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REVIEW ARTICLE

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

Diane F. Morean, PhD,[a,b] Linda O'Dwyer, MS, MSLIS,[b] Leora R. Cherney, PhD[a,b]

From the [a]Rehabilitation Institute of Chicago, Chicago, IL; and [b]Feinberg School of Medicine, Northwestern University, Chicago, IL.

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

Table 1 Quality assessment criteria

Criteria	Descriptions	Operational Definitions
Eligibility criteria	Eligibility criteria were specified.	The source of participants and participant eligibility criteria are described.
Group allocation	Subjects were randomly allocated to groups (in a crossover study, subjects were randomly allocated an order in which treatments were received).	The report states that participant group allocation was random.
Concealed allocation	Allocation was concealed.	The person who determined if a participant was eligible for inclusion in the trial was unaware, when this decision was made, of which group the participant would be allocated to.
Group similarity	The groups were similar at baseline regarding the most important prognostic indicators.	At least 1 measure of the severity of the condition being treated is described, and at least 1 (different) key outcome measure at baseline is described.
Subject blinding	There was blinding of all subjects.	Subjects did not know which group they were in and would have been unable to distinguish between the treatments applied to different groups.
Therapist blinding	There was blinding of all therapists who administered the therapy.	Therapists did not know which group participants were in and would have been unable to distinguish between the treatments applied to different groups.
Assessor blinding	There was blinding of all assessors who measured at least 1 key outcome.	Assessors did not know which group participants were in.
>85% outcome	Measurements of at least 1 key outcome after treatment were obtained from more than 85% of the subjects initially allocated to groups.	The report states both the number of subjects initially allocated to groups and the number of subjects from whom key outcome measures were obtained after treatment. If longitudinal, a key outcome must have been measured in more than 85% of subjects at 1 point in time after treatment.
Intention to treat	All subjects for whom outcome measurements were available received the treatment or control condition as allocated, or where this was not the case, data for at least 1 key outcome were analyzed by "intention to treat."	The report states that an "intention-to-treat" analysis was performed (ie, participants were analyzed according to allocation group regardless of whether treatment was performed) or that all subjects received treatment or control conditions as allocated. All existing data are used according to original group allocation.
Statistical comparison	The results of between-group statistical comparisons are reported for at least 1 key outcome.	The report provides a *P* value of a hypothesis test describing group differences or a confidence interval with an estimate (eg, mean or median difference, difference in proportions).
Point measure and variability	The article provides both point measurements and measurements of variability for at least 1 key outcome.	The report provides a point measure—that is, size of treatment effect (eg, difference in group outcomes or outcome of each group)—and a measure of variability. If data were continuous, SDs, SEs, etc, were provided (in text, numerically, or graphically). If data were categorical, the number of subjects in each category for each group was provided.
Treatment fidelity	Manipulation of the independent variable occurred as planned.	The report provides information on the treatment schedule (ie, dose, frequency, and number of sessions), treatment delivery (ie, monitoring adherence to the schedule), and the competence of the interventionist (ie, qualifications of person[s] delivering treatment and/or a statement of protocol training).

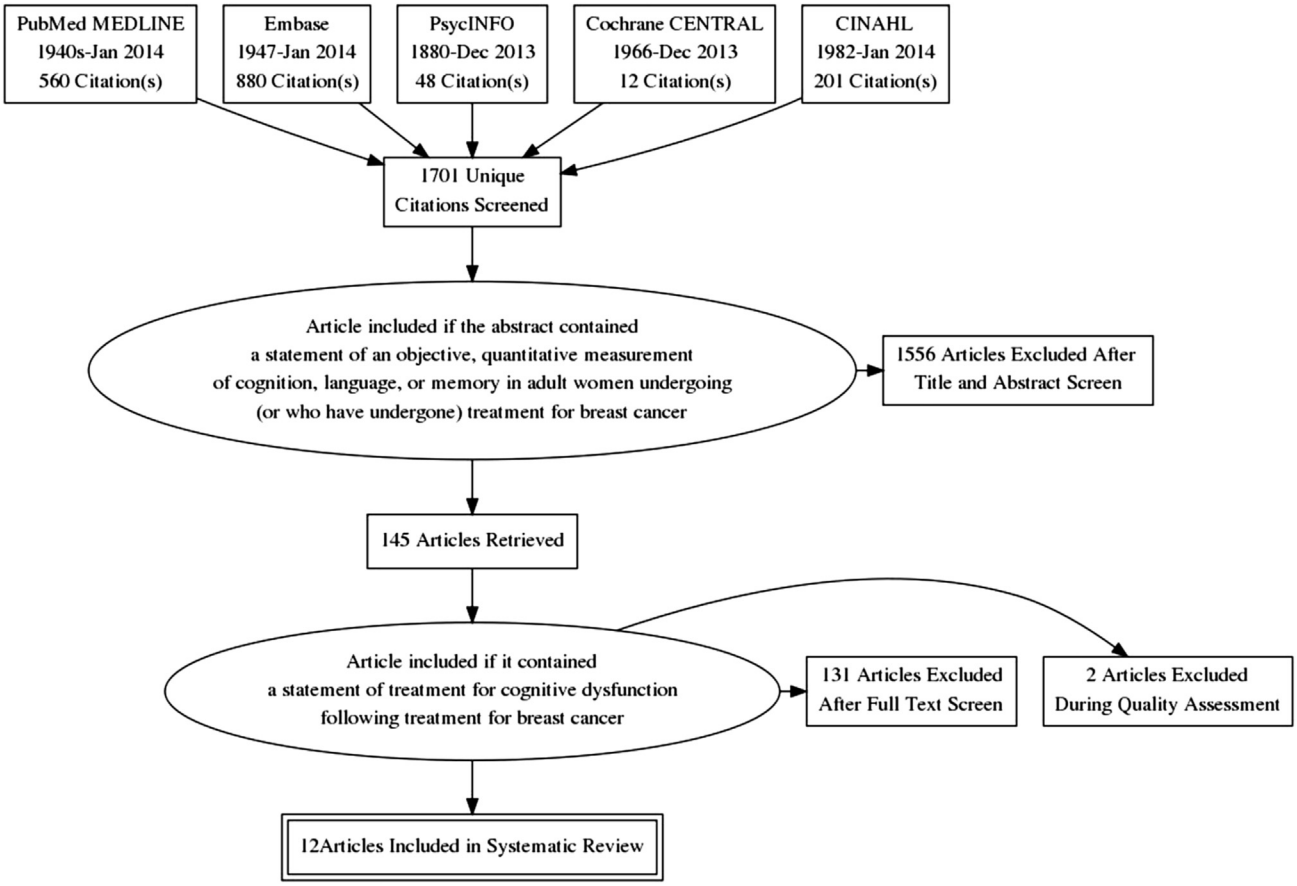

Fig 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram.

point was assigned for each of 10 PEDro criteria (the criterion for "eligibility" is not customarily awarded points). An additional point was awarded for treatment fidelity, which resulted in a total of 11 possible quality points per study. The research assistant performed quality assessments for all 12 articles, which resulted in 144 decisions (including the PEDro "eligibility" criterion). First-pass agreement was achieved on 131 decisions (ie, 91% agreement). After discussion, all quality assessment decisions were agreed on. Table 2 shows the quality assessment scores.

