Breast Cancer: Targets and Therapy

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REVIEW

Are there efficacious treatments for treating the fatigue–sleep disturbance–depression symptom cluster in breast cancer patients? A Rapid Evidence Assessment of the Literature (REAL©)

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Shamini Jain[1]
Courtney Boyd[2]
Lavinia Fiorentino[1]
Raheleh Khorsan[3]
Cindy Crawford[2]

[1]Department of Psychiatry, University of California San Diego, San Diego, CA, USA; [2]Samueli Institute, Alexandria, VA, USA; [3]Samueli Institute, Corona Del Mar, CA, USA

Purpose: While fatigue, sleep disturbance, and depression often co-occur in breast cancer patients, treatment efficacy for this symptom cluster is unknown. A systematic review was conducted to determine whether there are specific interventions (ie, medical, pharmacological, behavioral, psychological, and complementary medicine approaches) that are effective in mitigating the fatigue–sleep disturbance–depression symptom cluster in breast cancer patients, using the Rapid Evidence Assessment of the Literature (REAL©) process.

Methods: Peer-reviewed literature was searched across multiple databases; from database inception – October 2011, using keywords pre-identified to capture randomized controlled trials (RCT) relevant to the research question. Methodological bias was assessed using the Scottish Intercollegiate Guidelines Network (SIGN) 50 checklist. Confidence in the estimate of effect and assessment of safety were also evaluated across the categories of included interventions via the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) methodology.

Results: The initial search yielded 531 citations, of which 41 met the inclusion criteria. Of these, twelve RCTs reported on all three symptoms, and eight of these were able to be included in the GRADE analysis. The remaining 29 RCTs reported on two symptoms. Studies were of mixed quality and many were underpowered. Overall, results suggest that there is: 1) promising evidence for the effectiveness of various treatment types in mitigating sleep disturbance in breast cancer patients; 2) mixed evidence for fatigue; 3) little evidence for treating depression; and 4) no clear evidence that treatment of one symptom results in effective treatment for other symptoms.

Conclusion: More high-quality studies are needed to determine the impact of varied treatments in mitigating the fatigue–sleep disturbance–depression symptom cluster in breast cancer patients. Furthermore, we encourage future studies to examine the psychometric and clinical validity of the hypothesized relationship between the symptoms in the fatigue–sleep disturbance–depression symptom cluster.

Keywords: fatigue, sleep disturbance, depression, symptom cluster, breast cancer, Rapid Evidence Assessment of the Literature

Introduction

Treatments for breast cancer presently provide more hope than ever in terms of treating the cancer and reducing mortality. For nearly all women in the US, with the exception of Native American/Alaska Natives, breast cancer mortality continues to decline,[1] suggesting that our methods of screening and treatment are steadily improving for breast cancer treatment. While survival rates for breast cancer patients continue to improve, behavioral and psychosocial side effects from breast cancer and its treatment

Correspondence: Shamini Jain
Department of Psychiatry, University of California San Diego, 200 Gilman Drive, La Jolla, CA 92093-0818, USA
Email sjain@ucsd.edu

remain a large problem for these patients, impacting their day-to-day functioning as well as quality of life. Among the most common complaints reported by breast cancer patients during and after treatment are fatigue, sleep disturbance, and depression. These symptoms have often been found to co-occur in breast cancer populations both during and after treatment.[2–4] The co-occurrence of these and other related symptoms in breast and other cancers has spurred lively discussion about the existence of symptom clusters; an area of study that is relatively in its infancy with no consistent clinical or psychometric measurements.[5,6]

The etiology of each of these symptoms as well as the potential reasons for their co-occurrence is complex, with psychosocial and physical functioning, type of cancer treatment, and medical diagnostic variables all potentially playing roles in both the onset and maintenance of these symptoms. Current evidence suggests that inflammatory and neuroendocrine dysregulation are associated with, and may help perpetuate the co-occurrence of these symptoms within cancer and other populations,[7–9] through a process often termed "sickness behavior".[10] Chronic low-grade inflammation (which is thought to be primarily initiated by the cancer and some forms of cancer treatment) facilitates the manifestation of behavioral symptoms including sleep disturbance, fatigue, and depression in the patient. Evidence also suggests that the occurrence and perpetuation of sickness behavior responses to cancer and cancer treatment may be moderated by dispositional factors, including genetic polymorphisms in genes regulating inflammatory responses[11] and premorbid psychosocial functioning.[12]

While mechanistic research efforts continue to elucidate the pathophysiology underlying the co-occurrence and persistence of these symptoms, there is consistent evidence that a greater number of co-occurrence of symptoms leads to poorer quality of life,[13] increased neuropathic pain,[14] and impaired overall functioning[15] in breast cancer patients. It is therefore important to understand what types of treatments may be most successful not only in treating one symptom, but in potentially successfully treating symptoms that co-occur. Finding interventions that efficiently treat symptom clusters may yield better outcomes for patients as well as lead to greater cost-efficiency in terms of providing interventions that may target more than one symptom.

To our knowledge, there are no systematic reviews exploring the treatments for the co-occurring symptoms of fatigue, sleep disturbance, and depression in breast cancer patients and survivors. We conducted a systematic review to examine which treatments are the most efficacious for treating the fatigue–sleep disturbance–depression symptom cluster in breast cancer patients. The specific objectives of this review were to: 1) survey the literature on treatments addressing at least two of the three symptoms in the fatigue–sleep disturbance–depression symptom cluster; 2) examine and assess the quantity, quality and efficacy based on studies as reported in the literature; 3) characterize the treatments as behavioral, psychosocial, complementary/alternative medicine (CAM), medical, or pharmacological to better compare treatment types; 4) critically evaluate the efficacy and safety of interventions that examined the impact on the three symptoms based on the literature; and 5) identify gap areas that exist in the literature in order to suggest next steps in research based on our analysis of the pooled literature.

Methods

To conduct this systematic review, we utilized the Rapid Evidence Assessment of the Literature (REAL©; Samueli Institute, Alexandria, VA, USA) methodology, which is an expedient approach for conducting systematic reviews.[16,17] REAL© reviews primarily focus on synthesis of peer-reviewed randomized controlled trials (RCTs) published in the English language, and utilize searching across multiple databases. Details on the REAL© methodology for this review are described to follow.

Search strategy

The following databases were searched from database inception through October 2011: PubMed, EMBASE, CINAHL, Cochrane, and PsycINFO. The following four initial searches, as entered into PubMed, were combined to produce the final search: 1) (breast cancer) and (depression or depress* or "negative affect" or "negative mood"); 2) (breast cancer) and (fatigue or "vital exhaustion"); 3) (breast cancer) and ("sleep disturbance" or "insomnia" or "sleep disruption" or sleep); and 4) (breast cancer) and ("symptom cluster"). The Medical Subject Headings (MeSH) terms and explosions across the terms were applied where applicable and relevant; where MeSH did not apply, variations of the search strategy were used. As this REAL© focused on the fatigue–sleep disturbance–depression cluster components, we considered the terms depressed mood, dysthymia, negative affect, emotional distress and negative mood to be synonymous with depression; insomnia and sleep disruption synonymous with sleep disturbance; and vital exhaustion and cancer-related fatigue synonymous with fatigue. The complete search strategies in each of the databases searched can be obtained by contacting the primary author.

Inclusion/exclusion criteria

The inclusion criteria were developed in accordance with the Population, Intervention, Control, and Outcome[18] (PICO)

framework. Articles were included if they met the following criteria: 1) RCT study design; 2) population consisting of active patients and/or survivors of breast cancer who participated in any treatment intervention; and 3) included at least two of the three cluster symptoms of fatigue, sleep disturbance, and depression (as defined via the search strategy).

Two screeners (CL, RK) screened titles and abstracts for relevance based on the inclusion criteria. Once sufficient inter-rater reliability (Cohen's Kappa >88%) was achieved, the screeners screened the remaining articles independently, resolving arising queries through discussion with either the review manager (CC) and/or the subject matter experts (SMEs; SJ, LF).

