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REVIEW ARTICLE

Therapies for Cognitive Deficits Associated With Chemotherapy for Breast Cancer: A Systematic Review of Objective Outcomes

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Abstract

Objective: To systematically review evidence of treatments for cognitive impairments experienced by at least 20% of all women who undergo chemotherapy for breast cancer.

Data Sources: Searches of 5 databases (PubMed, Embase, Cochrane CENTRAL, PsycINFO, CINAHL), with no date or language restrictions, identified 1701 unique results. Search terms included breast cancer, chemotherapy, chemobrain, chemofog, and terms on cognition and language deficits.

Study Selection: Included only peer-reviewed journal articles that described therapies for cognitive dysfunction in women undergoing (or who had undergone) chemotherapy for breast cancer and provided objective measurements of cognition or language.

Data Extraction: Data were extracted according to Cochrane recommendations, including characteristics of participants, interventions, outcomes, and studies. Quality assessment of all 12 eligible studies was performed using the Physiotherapy Evidence Database scale and treatment fidelity criteria. Screening, data extraction, and quality assessment reliability were performed.

Data Synthesis: Six articles described interventions for cognition that took place during cancer treatment; 6, afterward. Five interventions were medical (including a strength-training program), 2 were restorative, and 5 were cognitive. Medicinal treatments were ineffective; restorative and exercise treatments had mixed results; cognitive therapy had success in varying cognitive domains. The domains most tested and most successfully treated were verbal memory, attention, and processing speed.

Conclusions: Cognitive therapy protocols delivered after chemotherapy and aimed at improving verbal memory, attention, and processing speed hold the most promise. Future research is needed to clarify whether computerized cognitive training can be effective in treating this population, and to identify objective assessment tools that are sensitive to this disorder.

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Worldwide, breast cancer is the most frequently diagnosed cancer in women, and about 1.4 million new cases are added each year.[1] In the United States alone, there are approximately 2.8 million survivors.[2] The increasing survival of patients with breast cancer has engendered an increasing awareness of the side effects and aftereffects of breast cancer treatment, including cognitive dysfunction. High rates of impairment were recently described in a meta-analysis[3] of cognitive functioning in breast cancer survivors previously treated with standard-dose chemotherapy, and high rates of persistence of cognitive decline after completion of chemotherapy have also been reported.[4] At least 20% of all women who undergo breast cancer treatment also experience cognitive dysfunction for a period during treatment, after treatment, or both.[5] This dysfunction begins during a stressful time, in which the ability to pay close attention to and recall new streams of medical information is of paramount importance; it continues while cognitive health is needed to make necessary life adjustments, to adhere to treatment protocols, and to resume normal activities of daily living.[6] This negative impact on health-related

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quality of life also extends to the ability to work, levels of confidence in the ability to work, and in subsequent employment decisions.[7] The pervasiveness of this impairment has given rise to much-needed research on rehabilitative therapies.

The objective of this systematic review was to identify and compare all quantitative research articles (ie, containing objective neuropsychological measures of cognitive performance) that have described therapies for the cognitive deficits associated with chemotherapy treatment for breast cancer in women.

Methods

This systematic review was performed in accord with the recommendations of the *Cochrane Handbook for Systematic Reviews of Interventions*.[8] The PICO (participants, interventions, comparisons, outcomes) framework was used to develop a literature search to answer the following question: For women undergoing (or who have undergone) chemotherapy for breast cancer, are there therapies that address cognitive dysfunction that result in improved cognitive abilities?

Data sources

In order to retrieve a complete international set of relevant articles on chemobrain or chemofog in breast cancer patients, a librarian systematically searched for articles in December 2013 and January 2014 in the following databases: PubMed MEDLINE (1940s−), Embase (1947−), PsycINFO (1880−), Cochrane CENTRAL (1966−), and CINAHL (1982−). Search terms included chemobrain, chemofog, breast cancer, chemotherapy, and an extensive list of terms related to cognition and language deficits. A full sample list of search terms and strategies for PubMed and Embase is provided in appendix 1. Because treatment for the cognitive deficits associated with breast cancer regimens is a relatively new topic, no year or language restrictions were applied.

Abstract screening

All titles and abstracts were screened by the first author and deemed eligible for assessment of methodological quality if the abstract contained a statement of an objective, quantitative measurement (ie, assessed with a neuropsychological instrument) of cognition or language in adult women undergoing (or who had undergone) chemotherapy for breast cancer. Subjective, qualitative studies were excluded, as were studies of animals, men, children, and other types of cancer. Eligibility criteria also specified experimental design: cross-sectional, longitudinal, or randomized control trial (in phase I, II, or III). Case studies, case series, commentaries, editorials, dissertations not published in a peer-reviewed journal, posters, stand-alone abstracts, systematic reviews, and meta-analyses were excluded. However, reference lists of on-topic systematic reviews and meta-analyses were handsearched to look for articles that were not retrieved in this extensive literature search.

List of abbreviations:

HVLT-R **Hopkins Verbal Learning Test−Revised**
PEDro **Physiotherapy Evidence Database**

Quality assessment

Assessment of the methodological quality and risk of bias of all eligible articles was performed by the first author using the Physiotherapy Evidence Database (PEDro) rating scale criteria,[9] plus criteria for treatment fidelity.[10] The PEDro scale specifically aims to determine "the likelihood of the trial design to generate unbiased results that are sufficiently precise and allow replication in clinical practice."[11(p714)] Table 1 lists the operational definitions of the methodological quality assessment criteria.

Data extraction

Data were collected by the first author and a research assistant with a master's degree in clinical psychology in accord with Cochrane recommendations, including characteristics of participants, interventions, outcomes (*P* values), and studies. The first author and research assistant cross-checked all extracted data for accuracy and completeness.

Results

Data sources and abstract screening

A total of 1745 articles were retrieved. In screening all titles and abstracts, the first author removed 44 articles (30 identified as duplicates between databases plus 14 titles for which abstracts could not be obtained). No additional articles were identified by means of the hand search of reference lists of on-topic systematic reviews and meta-analyses. This resulted in 1701 unique results: PubMed, 560; Embase, 880; PsycINFO, 48; Cochrane CENTRAL, 12; and CINAHL, 201.

The research assistant initially reviewed a pilot set of 50 randomly chosen abstracts in order to test the screening syllabus containing abstract eligibility criteria; 97% keep/reject agreement was achieved between the first author and the research assistant on the pilot set. Subsequently, 25% of the articles from each database were randomly selected (n=437) and screened for eligibility by the assistant; agreement was achieved on 424 decisions (97% agreement). After discussion, all keep/reject decisions were agreed on.

Screening resulted in identification of 144 on-topic (ie, cognitive dysfunction after treatment for breast cancer in women) abstracts. In reviewing those, the first author identified 14 abstracts which contained a statement of treatment for cognitive dysfunction after treatment for breast cancer. One of the 14 articles was written in German.[12] Because that author was unable to provide an English version, the article was translated to English using Google translate and the research assistant's knowledge of the German language. A complete PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram of records[13] is provided in figure 1.

Quality assessment

The first author then assessed these 14 articles for methodological quality and risk of bias, which resulted in the exclusion of 2 articles: 1 that did not provide separate results of cognitive measures for participants with breast cancer versus other cancer types,[14] and 1 that reported only preliminary results of a completed treatment study[15] that was already included in this systematic review.[16] One