All but 1 article[17] included a report of the source and eligibility criteria for study participants. Across studies, high total scores (7 of 11, or better) were achieved on 4 criteria: >85% outcome, intention to treat, statistical comparison, and random group allocation. Mediocre total scores (6 of 11) were achieved on group similarity, concealed allocation, and treatment fidelity. The primary reason for low treatment fidelity scores was no reporting of the qualifications of the person(s) delivering treatment or of dissemination of the research protocol; the secondary reason was no reporting of monitoring adherence to treatment. The lowest total quality assessment scores (only 3 of 12) across studies were given for point measure and variability (failing to provide information necessary to ascertain the magnitude of the difference of effect sizes between groups), and for blinding of subjects, therapists, and assessors. In part, low scores in subject and therapist blinding are explained by the study design. In studies with only 1 group[18,19] or with waitlist control groups,[17,20,21] both subjects and therapists were inherently aware of which participants were receiving treatment. However, such group characteristics do not account for lack of (or lack of reporting of) assessor blinding. The mean quality assessment score for all studies was 5.33 of 11.

Data extraction

Participant characteristics

Participant characteristics data included the number of groups, the number of participants within groups, age, education, menopausal status, breast cancer diagnosis, breast cancer treatment, and time since breast cancer treatment (table 3).

Barton et al[22] was unique in enrolling >100 participants in treatment and control groups; all other studies recruited <50 participants per group. Cimprich,[6] Kesler,[17] and Milbury[21] and colleagues performed comparative statistics to demonstrate that there were no significant differences in age between intervention and nonintervention groups. Most of the remaining studies provided only descriptive statistics of age differences. Although Barton[22] randomized subjects to achieve an even number of participants within groups above and below 50 years of age, a clear comparison cannot be made without mean ages and SDs for these subsets. Likewise, the collapsed group data in Poppelreuter et al[23] do not allow for group similarity assessment of any demographic variable. Level of education was not reported in 5[12,16,22,24,25] of 12 studies. Overall, groups that did provide descriptive statistics on

Table 2 Quality assessment scores: PEDro + treatment fidelity criteria

Study ID	Research Design	Participant Source + Eligibility Criteria	Group Allocation	Concealed Allocation	Group Similarity	Subject Blinding	Therapist Blinding	Assessor Blinding	>85% Outcome	Intention to Treat	Statistical Comparison	Point Measure + Variability	Treatment Fidelity	Total Score: PEDro + Tx Fidelity (Max=11)*
Barton et al,[22] 2013	RCT Phase II 2 groups	Yes	1	1	1	1	1	0	0	1	1	0	0	7 + 0 = 7 = 64%
Baumann et al,[12] 2009	Prospective Pre-post 2 groups	Yes	0	0	0	0	0	0	0	1	1	0	0	2 + 0 = 2 = 18%
Cimprich,[6] 1993	Longitudinal (4 time pts) 2 groups	Yes	1	0	0	0	0	0	0	1	1	0	1	3 + 1 = 4 = 36%
Ercoli et al,[18] 2013	Longitudinal (4 time pts) 1 group	Yes	0	0	0	0	0	0	1	1	0	0	1	2 + 1 = 3 = 27%
Ferguson et al,[19] 2007	Longitudinal (4 time pts) 1 group	Yes	0	0	0	0	0	0	0	1	0	0	1	1 + 1 = 2 = 18%
Ferguson et al,[20] 2012	RCT Phase I 2 groups	Yes	1	1	1	0	0	1	1	1	1	1	1	8 + 1 = 9 = 82%
Kesler et al,[17] 2013	RCT Phase I 2 groups	No	1	1	1	0	0	1	1	1	1	1	1	8 + 1 = 9 = 82%
Mar Fan et al,[24] 2008	Longitudinal (3 time pts) 2 groups	Yes	1	1	1	1	1	0	1	1	1	0	0	8 + 0 = 8 = 73%
Mar Fan et al,[25] 2009	Observational Follow-up study 2 groups	Yes	0	0	0	0	0	1	1	1	1	0	0	4 + 0 = 4 = 36%
Milbury et al,[21] 2013	RCT Phase I 2 groups	Yes	1	1	0	0	0	0	0	1	1	1	1	5 + 1 = 6 = 55%
O'Shaughnessy, et al,[16] 2005	Pilot RCT 2 groups	Yes	1	1	1	1	1	0	1	0	0	0	0	6 + 0 = 6 = 55%
Poppel-reuter et al,[23] 2009	Longitudinal (3 time pts) 3 groups	Yes	0	0	1	0	0	0	1	1	1	0	0	4 + 0 = 4 = 36%
Scores across studies			7/12	6/12	6/12	3/12	3/12	3/12	7/12	11/12	9/12	3/12	6/12	M = 5.33 = 48.5%

NOTE. Participant source and eligibility criteria of the PEDro scale are for informational purposes only and are not included in PEDro scoring.
Abbreviations: ID, identification; M, mean; Max, maximum; pts, points; RCT, randomized controlled trial; Tx, treatment; 1, yes; 0, no.
* Used as the denominator in calculating the percentage of earned points.

Table 3 Participant characteristics

	Treatment Group							Control Group						
Study ID	N	Age (y)	Education (y)	Menopausal Status	Breast Cancer Dx	Breast Cancer Tx	Time Post—Breast Cancer Tx	N	Age (y)	Education (y)	Menopausal Status	Breast Cancer Dx	Breast Cancer Tx	Time Post—Breast Cancer Tx
Barton et al,[22] 2013	107	50.0% <50 50.0% ≥50	NR	51.0% pre 41.0% post 8.0% unk	0—3 lymph ≥4 lymph involvement	S, C	Before 2nd C cycle	103	50.0% <50 50.0% ≥50	NR	54.0% pre 42.0% post 4.0% unk	0—3 lymph ≥4 lymph involvement	S, C	Before 2nd C cycle
Baumann et al,[12] 2009	12	46.2±6.7	NR	NR	All stages	S, C	6.0wk postsurgery / after start C	8	52.0±10.0	NR	NR	All stages	S, C	After C
Cimprich,[6] 1993	16	57.0±16.0	13.6±2.0	NR	Stages I, II	S, C, R, E: after 2nd data pt	Before discharge postsurgery	16	51.0±13.0	14.5±3.0	NR	Stages I, II	S, C, R, E	Before discharge postsurgery
Ercoli et al,[18] 2013	27	54.1±6.3	16.4±1.9	NR	Stages 0—III	S, C, R, E	18—60mo post-Tx	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Ferguson et al,[19] 2007	29	56.0±7.8	15.4±2.3	100% post	Stages I, II	S, C, E, R: not excl	8.2±4.4y	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Ferguson et al,[20] 2012	19	51.2±7.3	17.0±1.9	100% post	Stages I, II	S, C, E R: not excl	At least 18mo post-Tx	21	49.4±5.1	15.9±2.7	100% post	Stages I, II	S, C, E R: not excl	At least 18mo post-Tx
Kesler et al,[17] 2013	21	55.0±7.0	16.0±2.0	71.0% post	Stages I—II Stage IIIa	S, C, R, E	6.0±3.0y	20	56.0±6.0	16.0±3.0	65.0% post	Stages I—II Stage IIIa	S, C, R, E	6.0±3.0y
Mar Fan et al,[24] 2008	29	Med: 50 (36—72)	NR	58.6% pre	Early stage	S, C	After 1st C (or 2nd if 6mo C planned)	28	Med: 51 (37—74)	NR	35.7% pre	Early stage	S, C	After 1st C (or 2nd if 6mo C planned)
Mar Fan et al,[25] 2009 (follow-up study)	45	Med: 53	NR	48.9% pre	Early or advanced stage	S, C	During C according to hemoglobin %	42	Med: 50	NR	54.8% pre	Early or advanced stage	S, C	During C according to hemoglobin %
Milbury et al,[21] 2013	23	53.0±6.6	95.6% (of 22) some college or higher	82.6% post	Stages I—II Stage III	S, C, R, E	6—60mo Post-C	24	54.1±8.6	74.9% (of 18) some college or higher	79.2% post	Stages I—II Stage III	S, C, R, E	6—60mo Post-C
O'Shaughnessy et al,[16] 2005	47	53.3±9.7	NR	40.0% pre 60.0% post	Stages I—II Stages IIIa—b	S, C	At start C	47	54.3±12.0	NR	34.0% pre 66.0% post	Stages I—II Stages IIIa—b	S, C	At start C
Poppelreuter et al,[23] 2009*	67†	49.2±7.7	16.7% university degree	NR	Stages I—II	S, C, R, E	2.1±2.8 mo since last Tx	29	49.2±7.7	16.7% university degree	NR	Stages I—II	S, C, R, E	2.1±2.8mo since last Tx