Quality assessment and data extraction

Methodological quality of the included studies was assessed by two reviewers (CL, RK) using the Scottish Intercollegiate Guidelines Network (SIGN 50) checklist for RCTs, a widely accepted, reliable, and validated assessment tool[19] (see Figure 1). The reviewers were fully trained in the methodology.

The following information was extracted from each included study: population; initial sample and dropout rates; treatment and control interventions; relevant outcomes and results; the reporting and severity of adverse events; the informed consent process; power calculations; effect sizes; and author's main conclusions.

Section 1 Internal validity*	
Item	Description
1.1	The study addresses appropriate and clearly focused question
1.2	The assignment of subjects to treatment groups is randomized
1.3	An adequate concealment method is used
1.4	Subjects and investigators are kept blind about treatment allocation
1.5	The treatment and control groups are similar at the start of the trial
1.6	The only difference between groups is the treatment under investigation
1.7	All relevant outcomes are measured in a standard, valid and reliable way
1.8	What percentage of subjects in each treatment arm dropped out before the study was completed?
1.9	All subjects are analyzed in the groups to which they were randomly allocated (intention to treat analysis)
1.10	Where the study is carried out at more than one site, results are comparable for all sites
Each item in section 1 is to be evaluated using these criteria: (i) Well covered (ii) Adequately addressed (iii) Poorly addressed (iv) Not applicable (NA) only for questions 1.4, 1.6, 1.10	

Section 2 Overall assessment	
Score options: ++, +, – based on following (modifications to SIGN 50 criteria in italics):	
++	All or most of the criteria have been fulfilled. Where they have not been fulfilled the conclusions of the study are thought very unlikely to alter. *An article receives this score if there are 0 criteria scored as poorly addressed*
+	Some of the criteria have been fulfilled. Those criteria that have not been fulfilled or not adequately described are thought unlikely to alter the conclusions. *An article receives this score if 1–3 criteria are scored as poorly addressed*
–	Few or no criteria fulfilled. The conclusions of the study are thought likely or very likely to alter. *An article receives this score if more than 3 criteria are scored as poorly addressed*

Figure 1 SIGN 50 checklist for RCT Study Design.
Note: Adapted from Scottish Intercollegiate Guidelines Network (SIGN). A Guideline Developer's Handbook. Edinburgh: SIGN; 2001. (SIGN publication no. 50). [cited 24 June 2014]. Available from URL: http://www.sign.ac.uk.[19] Adapted from Crawford C, Wallerstedt DB, Khorsan R, Clausen SS, Jonas WB, Walter JA. A systematic review of biopsychosocial training programs for the self-management of emotional stress: potential applications for the military. Evid Based Complement Alternat Med. 2013;747694. Epub 2013 Sep 23.[72]
Abbreviations: RCT, randomized controlled trial; SIGN, Scottish Intercollegiate Guidelines Network.

Patients were grouped into the following categories: non-metastatic, metastatic, mixed (ie, population included both metastatic and non-metastatic patients), and survivors (those who were no longer receiving active treatment). Treatment interventions were grouped into the following categories: behavioral (eg, exercise), psychosocial (eg, cognitive–behavioral therapy and supportive counseling), CAM (eg, yoga and herbal medicine), medical procedures (eg, radiation, ovarian ablation), or pharmacological (eg, anti-depressants).

Data synthesis and analysis

Once the quality assessment of individual studies was completed, two SMEs (SJ and LF) performed a quality assessment of the overall literature pool for each treatment intervention and patient population using a modified version of the Grading of Recommendation Assessment, Development and Evaluation (GRADE), an internationally accepted approach to grading the quality of evidence and strength of recommendations.[20] SMEs used the GRADE to examine the results of the review for each population and treatment type in order to: 1) examine the confidence in and magnitude of the estimate of the effect; 2) assign a safety grade; and 3) develop recommendations (such as strong or weak recommendations in favor of or against the use of such treatments) for the included literature pool based on the REAL© results. The SMEs received formal training in the modified GRADE, conducted the GRADE independently, and then met as a team to resolve any discrepancies and come to consensus on overall recommendations.

Results

The main objective of this systematic review was to focus on the three symptom cluster for breast cancer. However, due to our comprehensive search strategy, the authors also found several articles that focused on two of the three symptoms. Due to resources and the main objective of this review however, the authors only report on the three symptom cluster in detail assessing the overall literature pool to come up with recommendations using GRADE methodology. The authors share the two symptom cluster studies in Table 1 as a frame of reference only and hope to perform future analysis of these studies in the future. The studies on two symptoms can be found in Table 1[21–49] and three symptoms in Table 2.[50–61]

Of the 531 citations yielded from the database searches, 41 RCTs fit the inclusion criteria and were subsequently included in the quality assessment and data extraction phase of the REAL©. Of these, 29 RCTs reported on two component clusters; Table 1 categorizes these by treatment type and population, and reports their individual characteristics and overall SIGN 50 scores. The remaining twelve RCTs reported on all three component clusters (Table 2), eight of which were able to be included in the GRADE analysis (Figure 2).

Both Tables 1 and 2 categorize studies according to treatment type (behavioral, CAM, medical procedures, psychosocial, or pharmacological) and across four population types including non-metastatic, metastatic, mixed (comprised of both non-metastatic and metastatic patients), and survivors.

Characteristics of included studies

Methodological quality of included studies according to SIGN 50 criteria

According to SIGN 50 criteria[19] (see Figure 1), the majority (63.4%) of the studies received an overall SIGN 50 score of + (high quality), with the remaining (26.8%) articles receiving scores of – (low quality), and fewer (9.8%) receiving a score of ++ (excellent quality).

Most of the 41 RCTs (92.6%) included in the review addressed an appropriate and clearly focused question either well or adequately. Almost half of the articles addressed randomization poorly (46.3%), with 22.0% of articles doing so adequately, and 31.7% doing so well. The majority of articles (65.8%) poorly addressed allocation concealment, with less than a third of articles addressing this criterion either well (22.0%) or adequately (12.2%). Baseline similarities between treatment and control groups were well addressed in the majority of articles (70.7%) with a small percentage of studies addressing it adequately (19.5%) or poorly (9.8%). Outcome reliability and validity was addressed well by 41.4% of articles with the remaining articles addressing this criterion adequately (22.0%) or poorly (36.6%). Although many studies (53.7%) reported attrition rates adequately or well, many articles also poorly addressed intention-to-treat analyses (46.3%).

Three criteria, blinding, treatment group differences, and multi-site differences, were not applicable to all studies (ie, blinding not possible, treatment groups are too inherently different from each other, study only conducted at one site). Consequently, we only assessed the articles where these criteria were applicable. Of the twelve RCTs where blinding was possible, blinding of treatment allocation was addressed well and adequately in 41.7% and 25.0% of the studies, respectively; approximately 33.3% of these studies addressed this criterion poorly. We were able to assess twelve RCTs for treatment difference between groups; many of these articles did so either well (33.3%) or adequately (41.7%), with

25.0% of the articles doing so poorly. Lastly, only a small number of studies (n=12) were conducted at multiple sites; the majority of these poorly addressed (66.6%) similarity of site results, with the remaining articles doing either well (16.7%) or adequately (16.7%).

Safety assessment

Of the 41 articles included in our review, only 16 reported on adverse events with four studies[30,36,46,55] reporting no adverse events. Ten studies reported adverse events including gastrointestinal problems,[31,32,43,53] dizziness,[31,32] changes in blood pressure,[31,34,60] weakness,[31] anemia,[32] pain/discomfort,[24,34,47] headache,[43,60] insomnia,[53] palpitations,[53] anxiety,[53] skin rashes and angioedema,[51] jaundice/liver damage,[51] dry mouth,[21] changes in taste,[21,51] and disease progression.[24] Additionally, two studies[22,23] reported adverse events occurred but did not describe them.

