year view

This review summarized the current state of the science, bringing up the various mechanisms proposed for CRCD, challenges in its assessment both pre- and posttreatment, and interventions that have been studied to improve CRCD and optimize a patient's quality of life. Our vision in the next five years is that the strides made in determining the causes of CRCD became clear. Uncovering these mechanisms will allow for more directed trials of interventions to combat its effects. If, in finding the mechanism, it is discovered that an FDA-approved therapy does not already exist, it allows for newly developed targeted therapies to be used as an adjunct to neurotoxic chemotherapeutic regimens in women who are at risk of developing CRCD. We also hope that in bringing light to this issue, an intentional effort is put forth by clinicians to address quality-of-life concerns, such as CRCD, that patients may not always know to bring up.

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Key issues

- Chemotherapy-related cognitive decline (CRCD) has been shown in multiple studies to affect women suffering from gynecologic cancers. Women with cognitive decline before a cancer diagnosis are at a higher risk for developing CRCD.
- Cancer, in itself, may cause a variable amount of cognitive decline, confounding the role chemotherapy plays in accelerating this decline. Other factors such as metastatic disease to the nervous system, age-related decline, and menopausal status need to be taken into account by providers when counseling patients regarding CRCD.
- Multiple mechanisms have been proposed for what causes CRCD however the underlying cause is still unknown.
- Promising trials in pharmacologic and behavioral interventions have shown that currently available, FDA-approved therapies for other cognitive diseases may hold promising results for CRCD. While some have shown inconsistent results in neurocognitive assessments, many have reported increased quality of life scores in patients.
- Referral to a neurologist whenever CRCD is reported or suspected is warranted to engage a multi-disciplinary approach in addressing this huge quality of life concern.

Table 1

Select studies exploring various mechanisms of CRCD.

Research group	Measurement	Groups	Results
Mayerhofer et al. [56]	Decreased brain connectivity (EEG pre-and posttreatment)	Carboplatin and paclitaxel	No differences seen
Kreukels et al. [57]	Decreased brain connectivity (EEG in patients treated and nontreated controls 4 years following therapy)	Cyclophosphamide, epirubicin, 5-fluorouracil or adjuvant high-dose cyclophosphamide, thiotepa, carboplatin	Decreased processing speeds in chemotherapy exposed group
Penson et al. [30]	Inflammatory markers	Carboplatin and Paclitaxel in ovarian cancer patients	Increased IL-6
Hess et al. [58]	Cognition tested through online modules at baseline, after 3 and 6 cycles of chemotherapy.	Patients with ovarian cancer treated with carboplatin and paclitaxel	Decreased cognitive function over treatment course
Hensley et al. [59]	Objective quality of life and cognitive measurements	Carboplatin, Paclitaxel, and Gemcitabine	No impairment on objective measures
Ahles et al. [60]	Brain structural changes seen on MRI	Breast cancer patients	Structural imaging correlates with poor performance on cognitive tests
Deprez et al. [61]	Structural changes correlated with cognitive changes	Breast cancer patients who have undergone chemotherapy	Slower fractional anisotropy
Hess et al. [14].	Web-based cognitive assessment and patient reported questionnaires	NRG Oncology/Gynecologic Oncology Group (GOG) study on patient receiving primary treatment of primary peritoneal, fallopian tube, or ovarian cancer	Patients experienced a decline in cognitive ability in at least one measured domain from baseline.

Table 2

Current and future CRCD interventions.

Author	Intervention	Study type	Population	Proposed mechanism	Findings
Pharmacologic interventions					
Kilgore et al. [39]	Class I HDAC inhibitor	*In vivo* mouse model of Alzheimer's disease	APPswe/PS I de9 mice	Countering epigenetic changes	Restored contextual memory in mice with results maintained for two weeks
Kohli et al. [40]	Modafinil	Open label followed by randomized clinical trial	Breast Cancer patients with reported persistent fatigue who had chemotherapy and/or radiation therapy	Unclear mechanism however likely acting centrally to decreasing GABA neurotransmission	Improved cognitive performance and attention skills
Lundorff et al. [41]	Modafinil	Double-blind randomized cross-over trial	Advanced cancer patients with tiredness scores >50 mm on Edmonton Symptom assessment system and Karnofsky performance status	Unclear mechanism however likely acting centrally to decreasing GABA neurotransmission	Increased psychomotor speed and attention during cognitive tests
Shaw et al. [38].	Donepezil	Open label, phase II clinical trial	Irradiated malignant glioma patients	Reversible, noncompetitive inhibition of central cholinesterase	Increased quality-of-life scores, cognitive function and mood with minimal toxicity
Meyers et al. [42]	Methylphenidate	Literature review, nonrandomized interventional study	Irradiated malignant glioma patients	Norepinephrine and dopamine reuptake inhibitor	Improved cognitive performance and function
Delong et al. [44].	Methylphenidate	Case Series	Children with brain tumors or acute lymphoblastic leukemia	Norepinephrine and dopamine reuptake inhibitor	Improved memory, language skills, and academic performance
Behavioral or Non-pharmacologic interventions					
Von Ah et al. [50]	Advanced Cognitive training	3-group randomized control trial	Breast cancer survivors	Speed of processing training with greater effects than memory training as a type of intervention in survivors.	
Ferguson et al. [47].	Cognitive Behavioral therapy	Single-arm pilot study	Stage I and II breast cancer survivors approximately 8 years chemotherapy	High treatment satisfaction and improvement in quality of life and neuropsychological testing.	
Wang et al. [54]	Acupuncture	Functional MRI study	Patients with mild cognitive impairment of Alzheimer's disease	Activated certain cognitive regions including frontal and temporal lobes related to memory and cognition	
Ling et al. [55]	Electro acupuncture in comparison to Nimodipine	RCT comparing electroacupuncture to nimodipine to combined electroacupuncture with nimodipine	Patients with vascular dementia	All three groups demonstrated reduced psychological stress and strengthened attention, with the highest effects in the combined electroacupuncture and nimodipine group.	
Galantino et al [52].	Yoga	Case series	Stage II breast cancer patients before, after and during chemotherapy	Improved quality of life. Cognitive skills on computerized testing had mixed results.	

Author	Intervention	Study type	Population	Proposed mechanism	Findings
Janelsins et al. [57]	Yoga (YOCAS study)	Nationwide phase III randomized-control trial	Cancer patients 2–24 months after adjuvant therapy	Decreased patient reported memory difficulty	
Rao et al. [58]	Yoga	Randomized control trial to receive yoga compared to standard treatment	Stage II and III breast cancer patients on conventional treatment	Decreased toxicity during chemotherapy was reported. Improved quality of life and decreased anxiety and depression.	
Amritanshu et al. [56]	Long-term yoga practice	Case–control study grouping patients based on prior yoga experience	Breast cancer patients >6 months from treatment	Patients with prior yoga experience had increased global quality-of-life scores, less stress and anxiety. Reported being better psychological states. Extrapolated data suggesting that cancer prognosis can be improved by long-term yoga practice.	

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