NOTE. Values are mean ± SD or as otherwise indicated.

Abbreviations: C, chemotherapy; Dx, diagnosis; E, endocrine; excl, excluded; Med, median; N/A, not applicable; NR, not reported; post, postmenopausal; pre, premenopausal; pt, point; R, radiation; S, surgery; Tx, treatment; unk, unknown menopausal status.

* Participant characteristics were reported as an aggregate for all 3 groups (2 treatment + 1 control).

† Two treatment groups: n=33 and n=34.

education seemed fairly well matched, except for Milbury[21] whose control group had 20.7% fewer individuals than in the treatment group who attended any college.

Menopausal status was not reported for participants in 4[6,12,18,23] of 12 studies. Overall, groups that did provide descriptive statistics on menopausal status seemed reasonably matched, except for Mar Fan et al[24] whose control group had 22.9% fewer individuals than in the treatment group who were premenopausal. Breast cancer diagnoses were clearly reported in all but 2 studies,[12,25] with enough detail to discern the numbers of participants with early versus late cancer stages and to confirm equitable distribution of this variable between treatment and control groups. Breast cancer treatment types were also primarily well reported. Examination of the time post−breast cancer treatment in which therapy began for associated cognitive deficits revealed that half began during breast cancer treatment and half began afterward.

Intervention variables

Therapies for the cognitive deficits associated with treatment for breast cancer in women included medical treatments, restorative therapies, and cognitive therapies. Cognitive intervention variables data included timing of cognitive treatment relative to breast cancer treatment, protocol, intervention schedule, setting, interventionist competence, and adherence monitoring. A summary of cognitive intervention variables is presented in table 4.

Medical treatments to address the cognitive deficits associated with breast cancer treatment included the use of ginkgo biloba,[22] epoetin alfa,[16,25] d-methylphenidate,[24] and although not pharmaceutical, physical strength-training.[12] Restorative therapies involved choosing calming experiences[6] and Tibetan sound meditation.[21] Cognitive therapies included explicit memory and attention behavioral training[18-20,23] and computerized training.[17,23] Training in self-awareness, relaxation,[18-20] and compensatory strategies[18-20,23] was also included in some cognitive therapies. Encouragement and support were offered in all nonmedical therapies but were not quantified as a variable of treatment.

Of the 6 studies that occurred during treatment for breast cancer, 5[12,16,22,24,25] were medical treatments that began during chemotherapy, and 1 was restorative therapy[6] that began before chemotherapy treatment. A second restorative treatment was performed 6 to 60 months postchemotherapy and therefore may have occurred during subsequent treatment for breast cancer for some participants.[21] The remaining studies were cognitive treatments that were administered after breast cancer chemotreatment,[17-20,23] with a range from a minimum of 2.1 months[23] to a maximum of about 12.5 years posttreatment[19] (mean ± SD, 8.2±4.4y).

On the whole, intervention schedules were clearly reported, although exact dosing was difficult to quantify in studies in which participants could choose to perform more of the assigned tasks at home, if desired.[6,18,21] Additionally, the number of administrations of medical treatment for cognition (during the course of chemotherapy treatment) varied between participants[24] because schedules for chemotherapy varied (4 and 6 cycles) and because the requirement for treatment to begin before the second chemotherapy cycle allowed for cognitive medical treatment to begin before or after the first cycle.[22]

Only 1 study[23] took place in an inpatient rehabilitation unit, and 3 took place in participants' homes: computerized cognitive training,[17] taking ginkgo biloba capsules,[22] and taking d-methylphenidate capsules.[24] Of the studies that required practice at home as part of the treatment, 3 were cognitive-behavioral therapies[18-20] and 2 were restorative therapies.[6,21]

All 5 cognitive-behavioral therapies[17-20,23] followed treatment manuals. On the other hand, dissemination of medical therapy research protocols[12,16,22,24,25] was not reported. Also, in 5[12,16,22,23,25] of 12 studies, monitoring adherence to the intervention schedule was not reported.

Neuropsychological test outcomes

Outcome data included objective neuropsychological test measures, measurement time points, and statistical outcomes, which were organized by the cognitive domains that were tested. Outcomes were *P* values that reflected significant within- or between-group differences (or lack thereof) at varying time points of treatment. A summary of outcomes is presented in table 5.

Overall, more than 30 different objective neuropsychological tests were used to measure cognitive function. Of those, only 7 were repeated across studies: High Sensitivity Cognitive Screen, Trail Making, Stroop, Digit Symbol Coding, Digit Span, Hopkins Verbal Learning Test−Revised (HVLT-R), and California Verbal Learning Test−Second Edition. Although language was a primary search term of this review, use of language-specific assessment tools was not reported. In addition to posttreatment testing, 8 studies[6,16,18-21,23,24] reported at least 1 follow-up testing between 1 and 6 months posttreatment. Only 2 studies[22,25] reported posttesting past the 1-year mark, and the remaining 2 studies[12,17] reported only having tested once past baseline, at posttreatment.

Half of the studies did not report any significant findings (ie, effects of treatment); of those, 4 were medical treatments[16,22,24,25] and 1 was restorative (ie, Tibetan sound meditation).[21] Poppelreuter[23] reported improved cognition in both treatment groups and the group that received standard care, reflecting no intervention effects. The most tested cognitive domains were attention, verbal memory, and processing speed. Other tested cognitive domains included visual-motor/spatial, working memory, verbal fluency, executive function, and cognitive flexibility. Only restorative activities[6] and medical strength training[12] resulted in improved measures of attention: at just 1 time point for Cimprich,[6] and only by comparison with a control group without a baseline measurement for Baumann et al.[12] Baumann[12] also reported improvements in verbal memory, as did Ferguson et al[19,20] with cognitive memory and attention adaption training. Cognitive therapies also resulted in some significant processing speed gains. Those therapies included memory and attention training[19]; memory, attention, plus executive function exercises[18]; and computerized home-based therapy.[17] Additionally, computerized training[17] led to significantly better cognitive flexibility scores (ie, scores on the Wisconsin Card Sorting Test) and letter fluency scores.