GRADE analysis

The GRADE analysis was conducted on studies addressing all three symptoms (fatigue, sleep disturbance, and depression) in order to provide recommendations regarding treatment of the symptom cluster as a whole. While we present the tables on studies that examined two of the three symptoms to familiarize the reader with the breadth of literature available on examining intervention effects on co-occurring symptoms within this cluster, as our primary interest was on examining studies that investigated effects on the symptom cluster as defined by sleep disturbance, depressed mood, and fatigue, we chose to conduct the GRADE on studies that examined these three symptoms. There were twelve RCTs that addressed all three symptoms that were included in this review; of these, one study[50] (examining a psychosocial intervention) reported results in metastatic breast cancer patients, five studies (two examining behavioral interventions,[54,55] two examining medical interventions,[51,52] and one examining a CAM intervention)[53] reported results in non-metastatic breast cancer patients, three studies (two examining psychosocial interventions,[57,58] one examining a pharmacological intervention)[56] reported results in mixed (metastatic and non-metastatic) breast cancer patients, and three studies (two examining pharmacological interventions,[59,60] one examining a CAM intervention)[61] reported results on survivors (patients who had completed adjuvant or neo-adjuvant treatment).

Because GRADE analyses require at least two studies per category, only eight of these three RCTs addressing three symptoms were included in the final analysis; four studies[50,53,56,61] were excluded because they were the only studies in their respective categories (ie, CAM treatment for non-metastatic and survivor populations, pharmacological treatment for mixed population, psychosocial treatment for metastatic population).

The GRADE results are presented in Table 3 and briefly summarized below. In this GRADE synthesis, we noted that most studies did not report effect sizes, nor describe the presence or absence of adverse events. Our final GRADE recommendations, therefore, are given considering these major omissions of reporting in the reviewed studies.

Non-metastatic population

Behavioral treatment

Two studies[54,55] comparing walking exercise programs to usual care in a non-metastatic population, were poor (–) quality and reported improvements in sleep disturbance, but no significant differences for depression. Results were mixed for fatigue symptoms, as one study[55] reported improvement in fatigue levels while the second study[54] reported no such differences. Adverse events were only discussed in one study,[55] which reported no adverse events. Because effect sizes were not reported, and both the quality and power of these studies was low, no recommendation could be given for this treatment type.

Medical treatment

Two studies[51,52] examined medical procedures as treatment options for reducing fatigue, sleep disturbance, and depression in this population. The higher (+) quality study,[51] comparing radiotherapy to no radiotherapy, reported improvements in insomnia with radiotherapy, but no significant differences between groups for depression and fatigue. The second study[52] was of poor (–) quality, and compared ovarian ablation with chemotherapy. This study reported lower levels of fatigue, sleep disturbance, and depression in the ovarian ablation versus chemotherapy group. Effect sizes were not reported in either study, and only one study[51] reported adverse events (such as skin rashes, angioedema, taste changes, jaundice, and liver damage). Consequently, a weak recommendation in favor was given for the usage of medical treatment methods for impacting the symptoms examined for this population.

CAM treatment

There was only one study (of high [++] quality)[53] examining a CAM treatment in a non-metastatic population. Although fatigue and sleep disturbance symptoms were improved following administration of the herbal compound guarana,

Table 1 Characteristics and SIGN 50 score of included studies, grouped by population and treatment type, that address two cluster components (n=29)

Citation	Cluster	Population description	Description of intervention	Description of control
Metastatic				
Pharmacological				
Bottomley et al[21]	Fatigue, sleep disturbance	275 patients with metastatic breast cancer patients[b] with a median age of 53 years (C) and 52 years (T) (SD = ND)	Doxorubicin 60 mg/m^2 as an iv bolus plus paclitaxel 175 mg/m^2 as a 3-hr infusion Assessment time points: 2 wks pre-intervention, midpoint (cycles 2, 4, and 6) and EoT (3 mons after the last cycle, with a time window of 10 wks)	Doxorubicin 60 mg/m^2 plus cyclophosphamide 600 mg/m^2
Svensson et al[22]	Fatigue, sleep disturbance	287 female metastatic breast cancer patients[b] (≤ Stage II) (mean age = ND)	ET (epirubicin plus paclitaxel): Epirubicin 75 mg/m^2 by iv infusion Assessment time points: baseline, 2 mons, and 9 mons	TEX (epirubicin plus paclitaxel plus capecitabine): Epirubicin 75 mg/m^2 by iv infusion Both groups were offered 2nd line treatment with oral capecitabine when the disease progressed
Hakamies-Blomqvist et al[23]	Fatigue, sleep disturbance	283 female metastatic breast cancer patients[d] with a mean age of 52.13 years (T) and 52.16 (C)	Docetaxel 100 mg/m^2 Assessment time points: baseline and before each treatment (cycles 2–6)	MF: sequential methotrexate and 5-fluorouracil at 200 mg/m^2 and 600 mg/m^2, respectively
Diel et al[24]	Fatigue, sleep disturbance	466 female breast cancer patients[d] (Stage = ND) with a mean age of 54.5±11.5 (C), 55.3±10.9 (2MGIBT) and 56.1±11.4 (6MGIBT) years	2MGIBT: Ibandronate 2 mg by iv bolus injection 6MGIBT: Ibandronate 6 mg by iv infusion Assessment time points: baseline, day before each study visit (Visits 2–5, 8, 11, 14, 17, 20, 23, 26)	Placebo
Geels et al[25]	Depression, sleep disturbance	300 female breast cancer patients[b] (Stage and mean age = ND)	Doxorubicin 40 mg by iv Assessment time points: baseline and every 3 wks (1st day of each new cycle)	Doxorubicin 60 mg by iv
Psychosocial				
Bordeleau et al[26]	Fatigue, sleep disturbance	215 female metastatic breast cancer patients[d] with a mean age of 49.4±8.4 (T) and 51.5±10.0 (C) years	Supportive-expressive therapy (SET): Supportive-expressive therapy receiving UC plus educational materials about breast cancer and its treatment, relaxation, and nutrition. Assessment time points: baseline, 4 mons, 8 mons, and FU (12 mons)	UC plus educational materials about treatment, relaxation, and nutrition at every 6 mons
Williams and Schreier[27]	Fatigue, sleep disturbance	71 breast cancer patients[b] (≤ Stage 4) with a mean age of 50.39 (T) and 50.42 (C) years, (SD = ND)	Audiotape on self-care behaviors and SE (SCB): 20-min audiotape that consisted of education about exercise and relaxation to manage anxiety, fatigue, and sleep problems Assessment time points: 1-mon, 3 mons	Received the standard education and care given to all patients during CHT
Low et al[28]	Depression sleep, disturbance	62 female breast cancer patients[h] (Stage IV) with a mean age of 53.8±10.3 years	Emotional writing (EMO): Participants wrote at home about cancer-related emotions Assessment time points: baseline, 3 mons	Control Writing Condition (CTL): Writing facts about diagnosis and treatment