Discussion

This systematic review was designed to identify and compare that which is known about objectively measured outcomes of therapies that address cognitive dysfunction after chemotherapy for breast cancer in women. We searched 5 databases, using an extensive and carefully chosen list of search terms with no year or language restrictions, and extracted data in accord with Cochrane recommendations. In assessing methodological quality, scores ranged from 2[12,19] to 9[17,20] of 11 (10 PEDro criteria plus a treatment fidelity criterion). Eight of the PEDro criteria are intended to ensure internal validity through the proper inclusion of control groups,

Table 4 Cognitive intervention variables

Study ID	Protocol	Timing of Cognitive Tx Relative to BC Tx	Intervention Schedule	Setting	Interventionist Competence	Adherence Monitoring
Barton et al,[22] 2013	Ginkgo biloba (EGB 761) capsules or matching placebo capsules	Beginning before 2nd C cycle and ending 1mo beyond completion of C	Dose: 60mg EGB 761 (or matching placebo) Frequency: 2×/d No. of administrations: Varied due to varied timing of the onset of treatment and unreported number of C cycles	Home	Qualifications: Qualifications of persons administering treatment were not reported. Protocol training: Dissemination of research protocol to 23 participating U.S. institutions was not reported.	Although potential side effects were evaluated at each data point, there was no report of monitoring adherence to protocol.
Baumann et al,[12] 2009	Structured classic resistance (device-based) strength-training program at about 55% maximum force: 1 warm-up set (20 repetitions, lower weight), plus 2 training sets, per session	Beginning 6wk postsurgery, after the start of C and ending in 12wk, when C was completed	Dose: 60min Frequency: 2×/wk No. of administrations: 24	Health-oriented fitness studio	Qualifications: Qualifications of persons administering treatment were not reported. Protocol training: Dissemination of research protocol was not reported.	Although training was reported to have always been performed under controlled and identical conditions, there was no report of monitoring adherence to protocol.
Cimprich,[6] 1993	Restorative experiences: 1. Explanation of restorative experiences and their purpose 2. Guidance in selecting 3—4 preferred activities (recommended observing wildlife, excursions, etc.) 3. Written contract to perform activities	Beginning before hospital discharge (after primary surgery for BC) and ending in 90d	Dose: 20—30min Frequency: ≥3×/wk No. of administrations: ≥36	Participant chosen	Qualifications: PhD, RN Protocol training: Investigator performed experiment.	Participation was assessed at each of 4 observation points; reports of adherence difficulty were rare.
Ercoli et al,[18] 2013	Cognitive rehabilitation program: 1. Attention, memory, and executive function exercises	Beginning 18mo to 5y after completion of primary treatments with surgery, radiation, and/or chemotherapy	Dose: In class: 2h At home: 20min recommended Frequency:	University of California at Los Angeles, plus homework at home or work	Qualifications: Clinician Protocol training: Manualized program with teaching materials for the participants	Short-term goal attainment was reviewed weekly. Participants attended regularly and discussed

(*continued on next page*)

Table 4 (*continued*)

Study ID	Protocol	Timing of Cognitive Tx Relative to BC Tx	Intervention Schedule	Setting	Interventionist Competence	Adherence Monitoring
	2. Education on cognition 3. Long- and short-term goal setting 4. Homework at 3 levels of difficulty All with encouragement and support Weeks 1—2: Emphasis on attention Week 3: Emphasis on executive function Week 4: Emphasis on memory Week 5: Review	(mean ± SD: 2.8±1.0y since diagnosis) and ending in 5wk, except for 1st cohort (ending in 6wk)	In class: 1×/wk At home: 4×/wk recommended No. of administrations: In class: 5 (except 1st cohort who received 6) At home: Varied			their experiences on the weekly homework assignments, which they were asked to track on a log that was provided for them.
Ferguson et al,[19] 2007	MAAT: 1. Education on memory and attention 2. Self-awareness training 3. Self-regulation emphasizing arousal reduction through relaxation training, activity scheduling, and pacing 4. Cognitive compensatory strategies training	Beginning a mean ± SD of 8.2±4.4y after C and ending in 1mo.	Dose: 30—50min Frequency: Monthly with between-visit phone contact No. of administrations: 4 (+3 interspersed phone contacts)	Primary investigator's office	Qualifications: PhD Protocol training: Followed MAAT clinician's manual	Phone contact was made between visits for support and review. 97.5% of all possible contacts were made. All participants attended all 4 MAAT office visits.
Ferguson et al,[20] 2012	MAAT: 1. Education on memory and attention 2. Self-awareness training 3. Self-regulation emphasizing arousal reduction through	Beginning at least 18mo post-Tx (disease-free) and ending in 8wk	Dose: 30—50min Frequency: Monthly with between-visit phone contact No. of administrations: 4 (+3 interspersed phone contacts)	Primary investigator's office	Qualifications: PhD Protocol training: Followed MAAT clinician's manual	Phone contact was made between visits to reinforce the use of new behaviors or to modify the strategy.

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Table 4 (*continued*)

Study ID	Protocol	Timing of Cognitive Tx Relative to BC Tx	Intervention Schedule	Setting	Interventionist Competence	Adherence Monitoring
	relaxation training, activity scheduling, and pacing 4. Cognitive compensatory strategies training					
Kesler et al,[17] 2013	Computerized cognitive training program: Sessions began with the option to view instructions or to begin a session of 5 exercises (games) on switching, mental rotation, n-back memory, spatial sequencing, word stem completion, route planning, and rule-based puzzle solving.	Beginning at least 18mo after C (mean ± SD: 6±3y after C, some also with radiation and/or endocrine therapy) and ending in 12wk	Dose: 20—30min Frequency: 4×/wk No. of administrations: 48	Home	Qualifications: Clinical psychologist chose exercises. Protocol training: Computerized program delivered by Lumos Labs	The online program recorded and stored time and date of exercise activity, which was used to monitor adherence. Tx group showed 95% adherence.
Mar Fan et al,[24] 2008	d-MPH or identical-appearing placebo	Beginning after 1 C cycle (if scheduled to receive 4 cycles) or beginning after up to 2 C cycles (if scheduled to receive 6 cycles) and ending with the final C cycle	Dose: 5mg d-MPH for 1 C cycle (ie, 3—4wk), then 10mg d-MPH for remaining cycles (unless not well-tolerated, then reduced to 5mg), or identical placebo Frequency: 2×/d, in the morning and at lunchtime No. of administrations: Varied because timing of the onset of treatment varied	Home	Qualifications: Qualifications of persons administering treatment were not reported. Protocol training: Dissemination of research protocol to 3 participating Toronto outpatient clinics was not reported.	Participants were required to demonstrate placebo compliance to be admitted to study randomization and were telephoned by a study nurse weekly until on a stable dose of study drug for 2wk.
Mar Fan et al,[25] 2009 (follow-up study)	Epoetin alfa or standard care	Beginning during C when hemoglobin decreased to ≤12g/dL and ending	Dose: 40,000U epoetin alfa (or standard care) Frequency: 1×/wk	9 Ontario C treatment offices	Qualifications: Qualifications of persons administering	Monitoring of adherence to Tx was not reported.

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Table 4 (*continued*)

Study ID	Protocol	Timing of Cognitive Tx Relative to BC Tx	Intervention Schedule	Setting	Interventionist Competence	Adherence Monitoring
		with the final cycle of C	No. of administrations: 16–28wk depending on remaining C cycles		treatment were not reported. Protocol training: Dissemination of research protocol to 9 participating Ontario outpatient clinics was not reported.	
Milbury et al,[21] 2013	TSM program: Breathing, awareness and concentration techniques, plus visualization and sound exercises. Also, encouraged to practice independently using protocol materials.	Beginning 6–60mo after C (mean ± SD: 35±14.6mo after diagnosis) and ending in 6wk	Dose: 60min Frequency: 2×/wk No. of administrations: 12	MD Anderson Cancer Center and home	Qualifications: 3 meditation instructors Protocol training: CD with TSM program recording and printed instructions for home use	Out of 12 sessions, 23.5% of women attended all sessions, 72.2% attended at least 75%, and none attended <50% of the classes. On average, 33.4% practiced every day outside of class, 46.5% practiced more than twice per week but not every day, 10.1% practiced once per week, and 9.5% did not practice.
O'Shaughnessy et al,[16] 2005	Epoetin alfa administered by subcutaneous injections, or placebo administered in the same way	Beginning on 1st day of 4 C cycles (administered every 3wk) and ending in a maximum of 12wk (C phase)	Dose: 40,000U epoetin alfa (or comparable volume of placebo) with a dose escalation or reduction schedule to keep hemoglobin levels between 12 and 14g/dL Frequency: 1×/wk No. of administrations: maximum 12	13 U.S. C treatment offices	Qualifications: Physicians Protocol training: Dissemination of research protocol to 13 U.S. sites was not reported.	Although clinical and laboratory evaluations were performed as part of safety monitoring, there was no report of monitoring adherence to protocol.
Poppelreuter et al,[23] 2009	NPT: Tx 1: NPT of functional attention and memory tasks, practice in compensatory	Beginning after last Tx for BC (including C) and ending in 3–5wk	Dose: 60min Frequency: 4×/wk No. of administrations: 12–20 Mean ± SD: 11.88±2.42	Inpatient rehabilitation unit of the Tumor Biology Center, Freiburg, Germany	Qualifications: Occupational therapist Protocol training: NPT training set out in manual. PC training	Monitoring adherence to Tx was not reported for NPT. The PC training was continuously adapted to skill level

(*continued on next page*)

Table 4 (*continued*)

Study ID	Protocol	Timing of Cognitive Tx Relative to BC Tx	Intervention Schedule	Setting	Interventionist Competence	Adherence Monitoring
	strategies, and group discussion of personal experiences Tx 2: Adaptive computer-based (PC) training of individualized attention and memory tasks and meetings with therapist to discuss results and future procedures Tx 3: Control group: Standard inpatient rehabilitation				followed a standard program.	and discussed with therapists.

Abbreviations: BC, breast cancer; CD, compact disc; C, chemotherapy; d-MPH, d-methylphenidate; MAAT, Memory and Attention Adaptive Training; NPT, neuropsychological training; PC, personal computer; PhD, Doctor of Philosophy; RN, registered nurse; TSM, Tibetan sound meditation; Tx, treatment.

which minimizes the effects of nontreatment variables. The very low scores of Ferguson[19] in 2007, Ercoli,[18] and Baumann[12] and colleagues are primarily explained by the lack of a control group (or lack of baseline control group data, in the case of Baumann[12]). The importance of a control group to the PEDro scoring of treatment studies is underscored by the fact that in 2012, Ferguson[20] earned one of the highest of all PEDro scores performing a replication of the 2007 protocol[19] by properly adding a control group.

Half of the studies could have been improved by providing a baseline measurement of the severity of the condition being treated[6,12,18,19,21,25] and by concealing group allocation from the person determining participant eligibility.[6,12,18,19,23,25] Further, requiring that participants, therapists, and assessors are blind to group allocation would help to ensure that outcomes are a result of treatment and not of expectation effects; complete blinding was particularly lacking in the studies included in this systematic review.[6,12,16-25] Also, in half of the studies,[12,16,22-25] confidence in the fidelity of treatment would have been gained in the explicit reporting of the qualifications of the person(s) delivering treatment, dissemination of the treatment protocol, and monitoring adherence.

In general, more consistent use of eligibility criteria, which account for participant characteristics that bear on cognition, would also help to ensure that outcome differences (or lack of differences) between groups are a product of treatment and not of inequitable distribution of these potential confounds. To that end, lack of group differences in age, education, and menopausal status could be more firmly established with more consistent use of statistical comparison. Continuing to provide information on breast cancer diagnoses, cancer treatment types, and time post-cancer treatment will ensure group similarity in terms of these relevant characteristics. Such assurance allows for better interpretation of experimental results according to varying aspects of treatment, including its timing.

The optimal time for treatment of cognitive deficits relative to the timing of cancer treatment (ie, during or after) is not yet equivocally clear, but current evidence[17-20] suggests that treatment after chemotherapy holds the most promise. All of the medicinal treatments for cognitive deficits (ie, gingko biloba,[22] d-methylphenidate,[24] epoetin alfa[16,25]) began during chemotherapy, to no avail. On the other hand, strength training during chemotherapy[12] resulted in better pre- to postperformance (coinciding with the end of chemotherapy) on measures of attention, and the strength-training intervention group performed significantly better than the control group on measures of both attention and verbal memory. Unfortunately, interpretation of these between-group differences is limited by the lack of baseline control group data. During breast cancer treatment, restorative activities also resulted in improved measures of attention.[6]

Conversely, after chemotherapy treatment, restorative, Tibetan sound meditation did not result in improved measures of attention, verbal memory, or processing speed.[21] Likewise, about 2 months after breast cancer treatment, inpatient rehabilitative cognitive therapy (ie, neuropsychological training and computer-based training) failed to elicit significantly different outcomes than produced through usual rehabilitative care.[23] However, all therapies that were delivered at least 18 months after chemotherapy[17-20] produced some objective measure of significantly improved cognitive performance. Ferguson[19] suggested that later cognitive treatment might control for a "recovery effect" from the acute effects of chemotherapy and concomitant stress that influence cognitive function and appear to diminish within a year for many patients.

Table 5 Outcomes: neuropsychological tests, measurement time points, and statistical outcomes by cognitive domain