Intervention duration	Relevant outcomes assessed/results	Adverse events	Quality
Every 3 wks for a max of 6 cycles.	EORTC QLQ-C30 (Fatigue): No significant difference between arms (NS). Across time, fatigue ↑ in both arms by the 2nd assessment. Fatigue ↓ for C arm to levels comparable with baseline. Fatigue remained moderately clinically meaningful in T arm but NS. EORTC QLQ-C30 (Sleep Disturbance): No significant difference between arms or across time (NS).	More headaches, feeling unwell, dry mouth, and food tasting unusual in both groups	+
ET: 30-min infusion followed by a 3-hr infusion with paclitaxel 175 mg/m^2 TEX: 30-min infusion followed by a 3-hr infusion with paclitaxel 155 mg/m^2. Oral capecitabine 825 mg/m^2 given 2× daily for 14 days; both treatments repeated every 3 wks for 9 mons.	EORTC QLQ-C30 (Fatigue): The ET arm scored clinically ↓ than TEX on fatigue at the 2 mons assessment but NS. EORTC QLQ-C30 (Sleep Disturbance): A small clinical difference was found for insomnia in favor of the TEX at the 2 and 9 mons assessments but NS.	Yes but ND	+
TD: Every 3 wks until treatment cycle 6 MF: Given at days 1 and 8 every 3 wks until treatment cycle 6	EORTC QLQ-C30 (Fatigue)[i]: At EoT, TD suffered ↑ fatigue compared to MF (P=0.04). EORTC QLQ-C30 (Sleep Disturbance)[i]: At EoT, the TD suffered ↑ from insomnia compared to MF (P=0.04).	Yes but ND	–
2MGIBT: iv over 1–2 hr at 3–4 wkly intervals limited to a max of 24 treatments for 96 wks 6MGIBT: iv over 1–2 hr at 3–4 wkly intervals limited to a max of 24 treatments for 96 wks	EORTC QLC-C30 (Fatigue)[i]: For 6MGIBT, fatigue had ↓ significantly ($P<0.05$) at the EoT compared with placebo. EORTC QLC-C30 (Sleep Disturbance): Insomnia ↓ in the 6MGIBT compared with placebo, but NS.	Disease progression, bone pain, and spontaneous bone fracture-	–
ID40: 40 mg/m^2 (day 1) plus iv vinorelbine 20 mg/m^2 (days 1 and 8) at every 3 wks ID60: 60 mg/m^2 day 1 at every 3 wks	EORTC QLQ-C30 (Depression)[i]: 60.3% patients showed ↓ depression scores, 26.3% were stable and 13.4% worsened. A positive relationship between likelihood of improvement and objective tumor response (P=0.046). EORTC QLQ-C30 (Sleep Disturbance): Clinical ↓ in sleep disturbance but no significant difference between arms or across time (NS). CRF (Insomnia): Clinical ↓ in insomnia but no significant difference between arms or across time (NS).	ND	–
SET: wkly 90-min therapist-led support group + participated in 2-day workshops every 9–12 mons and received monthly reviews of videotapes of randomly selected sessions.	EORTC QLC-C30 (Fatigue)[i]: A significant across-time deterioration (time effect) in fatigue regardless of study arm (P=0.003). EORTC QLC-C30 (Sleep Disturbance): There were no significant differences across-time (NS).	ND	+
The subjects were instructed to listen to the audiotape 12–24 hr before the start of CHT cycles and as often as desired during the course of their treatment.	SCD (Fatigue): There were no significant differences between SCB and control in severity of SE for fatigue (NS). Higher percentage in the control arm than in the SECA arm reported fatigue. The fatigue severity ratings significantly ↑ from the 1st SCD to the 2nd SCD for both arms. Overall fatigue remained a troublesome SE during the study. SCD (Sleep Disturbance): There were no significant differences between the arms in severity of SEs for sleep disturbance (NS). More women in control than in the SCB arm reported difficulty in sleeping whereas the severity significantly increased between the 1st SCD and the 2nd SCD for both arms but NS.	ND	+
4 × 20 min sessions for 3 wks	CES-D (Depression): No differences between arms or across time (NS). PSQI (Sleep Disturbance): No differences between arms or across time (NS).	ND	+

(*Continued*)

Table 1 (*Continued*)

Citation	Cluster	Population description	Description of intervention	Description of control
Multi-modal lifestyle				
Targ and Levine[29]	Fatigue, depression	181 female breast cancer patients[f] (≤ Stage IV) with a mean age of 49±8.6 (T) and 47±8.8 (C) years	CAM program (CAM): Intensive lifestyle change and group support program with an emphasis on psychospiritual issues, and inner process Assessment time points: pre-test, post-test	Standard Program (SP): 1.5 hrs/wk unstructured psycho-educational support group led by a psychologist with emphasis on coping with real life issues
Non-metastatic				
Medical procedures				
Bonnema et al[30]	Depression, sleep disturbance	139 female breast cancer[a] patients (≤ Stage II) with a mean age = ND	Short hospital stay: Evaluating the medical and psychosocial effects of short hospital stays after surgery for breast cancer Assessment time points: Baseline, 1-mon after surgery EoT (4 mons); During outpatient visits	Long Hospital Stay: Effects of long hospital stay after surgery for breast cancer
Behavioral				
Courneya et al[31]	Fatigue, depression	242 breast cancer patients[b] (≤ Stages IIIA) with a mean age of 49.2 years, (SD = ND)	Aerobic exercise (AET): Exercise on a cycle ergometer, treadmill, or elliptical Resistance exercise (RET): Exercise performing two sets of 8–12 reps included leg extension, leg curl, leg press, calf raises, chest press, seated row, triceps extension, biceps curls, and modified curl-ups Assessment Time Points: baseline (1–2 wks after starting CHT), midpoint (middle of CHT), EoT (3–4 wks after CHT), and FU (6 mons)	UC: Offered a 1-mon exercise program after post intervention assessment
Wang et al[32]	Fatigue, sleep disturbance	72 Taiwanese breast cancer patients[d] (≤ Stage II) with a mean age of 48.40±10.15 years (T) and 52.30±8.84 years (C)	BSET-based: Home-based self-efficacy related exercise (walking) program Assessment Time Points: baseline (24 hrs prior to the surgery), 24 hrs prior to the day of the one cycle of CHT (2–3 wks after surgery), day of expected nadir (7–10 days after CHT), and EoT (6 wks)	UC
Mock et al[33]	Fatigue, depression	52 female breast cancer patients[d] (≤ Stage III) with a mean age of 47.14±11.72 years (LW) and 48.64±10.69 (HW) years	Low walk (LW): <90 min of walking/wk + adjuvant CT or RT after breast cancer surgery High walk (HW): >90 min of walking/wk + adjuvant CT or RT after breast cancer surgery. Assessment time points: baseline, 6 wks of RT, and EoT (during 4–6 mons of adjuvant CHT)	UC
CAM				
Listing et al[34]	Fatigue, depression	34 female breast cancer patients[d] (≤ Stage II) with a mean age of 59.2±12.1 (T) and 59.9±11.5 (C) years	Classical massage (CM): Swedish techniques while subjects were in prone position Assessment time points: baseline, 5 wks; and FU (11 wks)	No treatment: wait list
Listing et al[35]	Fatigue, depression	115 female breast cancer patients[b] (≤ Stage II) with a mean age of 57.6±10.8 years (T) and 61.4±10.9 years (C)	Classical massage: Standardized Swedish techniques on back, neck and head Assessment time points: baseline (T1), EoT (5-wks;T2), and FU (11 wks;T3)	UC: waiting list
da Costa et al[36]	Fatigue, depression	36 breast cancer patients[c] (≤ Stage II) with a mean age of 59 (A) and 57 (B) years, (SD = ND)	Guarana A: Guarana extract daily; before beginning 14th RT, group switched to placebo for remainder of study Guarana B: Received placebo; before beginning 14th RT, group switched guarana daily for remainder of study Assessment time points: Beginning of RT, midpoint of RT, (before the 14th RT session), and EoT (last session of RT or 28th session)	Placebo: crossover