Study	Objective Neuropsychological Test Measures	Measurement Time Points	Statistical Outcomes by Cognitive Domain			
			Attention	Verbal Memory	Processing Speed	Other
Barton et al,[22] 2013: Ginkgo biloba vs Placebo	HSCS	Pre-Tx to 12mo post-C	NS	NS		NS
	TMT-A	Pre-Tx to 24mo post-C			NS	
	TMT-B	Pre-Tx to 24mo post-C			NS	
Baumann et al,[12] 2009: Strength-training intervention vs No intervention	d2 Test of Attention, Stress Test	Post-Tx comparison	$P=.019$ Tx>Ctrl			
	Memo-Test	Post-Tx comparison		$P=.048$ Tx>Ctrl		
	Wild-Intelligenz-Test (testing working memory)	Post-Tx comparison				NS
Cimprich,[6] 1993: Restorative intervention vs No intervention	TAS WAIS, Digit Span Forward Symbol Digit Modalities Letter Cancellation Necker Cube Pattern Control	3–18d, 18–60d, 60–90d	NS			
	TAS	3–90d postsurgery	$P=.01$ Tx>Ctrl			
Ercoli et al,[18] 2013: Cognitive rehabilitation program (within group)	CNS, Symbol Digit Test	Pre-Tx to post-Tx + 4mo f/u			$P<.05$ Post+4m> Pre	
	TMT-A	Pre-Tx to post-Tx + 4mo f/u			$P<.05$ Post+4m> Pre	
	CNS, Stroop Reaction Time	Pre-Tx to post-Tx + 4mo f/u			$P<.05$ Post+4m> Pre	
	CNS, Stroop Complex Reaction Time	Pre-Tx to post-Tx + 4mo f/u			$P<.05$ Post+4m>Pre	
	CNS, Finger Tapping	Pre-Tx to post-Tx + 4mo f/u			NS	
	CNS, Continuous Performance	Pre-Tx to post-Tx + 4mo f/u	NS			
	CNS, Shifting Attention (testing cognitive flexibility)	Pre-Tx to post-Tx + 4mo f/u				NS
Ercoli et al,[18] 2013: Cognitive rehabilitation program (within group) - continued	HVLT-R (testing total and delayed recall)	Pre-Tx to post-Tx + 4mo f/u		NS		NS
	Brief Visuospatial Memory Test (testing visuospatial memory)	Pre-Tx to post-Tx + 4mo f/u				
	TMT-B	Pre-Tx to post-Tx + 4mo f/u				NS
	Paced Auditory Serial Addition Test (testing processing speed and flexibility)	Pre-Tx to post-Tx + 4mo f/u			NS	
	Benton Judgment of Line Orientation (testing visuospatial)	Pre-Tx to post-Tx + 4mo f/u				NS

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Table 5 (*continued*)

Study	Objective Neuropsychological Test Measures	Measurement Time Points	Statistical Outcomes by Cognitive Domain			
			Attention	Verbal Memory	Processing Speed	Other
Ferguson et al,[19] 2007: Memory and attention training (within group)	CVLT-II	Pre-Tx to 2mo f/u		*P*=.00012mo f/u>Pre		
	WMS-III, Logical Memory I	Pre- to post-Tx		*P*<.0001 Post>Pre		
	WMS-III, Logical Memory II	Pre- to post-Tx		*P*<.0001 Post>Pre		
	WAIS-III, Digit Symbol Coding	Pre-Tx to 2mo f/u			*P*<.0001 2mo f/u>Pre	
	Stroop Color-Word Test, Interference	Pre- to post-Tx			*P*<.0001 Post>Pre	
	TMT-A	Pre-Tx to 2mo f/u			*P*=.001 2mo f/u>Pre	
	TMT-B	Pre-Tx to 6mo f/u			*P*=.01 6mo f/u>Pre	
Ferguson et al,[20] 2012: Memory and attention training vs Waitlist control	CVLT-II	Pre- to post-Tx		*P*<.05 Tx>Ctrl		
	CVLT-II	Pre-Tx to 2mo f/u		*P*<.05 Tx>Ctrl		
	CVLT-II	Pre-Tx to post-Tx		*P*<.001 Tx: Post>Pre		
	CVLT-II	Pre-Tx to 2mo f/u		*P*<.001 Tx: 2mo f/u>Pre		
Ferguson et al,[20] 2012: Memory and attention training vs Waitlist control - continued	D-KEFS: Trail Making Number Letter Trial Color-Word Interference Trial Color-Word and Switching Trial	Pre- to post-Tx + 2mo f/u			NS	
	WAIS-III: Digit Symbol Coding	Pre- to post-Tx + 2mo f/u			NS	
Kesler et al,[17] 2013: Computerized EF training vs Waitlist control	WAIS-IV, Symbol Search	Pre- to post-Tx			*P*=.009 Tx>Ctrl	
	Wisconsin Card Sorting Test (testing EF and cognitive flexibility)	Pre- to post-Tx				*P*=.008 Tx>Ctrl
	D-KEFS, Letter Fluency (testing EF and language)	Pre- to post-Tx				*P*=.003 Tx>Ctrl
	HVLT—Revised	Pre- to post-Tx		NS		
	WAIS-IV, Digit Span (testing working memory)			NS		

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Table 5 (*continued*)

Study	Objective Neuropsychological Test Measures	Measurement Time Points	Statistical Outcomes by Cognitive Domain			
			Attention	Verbal Memory	Processing Speed	Other
Mar Fan et al,[24] 2008*,†: d-methylphenidate vs Placebo	Mini-Mental State Exam					NS*
	HSCS (testing cognitive impairment)	Pre- to Post-Tx + 4—6mo f/u*				NS*
	HVLT-R (testing total recall, delayed recall, percent retained + discrimination index)	Pre- to Post-Tx + 4—6mo f/u†		NS†		
Mar Fan et al,[25] 2009*,†: Epoetin alfa vs Standard care (follow-up study)	Mini-Mental State Exam	12—30mo Post-C*				NS*
	HSCS (testing cognitive impairment)	12—30mo Post-C†				NS*
	HVLT-R (testing total recall, delayed recall, percent retained + discrimination index)			NS†		
Milbury et al,[21] 2013: Tibetan sound meditation vs Waitlist control	WAIS-III, Digit Span	Pre-Tx to 1mo f/u	NS			
	WAIS-III, Digit Symbol Coding	Pre-Tx to 1mo f/u			NS	
	Controlled Oral Word Association (testing verbal fluency)	Pre-Tx to 1mo f/u				NS
	Rey Auditory Verbal Learning Test	Pre-Tx to 1mo f/u		NS		
O'Shaughnessy et al,[16] 2005: Epoetin alfa vs Placebo	EXIT 25 (testing executive control function)	Pre-Tx to before C cycle 4 + 6mo f/u				No *P* values
	Clock Drawing Task 1 and 2 (testing cognitive impairment)	Pre-Tx to before C cycle 4 + 6mo f/u				No *P* values
Poppelreuter et al,[23] 2009‡: Neuropsychological training vs Computer-based training vs Tx as usual	TAP, Alertness without signal	Pre- to post-Tx‡			*P*<.001‡ Post>Pre	
	Rivermead Behavioral Memory Test	Pre- to post-Tx‡		*P*<.001‡ Post>Pre	All groups	
	Story: delayed recall					
	TAP, Alertness	Post-Tx to 6mo f/u‡		All groups		
	Rivermead Behavioral Memory Test	Post-Tx to 6mo f/u‡		NS	NS	

Abbreviations: C, chemotherapy; Ctrl, control; CVLT-II, California Verbal Learning Test—Second Edition; D-KEFS, Delis-Kaplan Executive Function System; EF, executive function; EXIT 25, Executive Interview; f/u, follow up; HSCS, High Sensitivity Cognitive Screen; NS, not significant; TAP, Test Battery for Attentional Performance; TAS, Total Attention Score; TMT, Trail Making Test; Tx, treatment; WAIS, Wechsler Adult Intelligence Scale; WMS, Wechsler Memory Scale.

* Comparing proportion of patients with moderate to severe impairment on HSCS.

† Comparing proportion of patients who scored in the lowest quartile of the HVLT-R.

‡ No group differences were reported.