Intervention duration	Relevant outcomes assessed/results	Adverse events	Quality
2/wk for 2.5 hrs each time; each wk included 1 hr health series; 90 mins of dance/movement program; experiential work; and 90 min discussion group led by a licensed clinical social for a total of 12 wks.	POMS (Depression)[i]: Both the CAM arm ($P<0.004$) and control ($P<0.02$) showed a significant ↓ in depression at EoT. POMS (Fatigue): No significant difference between arms or across time (NS).	ND	+
At admission, patients were given a daily diary, to be used for 1 mon, and a wkly diary to be used for the next 3 mons for a total 4 mons. The length of hospital stay was recorded.	VDBP (Sleep Disturbance): No differences between arms at EoT (NS). VDBP (Depression): No differences between arms at EoT (NS).	None	+
AET: 3×/wk for ~4 wks: duration began at 15 min for wks 1–3. It ↑ by 5 min every 3 wks until the duration reached 45 min at wk 18. RET: 3×/wk: performing 2 sets of 8–12 reps of 9 different exercises. Resistance was ↑ by 10% when participants completed more than 12 reps at wk 18.	FACT-A (Fatigue): No differences between AET, RET and UC arms (NS). However, for AET adherence ($P=0.002$) had greater mean changes at EoT compared to UC. CES-D (Depression): No differences between AET, RET and UC arms (NS). However, for adherence to AET ($P=0.003$) and RET ($P=0.019$) had greater mean changes at EoT compared to UC; no differences between arms at FU (NS). Effect Size: 0.30	Lightheaded, hypotensive, moderately nauseous (n=1), experienced dizziness, weakness and mild diarrhea (n=1)	+
Low to moderate intensity exercise per wk, and at least 30 mins per session or the accumulation of 10-min sessions to reach 30 mins for 6 wks.	FACIT-F (Fatigue)[i]: Fatigue ↓ in the BSET arm with significant differences between arms at time-3 ($P=0.001$) and at EoT ($P=0.001$). PSQI (Sleep Disturbance)[i]: BSET had significantly ↓ sleep disturbances than those in control over the intervention period ($P=0.006$).	Anemia and dizziness with dyspnea (n=2)	+
6 wks of RT and 4–6 mons of CT. Most exercise prescriptions began at 10–15 mins per session and 5–6 sessions per wk. Subjects were advanced to 30 mins per session, 5–6 daily sessions per wk.	POMS (Fatigue)[i]: HW had significantly ↓ fatigue at EoT compared to LW ($P=0.001$). POMS (Depression)[i]: HW had significantly ↓ depression at EoT compared to LW ($P=0.03$). Diary (Fatigue)[i]: Mean fatigue on the daily diaries was significantly ↓ for the HW compared to LW ($P=0.001$). CHT was significantly ↑ than RT ($P=0.01$). PFS (Fatigue Total Score)[i]: HW had ↓ total fatigue at EoT compared to LW but not NS.	ND	–
30 min/day for 5 wks plus FU.	BSF (Tiredness)[i]: No differences between arms at EoT (NS); CM had ↓ levels of tiredness compared to control at FU ($P<0.01$). BSF (Anxious Depression)[i]: CM had ↓ levels of anxious depression compared to control at EoT ($P=0.03$); no differences between arms at FU (NS).	Higher level of back pain (n=1), increase in blood pressure (n=1)	++
2 × 30 min/wk for 5 wks plus FU.	BSF (Anxious Depression): Anxious depressions between arms were NS. BFS (Tiredness): Tiredness between arms was NS. GBB (Fatigue): Fatigue was ↓ at the EoT between arms but was NS. This positive effect was sustained over time and achieved significance compared with control at FU ($P=0.048$). Effect Size: 0.3	ND	–
75 mg of guarana extract daily for last session of RT or 28th session.	CFS (Fatigue): Fatigue between all arms was NS. MDA BFI (Fatigue): Fatigue between all arms was NS BDI-II (Depression): Depression between all arms was NS.	None	–

(*Continued*)

Table 1 (*Continued*)

Citation	Cluster	Population description	Description of intervention	Description of control
Psychosocial				
Berger et al[37]	Fatigue, sleep disturbance	219 female breast cancer patients[e] (≤ Stage IIIA) with a mean age of 52.13 years (T) and 52.16 (C), (SD = ND)	Behavioral therapy (BT): Individualized sleep promotion plan (ISPPr): Modified stimulus control, modified sleep restriction, relaxation therapy, and sleep hygiene Assessment time points: Baseline (2 days prior CT), during the 7 days after each treatment, and FU (30 days after the last treatment)	HEC: Healthy Eating Control received healthy eating information and attention
Cohen and Fried[38]	Fatigue, sleep disturbance	154 female early-stage breast cancer patients[d] (≤ Stage II) with a mean age of 55.9±10.4 (CBT), 51.8±11.6 (RGI), and 52.9±11.8 (C) years	Cognitive behavior (CBT): cognitive and behavioral strategies Relaxation and guided imagery (RGI): systematic learning of deep RGI plus deep breathing and autogenic relaxation Assessment time points: preintervention, EoT (3 mons), and FU (4 mons)	UC
Badger et al[39]	Fatigue, depression	48 female breast cancer patients[f] (≤ Stage III) with a mean age of 53.04±8.72 (T) and 54.71±10.34 (C) years	Telephone interpersonal counseling (TIPC): telephone calls from a nurse counselor; sessions focused on issues such as cancer education, interpersonal role disputes, social support, awareness, management of depressive symptoms, and role transitions Assessment time points: baseline, post-intervention (wk 6), and FU (wk 10)	Usual Care Attentional Control Group (UC): calls from nurse counselor and 3 calls for partner plus resource list
Sandgren et al[40]	Fatigue, depression	62 female breast cancer patients[d] (≤ Stage II) with a mean age of 51.23±12.5 years	Telephone therapy: therapy included providing support, teaching coping skills, managing anxiety and stress, and helping to solve patient-generated problems (eg, interpersonal problems, problems returning to work) Assessment time points: baseline, 4 mons, 10 mons	No treatment
Dolbeault et al[41]	Fatigue, depression	203 breast cancer patients[b] with a mean age of 54.5±9.3 (T) and 51.6±9.6 (C) years	Psychoeducationally structured model (PSM): Based on CBT principles, exercises were initiations combined with general medical information and peer exchanges on defined themes; 8–12 participants, led by 2 psychologists or psychiatrists Assessment time points: 1-wk pre-intervention, EoT (8 wks), and FU (1-wk pre-deferred intervention)	Wait list
Multimodal lifestyle				
Lindemalm et al[42]	Fatigue, depression	41 female low-stage breast cancer patients[d] with a mean age of 56.5 (T) and 66 years (C), (Stage and SD = ND)	Support group program CT-RT: Support team + adjuvant-combined CT and RT Support Group Program RT: Support team + adjuvant RT only Assessment time points: Pre-intervention, and FU (2 mons, 6 mons, 12 mons)	UC

Intervention duration	Relevant outcomes assessed/results	Adverse events	Quality
Prior to the initial CT, BT participants developed an ISPP plan that was regularly reinforced and revised for 30 days after the last CT, compared with scores prior to the initial treatment. HEC group participants received equal time and attention at each home visit.	PFS (Fatigue)[i]: Fatigue in both arms changed over time, with ↑ during the treatments and ↓ after treatments ended (P=0.001). The fatigue pattern was similar between the BT and HEC arms (NS). PSQI (Sleep)[i]: Significant changes in sleep quality in the arms over time (P=0.003). A group by time interaction was found (P=0.04). Sleep quality ↑ significantly in BT arm, but sleep of the HEC arm was more disturbed at treatment 4 and remained more disturbed at FU. Diary (Sleep): Significant ↓ number of awakenings (P=0.032), ↓ WASO-M (P=0.027), and ↑ sleep efficiency P=0.001) in the BT arm over time. But sleep efficiency favoring BT was significant between arms (P=0.075). Effect size: 0.17	ND	+
9 × 90 min sessions/wk for 3 mons plus FU	FSI (Fatigue symptoms): Mean of fatigue symptoms ↓ in both intervention arms (P<0.001) but only the reduction in the RGI arm from pre-to-post intervention appeared significant. Fatigue remained significantly ↓ in the RGI arm than in CB and UC, (P<0.01). Effect Size =0.20 MSQ (Sleep difficulties): Mean of sleep difficulties ↓ in both intervention arms (P<0.001), but only the reduction in the RGI arm from pre-to-post intervention appeared significant. Sleep difficulties remained significantly ↓ in the RGI arm than in CB and UC (P<0.001). Effect Size: 0.10	ND	–
6 wkly sessions for 6 wks plus FU	CES-D (Depression): No difference between arms or across time (NS). PANAS (Negative Affect): No difference between arms or across time (NS). MFI (Fatigue)[i]: No significant main effect existed for time. However, a trend was found in the time by group interaction that indicate a ↓ for TIPC arm but not for those in control but NS (P=0.09).	ND	+
1/wk for 4 wks and then every other wk for 10 mons; phone sessions lasted up to 30 mins	POMS (Fatigue): No difference between arms or across time (NS). POMS (Depression): No difference between arms or across time (NS).	ND	+
8 × 2 hr sessions/wk for 8 wks pus FU	POMS (Depression)[i]: PSM had ↓ levels of depression compared to control (P<0.05); depression scores ↓ over time in both arms (P<0.05). POMS (Fatigue)[i]: Greater ↓ of fatigue in the PSM arm compared to control (P<0.01). EORTC QLQ-C30 (Fatigue)[i]: Greater ↓ of fatigue in the PSM arm compared to control (P<0.01). POMS Global (Negative Affect)[i]: A greater reduction of negative effects were observed in the TG compared with the CG arm but NS.	ND	+
From Sunday to Saturday on a residential basis followed by 4-days and FU (2 mons after initial visit)	NFQ (Fatigue)[q]: No difference between arms (NS); both arms showed significant ↓ of total fatigue (P=0.01) and physical fatigue (P=0.015) over time compared to control. HADS (Depression)[q]: No differences between arms or across time (NS).	ND	–

(*Continued*)

Table 1 (*Continued*)

Citation	Cluster	Population description	Description of intervention	Description of control
Mixed				
Pharmacological				
Roscoe et al[43]	Fatigue, depression	122 female breast cancer patients[b] (Stage = ND) with a mean age of 52.2±9.3 (T) and 52.2±10.2 (C) years	Paroxetine: 20 mg Assessment time points: Cycle 1–4 of CHT	Placebo
Psychosocial				
Thornton et al[44]	Fatigue, depression	45 female breast cancer patients[d] (Stage II, III) with a mean age of 50±11.6 (C) and 50±8.6 (T) years	Psychological intervention: conducted in groups of 8–12 patients led by two psychologists; Assessment time points: baseline, 4 mons, 8 mons, 12 mons	No treatment
Sandgren and McCaul[49]	Fatigue, depression	235 female breast cancer patients[d] (≤ Stage III) with a mean age of 54.5±11.8 years	Cancer health education (CHE): Structured curriculum presented by the nurse with time for brief discussion and questions. Emotional expression therapy (EET): Same number of calls from the same nurses; nurses instructed patients to feel free to explore their emotions and the things that are on their mind Assessment time points: pre-intervention, and FU: approx 5-mons	UC
Sandgren and McCaul[45]	Fatigue, sleep disturbance	237 female breast cancer patients[d] (≤ Stage III) with a mean age of 54.4 years, (SD = ND)	Health education group (HET): topics included: 1) understanding breast cancer, 2) managing post-surgical changes, 3) understanding treatment, 4) managing treatment side effects and fatigue, 5) healthy lifestyle, and 6) FU review. Emotional expression therapy (EET): nurse instructed patients to describe their thoughts and feelings about breast cancer, and any emotional issues about breast cancer Assessment time points: pre-test, 6 mons, 13 mons	No treatment: not restricted from participating in community support groups, receiving mental health care or using standard clinic nurse helpline
Survivors				
CAM				
Jain et al[46]	Fatigue, depression	76 breast cancer survivors (≤ Stage IIIA) with a mean age of 52 (BH), 52 (MH) and 19 (C) years, (SD = ND)	Biofield healing (BH): practitioner practices hands-on healing with standard hand positions for 45–60 min (energy chelation technique) Mock healing (MH): delivered by practitioners who were skeptical scientists trained to use the identical hand placements as biofield healing practitioners Assessment time points: pre-intervention, post-session 2, midpoint, post-session 6, and EoT (4 wks)	Waitlist

Intervention duration	Relevant outcomes assessed/results	Adverse events	Quality
Daily starting 7 days after 1st on-study treatment (1st cycle of CHT) and stopping 7 days after 4th on-study treatment (4th cycle of CHT)	CES-D (Depression)[i]: Paroxetine had greater effective than control in ↓ depression across all CHT cycles ($P<0.001$); paroxetine arm ($P<0.01$) showed a significant ↓ in depression between treatments 1 and 4 while control showed no significant differences (NS). POMS-DD (Depression)[i]: Paroxetine ($P<0.01$) and control ($P=0.03$) both showed significant ↑ in depression between treatments 1 and 4 POMS-FI (Fatigue): There were no significant differences between arms at any time point (NS). FSCL (Fatigue): There were no significant differences between arms at any time point (NS). MAF (Fatigue): There were no significant differences between arms at any time point (NS).	Nausea and headache	+
Two sessions over 12 mons consisting of 4 mons of 1.5 hr sessions (intensive phase) followed by 8 monthly sessions (maintenance phase)	CES-D (Depression)[i]: Depression symptoms ↓ faster over time for psychological arm when compared to control ($P<0.04$). POMS (Depression)[i]: Depression ↓ faster over time for psychological arm when compared to control ($P=0.02$). POMS (Fatigue)[i]: The psychological arm showed greater ↓ in fatigue over time when compared to control ($P=0.048$)	ND	+
Both interventions: 5 × 30 min phone calls/wk, plus 6th FU call at 3 mons	POMS (Fatigue): No differences between the CHE, EET, and control arms (NS); pooled analyses show no differences across time (NS). POMS (Depression)[i]: No differences between the CHE, EET, and control arms (NS), pooled analyses show an improvement in depressed scores over time ($P<0.01$).	ND	+
Both interventions: 5 × 30 min phone calls/wk, plus 6th FU call at 3 mons. Seven oncology nurses delivered both interventions for a total 13 mons	POMS (Depression)[i]: No differences between the HET, EET and control arms (NS), combined group scores show a decrease in depression over time ($P<0.03$). POMS (Fatigue)[i]: No differences between the HET, EET and control arms (NS), combined group scores show a ↓ in fatigue over time ($P<0.03$).	ND	+
Two sessions/wk × 4 wks	MFI (Fatigue)[i]: Both the BH ($P<0.0005$) and MH ($P=0.02$) arms had a greater ↓ in fatigue symptoms than the control. There were no significant changes in fatigue for control (NS). Effect size: Biofield healing vs Control ($d=1.04$), Mock healing versus control ($d=0.68$) CES-D (Depression): There were no significant interactions (NS).	None	++

(*Continued*)

Table 1 (*Continued*)

Citation	Cluster	Population description	Description of intervention	Description of control
Behavioral				
Lee et al[47]	Fatigue, depression	50 breast cancer survivors with a mean age of 47.5±5.1 (SSEP), 45.6±7.0 (GEP) and 47.6±9.2 (C) years	Both training interventions: include stretching and strengthening Scapula-oriented shoulder exercise program (SSEP): Adopted from scapular mobilization exercises for shoulder dyskinesis and kinetic chain-based shoulder rehabilitation. Participants were asked to do exercises from simple motions to advanced strengthening. General Exercise Program (GEP): regular exercise program for shoulder and whole body Assessment time points: 1 and 4 wks after the EoT for 8-wks	UC: A leaflet guiding self-care including general shoulder range of motion exercise after surgery was provided as a UC
Multimodal lifestyle				
Kim et al[48]	Fatigue, depression	45 female breast cancer (≤ Stage III) survivors with a mean age of 44.6±9.9 (T) and 47.1±7.3 (C) years	Simultaneous stage-matched exercise and diet (SSED): Stage-matched telephone counseling complimented with a workbook, individualized prescription for regular moderate exercise, a balanced diet program, exercise and diet prescriptions Assessment time points: baseline and wk 12	ND

Notes: 31% of the studies did not have sufficient statistical power and 41% of studies did not report a power calculation: [a]patients receiving surgery; [b]patients receiving chemotherapy; [c]patients receiving radiation; [d]patients receiving surgery, chemotherapy, and radiation; [e]patients receiving surgery and chemotherapy; [f]patients receiving chemotherapy and radiation; [g]patients receiving hormone therapy; [h]treatment received not described; [i]effect size not reported.