It is important to consider that patients experience stress not only in the cancer (treatment) experience, but also in being confronted with cognitive deficits.[23] To address the stress factor, Kesler[17] suggested that relaxation exercises might enhance cognitive treatment protocols. In fact, the cognitive treatment protocols of both Ercoli[18] and Ferguson[19,20] incorporated a relaxation training component and resulted in varying levels of success in improving verbal memory and processing speed. However, as previously discussed, the Tibetan sound meditation program,[21] which was chiefly relaxation training, failed to achieve any objective measure of cognitive improvement.

The failure of the meditation program[21] may have been due to an inherent lack of efficacy in principally training relaxation to treat this disorder or may have been due to a dosing confound. The quantity of meditation exercise was not controlled given that in addition to the in-class protocol, participants were encouraged to practice on their own on the days that they did not meet with the instructor. Furthermore, the authors point out that participants in the control group may not have refrained from meditation training. Such potential dosing confounds were also evident in other protocols in which the amount of treatment was not controlled because intervention participants were free to choose to do more than the assigned amount of practice at home,[6,18] and nonintervention participants were not assessed for engaging in protocol-like activities.[6] Certainly, epoetin alfa dosing may have been a confounding factor in cognitive measurements taken at 6-month follow-up in O'Shaughnessy's investigation[16] because patients who completed the treatment phase according to protocol could also subsequently receive commercial epoetin alfa (if deemed clinically necessary by the investigator) and remain in the study. Such ambiguities in dosing muddle an understanding of optimal treatment types.

However, current evidence suggests that cognitive therapy may be the optimal type of treatment for cognitive deficits associated with treatment for breast cancer. Thus far, medicinal treatments (ie, ginkgo biloba,[22] d-methylphenidate,[24] and epoetin alfa[16,25]) have been ineffective in producing objective measurements of improved cognition. Although strength-training exercises produced promising outcomes,[12] efficacy evaluation is limited by methodological shortcomings. It is possible that exercise was a hidden factor in the positive outcomes of participant-chosen restorative activities (eg, walking in a park, playing with pets) in the study performed by Cimprich.[6] Future research that entails forms of exercise would benefit from operationalizing and measuring this variable (akin to the need for quantifying encouragement and support as treatment variables).

Another type of treatment, home-based computerized cognitive training,[17] resulted in improved measures of processing speed but not of verbal memory. In contrast, inpatient, adaptive computerized cognitive training[23] may have been successful in improving measures of verbal memory and attention, but not more so than engaging in neuropsychological training or standard rehabilitative care. Therefore, it remains unclear whether computer-based training is an effective type of treatment for the cognitive deficits associated with treatment for breast cancer.

Inpatient, cognitive neuropsychological training[23] of everyday memory and attention activities, together with compensatory strategies, may have been successful in improving scores of memory and attention (but again, not more than computer-based training or standard rehabilitative care). However, 2 other cognitive rehabilitation programs[18-20] that included training in everyday memory and attention activities, together with compensatory strategies (eg, using planners, calendars, sticky notes), were successful in achieving significant improvement in pre-to postmeasures of cognition. These programs also included training in relaxation and self-pacing, education on empirical findings of the effects of chemotherapy on cognition, and practice outside the research setting. Furthermore, Ferguson[19,20] included self-awareness training (ie, learning to self-monitor and to identify situations in which cognitive failures are likely to occur). Likewise, Ercoli[18] included a meta-awareness component in requiring participants to note how much time passed before they felt their attention wane.

Comparing the results of these 2 cognitive therapies[18,19] in relation to neuropsychological test measures reveals that Ercoli[18] and Ferguson[19] both achieved significant within-group improvement in scores of processing speed, measured with Stroop, Symbol Digit, and Trail Making tests. However, in 2012, Ferguson[20] did not achieve significant differences in processing speed. Ferguson[19,20] did demonstrate significant improvement in verbal learning both within the intervention groups and between the intervention group and the control group,[20] measured with the California Verbal Learning Test−Second Edition. In contrast, Ercoli[18] did not achieve significant improvement in verbal learning scores measured with the HVLT-R. Notably, Ferguson[19,20] stated that neuropsychological tests were specifically chosen on the basis of sensitivity to the cognitive impairments of breast cancer survivors treated with chemotherapy.

Considering the similarities between protocols (Ercoli[18] and Ferguson[19,20]), it is not apparent whether the lack of improved measures of verbal learning (Ercoli[18]) reflects a lack of treatment effects or a lack of HVLT-R sensitivity to detect changes in this population. Using the HVLT-R, Kesler[17] and Mar Fan[24,25] and colleagues also failed to demonstrate a significant change. On the topic of assessment instruments, Poppelreuter[23] points to both the low ecologic validity of many neuropsychological tests and the fact that they were developed for other target groups and therefore may not detect subtle deficits in this population. In accord, in using the High Sensitivity Cognitive Screen, both Barton[22] and Mar Fan[24] suggested that its results be interpreted with caution because of the confounding influence of known practice effects. Further, Kesler[17] postulated that a seeming lack of training effects on working memory, despite several exercises in the protocol that focused on that particular skill, may have reflected an incorrect choice of outcome measure. Additionally, the ill-suited use of some neuropsychological tests in this population may, at least in part, account for oft-reported poor correlations between objective and subjective measures of cognitive impairment after treatment for breast cancer.[20-23] Identifying objective measures that are adequately sensitive to this disorder would aid in setting optimal therapy goals.

Study limitations

This review is limited by having only included articles that reported objective neuropsychological measures of cognitive performance. Articles that strictly reported subjective measurement outcomes of treatments are not included. This decision was made in recognition of the standing poor correlations between objective and subjective measurements of cognition in this population.[20-23] The aim was to reach an understanding of that which is known from an objective standpoint, although certainly the subjective experience of cognitive deficits is at least equally important. This review is also limited in having only included articles reporting on treatments for cognitive dysfunction after treatment for breast cancer in women. This decision was made to control for relevant biological differences in cancer types and in sex.

Conclusions

In summary, the primary set of cognitive domains that have been tested and for which treatment has resulted in significantly improved objective measures of assessment were verbal memory,[12,19,20] attention,[6,12] and processing speed.[17-19] Secondarily, Baumann[12] demonstrated improved measures of working memory, and Kesler[17] demonstrated some improved measures of executive function using computerized cognitive training. Future research is needed to establish whether computerized cognitive training is an effective type of treatment for the cognitive deficits associated with chemotherapy treatment for breast cancer in women. Additionally, research is needed to identify objective assessment tools that are sensitive to this disorder. Certainly, linguistic measures (eg, naming tasks) should be added to neuropsychological test batteries to specifically assess language, including word retrieval. Close attention to research methodology, especially the blinding of researchers, participants, and assessors, along with eligibility criteria, which account for participant characteristics that bear on cognition, is warranted. Furthermore, more precise accounts of the dose of treatment would allow for more accurate replication of studies, particularly when practice at home is assigned. In addition, the stress associated with the breast cancer (treatment) experience, as well as the distress in being confronted with cognitive deficits, should be considered. To date, it seems that cognitive therapy protocols delivered after chemotherapy and aimed at improving verbal memory, attention, and processing speed hold the most promise.

From both patient and provider perspectives, addressing these fundamental cognitive abilities is a critical component in breast cancer rehabilitation. Developing effective cognitive therapies will support the ability of survivors to resume normal activities of daily living and to adhere to cancer treatment protocols. Patient capacities to attend to incoming information, to process with adequate efficiency, and to recall and produce words normally have far-reaching impact. There are profound implications for self-esteem, the quality of familial and social relationships, occupational aptitude, and the ability to sustain the conscientious self-care necessary to comply with all aspects of continuing cancer care. Furthermore, awareness of the impact of these deficits, as well as the state of the science in treating them, has important clinical implications for the entire health care team. Key implications include improving the quality of interactions with breast cancer patients, facilitating collaborative relationships, and communicating with enhanced clarity about these cognitive deficits and about relevant treatment protocols under development.