Abbreviations: 95% CI, 95% Confidence Interval; BDI, Beck Depression Inventory; BFI, Brief Fatigue Inventory; BSF, Berlin Mood Questionnaire; C, control Group; CBT, Cognitive Behavioral Therapy; CES-D, Center for Epidemiological Studies-Depression Scale; CFS, Chalder Fatigue Scale; CHT, chemotherapy; CRF, Case Report Form; EORTC QLC-C30, European Organization for Research and Treatment of Cancer Health Related Quality of Life Questionnaire; EoT, end of treatment; FACIT-F, Functional Assessment of Chronic Illness Therapy; FACT-A, Functional Assessment of Cancer Therapy-Anemia; FSCL, Fatigue Symptom Checklist; FSI, Fatigue Symptom Inventory; FU, follow-up; GBB, Geissen Complaints Inventory; GHQ, General Health Questionnaire; HADS, Hospital Anxiety Depression Score; HDRS, Hamilton Depression Rating Scale; hr, hour; HSCL-25, Hopkins Symptom Checklist-25; iv, intravenous; ISI, Insomnia Severity Index; MAF, Multidimensional Assessment of Fatigue; Max, maximum; MD, mean difference; MDA BFI, Anderson Brief Fatigue Inventory; MFI, Multidimensional Fatigue Inventory; Min, minutes; Mon(s), month(s); MSQ, Mini Sleep Questionnaire; NCI-CTC, National Cancer Institute Common Toxicity Criteria; ND, not described; NFQ, Norwegian Fatigue Questionnaire; NS, not significant; PANAS, Positive and Negative Affect Scale; PFS, Piper Revised Fatigue Scale; POMS-DD, Monopolar Profile of Mood States; POMS, Profile of Mood States; PSQI, Pittsburgh Sleep Quality Index; QOL, quality of life; RT, radiation therapy; reps, repetitions; SAS, Self-rating Anxiety Scale; SCD, Self Care Diary; SD, standard deviation; SE, side effect; T, treatment group; SIGN, Scottish Intercollegiate Guidelines Network; UC, usual care; VDBP, van den Borne and Pruyn; wk(s), week(s); wkly, weekly.

no such improvements in depression were found. Adverse events including insomnia, palpitations, nausea, and anxiety were reported. Because this was the only study in this treatment and population category, however, it was not included in the GRADE analysis.

Metastatic population

Psychosocial treatment

One high (+) quality study[50] investigating psychosocial (cognitive behavioral therapy) treatment for metastatic patients reported mixed results for depression, and null results for fatigue and insomnia. Because this was the only study in this population, it could not be examined via GRADE.

Mixed population

Psychosocial treatment

Both studies[57,58] examining psychosocial treatments were of high (+) quality and reported significant improvements in insomnia, no improvements in fatigue and mixed results for depression. Specifically, the first study,[57] comparing psychosocial support with either a nurse or psychologist to usual care, found significant improvements in insomnia, but no differences for fatigue or depression symptoms. The second study[58] compared cognitive behavioral therapy to a wait list control. Results showed improvements in both insomnia and depression, but no differences in fatigue. Adverse events were not reported in either study. Given the promising results for sleep improvement in these adequate quality studies, but a lack of information on adverse events, a weak recommendation in favor of psychosocial treatments was given.

Medical treatment

Although one high (+) quality study[56] investigating chemotherapy dosages with tamoxifen reported lower fatigue and depression with the lower versus higher dose of chemotherapy, because there was only one study in this category, a GRADE recommendation could not be provided for medical treatments for a mixed population.

Intervention duration	Relevant outcomes assessed/results	Adverse events	Quality
Gradually with an interval of 2 wks for a total 8 wks	EORTC QLQ-C30 (Fatigue)[i]: No differences between SSEP, GEP and control arms (NS); fatigue scores of GEP arm ↓ at FU (P=0.027); no differences over time were seen in the SSEP (NS) or control (NS). BDI (Depression): No significant differences between arms or across time (NS).	Shoulder discomfort (scapula-oriented exercise group)	++
Delivered wkly during 30 min telephone counseling session for 12 wks	BFI (Fatigue)[i]: SSED arm had greater ↓ in fatigue levels compared to control (P=0.001). HADS (Depression)[i]: SSED arm had greater ↓ on depression scores compared to control (P=0.035).	ND	+

Survivor population

Pharmacological treatment

One high (+) quality and one poor (–) quality study investigating pharmacological treatments cited mixed results for sleep improvement and no improvement in either fatigue or depression. The higher quality study[60] compared low and high dosages of venlafaxine to placebo and found no significant differences for any of the cluster symptoms. The poor quality study[59] also did not find differences for depression or fatigue, however, the authors reported improvements in insomnia. Effect sizes were not reported in either of the two studies, and only one study[60] reported an adverse event (ie, hypertension). Consequently, no recommendation could be given.

CAM treatment

One high (+) quality CAM study[61] reported improvements in sleep disturbance and fatigue symptoms of breast cancer survivors following a yoga intervention, but no differences in negative mood. Because this was the only CAM study for a survivor population, however, it was not included in the GRADE analysis.

Discussion

The purpose of this review was to identify and systematically evaluate the current literature that examined the impact of interventions for the fatigue–sleep disturbance–depression symptom cluster in breast cancer patients and survivors. Of the 41 RCTs included in this review, 29 articles reported on two of the three symptom clusters and twelve reported on all three symptoms. It is important to note that many of these studies did not specify these symptoms as primary aims; in fact, 75% of the studies with three symptoms did not overtly specify the primary aim, and 58% of the studies with two symptoms did not specify the primary aim. Many of the studies assessed fatigue and insomnia via the European Organization for Research and Treatment of Cancer Quality of Life questionnaire (EORTC QLQ-30) subscales; while these subscales are considered reliable and valid, they are not as comprehensive in their

Table 2 Characteristics and SIGN 50 score of included studies, grouped by population and treatment type, that address three cluster components (n=12)

Citation	Population description	Description of intervention	Description of control
Metastatic			
Psychosocial			
Savard et al[50]	45 depressed female breast cancer patients[d] (≤ Stage IV) with a mean age of 51.4±8.05 (T) and 51.66±8.62 (C) years	CBT: Strategies meant for treating depression including coping strategies identified Assessment time points: pre-treatment, EoT (8 wks), and FU: 3 mons, 6 mons	Wait list: Waited a minimum of 8 wks before receiving CBT
Non-metastatic			
Medical procedures			
Prescott et al[51]	255 breast cancer (≤ Stage III) patients[c] with a mean age of 72.3±5.0 (T) and 72.8±5.2 (C) years	RT: Standard treatment of postoperative breast irradiation Assessment time points: baseline, 2 wks, 9 mons, 15 mons	No RT treatment
Groenvold et al[52]	303 premenopausal breast cancer patients[d] with a mean age of 45.0 (CHT) and 44.4 (ovarian ablation) years (Stage and SD = ND)	CHT: Intravenous cyclophosphamide, methotrexate, fluouracil Assessment Time points: 1 mon, 3 mons, 5 mons, 9 mons, 15 mons, 24 mons	Ovarian ablation (OA): Pelvic irradiation or surgical oophorectomy
CAM			
de Oliveira Campos et al[53]	75 breast cancer patients[b] (≤ Stage III) with a mean age of 50.2±11.95 (Placebo-guarana group) and 51.76±9.73 (Guarana-placebo group) years	Guarana: Standardized dried extract from P cupana; cornstarch; guarana preparation had a pH of 4.83 (10% solution in water), a water content of 3.9%, a concentration of 1.7% tannins, and 6.46% caffeine Assessment time points: Day 1, Day 21, Day 49	Crossover: Placebo capsules
Behavioral			
Payne et al[54]	20 female breast cancer patients[g] receiving hormonal therapy with a mean age of 64.7±6.3 years	Exercise: Moderate walking Assessment time points: baseline, 2 wks, 12 wks and EoT (14 wks)	UC: Standard interaction with nurses, physicians and staff