Keywords

Attention; Breast neoplasms; Cognition; Drug therapy; Mental processes; Rehabilitation; Psychological tests

Corresponding author

Diane F. Morean, PhD, 345 E Superior St, Ste 1328, Chicago, IL 60611. *E-mail address:* dmorean@ricres.org.

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Appendix 1 Search Terms and Strategies

MEDLINE (PubMed), January 22, 2014: Retrieved 560 results.

((((((“Consolidation Chemotherapy”[Mesh] OR “Induction Chemotherapy”[Mesh] OR “Maintenance Chemotherapy”[Mesh] OR “Chemotherapy, Adjuvant”[Mesh] OR “Chemotherapy, Cancer, Regional Perfusion”[Mesh] OR “Antineoplastic Combined Chemotherapy Protocols”[Mesh] OR “Antineoplastic Agents”[Mesh] OR “chemo”[all fields] OR “chemotherapy”[all fields])

AND (“breast neoplasms”[MeSH Terms] OR “breast cancer”[all fields]))

AND (((“Recognition (Psychology)”[Mesh] OR “Mental Recall”[Mesh] OR “Memory”[Mesh] OR “Memory Disorders”[Mesh:noexp] OR “object naming”[all fields] OR “action naming”[all fields] OR “forgetting”[all fields] OR “rehearsal”[all fields] OR “word finding”[all fields] OR “word retrieval”[All Fields] OR “delayed recall”[all fields] OR “verbal recall”[all fields] OR “semantic memory”[all fields] OR “memory consolidation”[all fields] OR “working memory”[all fields] OR “short-term memory”[all fields] OR “long-term memory”[all fields] OR “declarative memory”[all fields] OR “non-declarative memory”[all fields] OR “explicit memory”[all fields] OR “implicit memory”[all fields] OR “episodic memory”[all fields] OR “procedural memory”[all fields])

OR (“Language Disorders”[Mesh] OR “Anomia”[Mesh] OR “Speech Disorders”[Mesh:noexp] OR “Language”[Mesh:noexp] OR “Linguistics”[Mesh:noexp] OR “Psycholinguistics”[Mesh] OR “Semantics”[Mesh] OR “Vocabulary”[Mesh] OR “Learning disorders”[MeSH] OR “Speech”[MeSH] OR “Communication disorders”[MeSH:noexp] OR “verbal fluency”[all fields] OR “linguistic”[all fields] OR “naming”[all fields] OR “noun retrieval”[All Fields] OR “verb retrieval”[All Fields] OR “noun naming”[All Fields] OR “verb naming”[All Fields]))

OR (“Cognition”[Mesh] OR “Executive Function”[Mesh] OR “Attention”[Mesh] OR “Cognition Disorders”[Mesh] OR “Mild Cognitive Impairment”[Mesh] OR “Mental Status Schedule”[Mesh] OR “Psychiatric Status Rating Scales”[Mesh] OR “Learning”[Mesh] OR “Thinking”[Mesh:noexp] OR “Judgment”[Mesh] OR “Problem Solving”[Mesh] OR “Confusion”[Mesh:noexp] OR “Dyscalculia”[Mesh] OR “neurocognition”[All Fields] OR “mental status”[All Fields] OR “multi-tasking”[All Fields] OR “Dyscalculia”[all fields] OR “confusion”[all fields] OR “cognitive”[all fields])))

NOT “child”[MeSH])

NOT (“animals”[MeSH Terms] NOT (“animals”[MeSH Terms] AND “humans”[MeSH Terms])))

OR (((chemobrain OR “chemo brain” OR “chemofog” OR “chemo fog”)) AND (“breast neoplasms”[MeSH Terms] OR “breast cancer”[all fields]))

EMBASE, January 22, 2014: Retrieved 900 results

‘memory disorder’/de OR ‘memory’/exp OR ‘mental capacity’/exp OR ‘mental performance’/de OR ‘mental load’/de OR ‘mental task’/de OR ‘social cognition’/de OR ‘thinking’/de OR ‘anticipation’/de OR ‘association’/de OR ‘concept analysis’/de OR ‘concept formation’/de OR ‘critical thinking’/de OR ‘problem

identification'/de OR 'problem solving'/de OR 'retention, psychology' OR 'recognition, psychology' OR 'mental recall' OR 'non-declarative memory' OR 'object naming' OR 'action naming' OR 'forgetting' OR 'rehearsal' OR 'word finding' OR 'word retrieval' OR 'delayed recall' OR 'verbal recall'

OR

'language'/de OR 'language processing'/de OR 'communication disorder'/de OR 'language disability'/de OR 'agraphia'/de OR 'alexia'/exp OR 'aphasia'/de OR 'anomia'/exp OR 'auditory processing disorder'/de OR 'dysgraphia'/de OR 'dyslexia'/de OR 'dysphasia'/de OR 'speech disorder'/de OR 'cluttering'/de OR 'echolalia'/de OR 'fluency disorder'/de OR 'logorrhea'/de OR 'stuttering'/de OR 'speech'/de OR 'learning disorder'/de OR 'concentration loss'/de OR 'dyscalculia'/de OR 'linguistics'/de OR 'psycholinguistics':ab,ti OR 'neurolinguistic programming':ab,ti OR 'semantic differential method'/de OR 'semantics'/de OR 'semantics' OR 'vocabulary':ab,ti OR 'voice'/de OR 'speech articulation'/de OR 'verbal fluency' OR 'linguistic' OR 'naming' OR 'noun retrieval' OR 'verb retrieval' OR 'noun naming' OR 'verb naming'

OR

'cognitive defect'/de OR 'mental health'/de OR 'confusion'/de OR 'cognition'/de OR 'alertness'/de OR 'awareness'/de OR 'attention'/de OR 'distractibility'/de OR 'mental concentration'/de OR 'selective attention'/de OR 'cognitive reserve'/de OR 'confusion (uncertainty)'/de OR 'executive function'/de OR 'learning'/exp OR 'cognition disorders' OR 'cognitive disorders' OR 'mental status schedule' OR 'psychological rating scale'/de OR 'psychiatric status rating scales' OR 'judgment' OR 'neurocognition' OR 'mental status' OR 'multi-tasking' OR 'confusion' OR 'cognitive'

COMBINED using AND with:

'antineoplastic agent'/exp OR 'antineoplastic agent' OR 'chemo' OR 'chemotherapy'/exp OR 'chemotherapy'

AND

'breast cancer'/exp OR 'breast cancer':ti

Animal and children studies were removed using a special filter: [humans]/lim NOT ('child'/exp OR 'adolescent'/exp)

Added search string to eliminate MEDLINE articles and keep content Embase unique.

[embase]/lim OR [embase classic]/lim NOT [medline]/lim

934 articles.

'chemotherapy'/exp OR 'antineoplastic agent'/exp OR 'chemo' OR 'chemotherapy'

+ breast cancer − 45

Combine these 2 sets using OR = 945

After removing duplicates against PubMed, down to 900.

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