Intervention duration	Relevant outcomes assessed/results	Adverse events	Quality
CBT: 8 × 60–90 min sessions; plus 3 booster sessions administered every 3 wks following treatment during which psychologists reviewed the difficulties the patient had experienced since the last session and the strategies used/could have been used to cope with them	HDRS (Depression): Depression ↓ over time in the CBT arm ($P<0.0001$) but not in the control (NS); combined scores across both arms ↓ from pre to Eot ($P<0.0001$) and from EoT to FU ($P<0.01$). Effect size: Treatment ($d=-1.811$), Control ($d=-0.544$) BDI (Depression): No differences between arms (NS); combined scores across both arms ↓ from pre to EoT ($P<0.0001$) but not from EoT to FU (NS). Effect size: Treatment ($d=1.859$), Control ($d=0.84$) HADS (Depression): No differences between arms (NS); combined scores across both arms ↓ from pre to EoT ($P<0.0001$) but not from EoT to FU (NS). Effect size: Treatment ($d=-1.82$), control ($d=-1.30$) MFI (Fatigue): No differences between arms and across time (NS); combined scores across both arms ↓ from pre to EoT ($P<0.01$) but not from EoT to FU (NS). Effect size: Treatment ($d=-0.940$), control ($d=-0.736$) ISI (Insomnia): No differences between arms and across time (NS); combined scores across both arms ↓ from pre to EoT ($P<0.01$) but not from EoT to FU (NS). Effect Size: Treatment ($d=0.958$), control ($d=-0.089$)	ND	+
Standard treatment of postoperative breast irradiation for 15 mons total	EORTC QLQ-C30 (Insomnia)[i]: Mean levels of insomnia tended to ↑ slightly in the control arm, whereas insomnia levels were ↓ in the RT arm. The treatment difference is statistically significant ($P=0.01$) which remained consistent throughout FU. HADS (Depression)[i]: There is evidence of ↑ depression scores over time ($P=0.04$), but there is no evidence of a treatment effect. Although the ↑ in mean depression scores is significant, the absolute change is small. EORTC QLQ-C30 (Fatigue): There was no evidence of a time, treatment, or time by treatment effect (NS).	Skin rashes, angioedema, taste changes, jaundice and liver damage	+
CHT: Nine cycles given every 3 wks for 2 years Ovarian Ablation: Pelvic irradiation with a total dose of 15 Gy given as 5 daily fractions or surgical oophorectomy for 2 years	EORTC QLQ-C30 (Fatigue)[i]: CHT had ↑ levels of fatigue compared to the OA arm at 3 mons ($P<0.001$) and 5 mons ($P<0.001$) but not at other time points (NS). EORTC QLQ-C30 (Sleep)[i]: CHT had ↑ levels of sleep disturbances at 1 mon ($P<0.05$) and 5 mons ($P<0.001$) but not at other time points (NS). HADS (Depression)[i]: CHT had ↑ levels of depression at 3 mons ($P<0.05$) and 5 mons ($P<0.01$) but not at other time points (NS).	ND	–
Guarana 50 mg by mouth 2× daily or placebo for 21 days. After a 7-day washout period, patients were crossed over to the opposite experimental arm for 49 days total	CFS (Fatigue)[i]: Guarana arm had ↓ fatigue compared to placebo on day 21 ($P<0.01$) but not on day 49 (NS). PSQI (Sleep Disturbance)[i]: Guarana group had ↓ sleep disturbances compared to placebo on day 49 ($P=0.05$) but not day 21 (NS). BFI (Fatigue)[i]: Guarana arm had ↓ global fatigue compared to placebo on days 21 and 49 ($P<0.01$). HADS (Depression): No significant difference on depression between arms (NS). FACIT-F (Fatigue Global Scores)[i]: The average of fatigue scores ↓ from baseline to EoT for the patients receiving guarana for both arms (ie, received guarana first and the group that switched to guarana after receiving placebo) (NS).	Insomnia, palpitations, nausea, anxiety	++
4 × 20 min of moderate walking each wk for 14 wks total	PFS(Fatigue)[i]: Fatigue levels between arms and across time were NS. PSQI (Sleep Disturbance)[q]: PSQI scores in the exercise arm ↓ significantly over time ($P=0.007$). PSQI (Actual Wake Time)[i]: After 12 wks, actual wake time was shorter in the exercise arm compared to control ($P=0.002$). PSQI (Actual Sleep Time)[i]: After 12 wks, actual sleep time was shorter in the exercise arm compared to control ($P=0.005$). PSQI (Movement During Sleep)[i]: After 12 wks, exercise showed less movement during sleep compared to control ($P=0.002$). PSQI (Sleep Efficiency): No differences between arms (NS). CES-D (Depression): No difference between arms or over time (NS).	ND	–

(*Continued*)

Table 2 (*Continued*)

Citation	Population description	Description of intervention	Description of control
Mock et al[55]	50 women with early stage breast cancer[c] (≤ stage II) with a mean age of 49 years, 48.09±5.42 years (T) and 50.29±8.47 (C)	Exercise: Individualized, home-based walking program Assessment time points: baseline (before or during the first days of radiation therapy), end of 3-wks and end of radiation therapy (about 6 wks)	UC
Mixed			
Pharmacological			
van Dam et al[56]	104 female breast cancer patients[d] (≤ Stage III) with a mean age of 45.5±6.2 (CTC), 48.1±6.8 (FEV) and 46.1±5.2 (C) years	CTC: High-risk breast cancer who were treated with high-dose CHT plus tamoxifen FEV: High-risk breast cancer who were treated with standard-dose CHT plus tamoxifen Assessment time points: ND	No treatment
Psychosocial			
Arving et al[57]	179 breast cancer patients[d] (≤ Stage N0) with a mean age of 55 years, (SD = ND)	Psychosocial support with nurse (INS): Carried out by two oncology nurses specially trained in psychosocial support including lectures covering knowledge and skills to assess and treat common psychosocial problems in cancer patients. Psychosocial support with psychologist (IPS): Delivered by two psychologists with theoretical knowledge about cancer diseases and treatment, and had experience of counseling Assessment time points: baseline, 1-mon, 3 mons, 6 mons	UC: regular contact with patient's oncologist and medical staff
Savard et al[58]	58 female breast cancer patients[d] (≤ Stage III) with a mean age of 54.81±7.01 (T) and 53.37±7.72 (C) years	CBT: Combined approach combining behavioral and educational strategies Assessment time points: baseline, EoT (8 wks), and FU: 3 mons, 6 mons, 12 mons	Wait List: waited a minimum of 8 wks before receiving CBT
Survivors			
Pharmacological			
Fahlen et al[59]	75 female breast cancer survivors[g] with a mean age of 57.0±5.6 years	Menopausal hormone therapy (HT): Estradiol 2 mg and progestogen Assessment time points: baseline, 6 mons, 12 mons	No HT
Carpenter et al[60]	70 breast cancer survivors[g] (Stage = ND) with a mean age of 50.5±8.7 years	Low dose: Venlafaxine High dose: Additional dose of venlafaxine Assessment Time points: baseline, wkly for 14 wks, and FU: 1 mon, 6 mons, 12 mons	Placebo: Crossover

Intervention duration	Relevant outcomes assessed/results	Adverse events	Quality
Self-paced, progressive program, with 20–30 min brisk walk increments followed by 5-min slow walk for 6 wks total	SAS (Fatigue)[i]: Fatigue levels significantly ↓ between arms and across time (P=0.018). SAS (Sleep Disturbance)[q]: Sleep disturbance ↓ significantly between arms and across time (P=0.027). PFS (Fatigue)[i]: Fatigue ↓ significantly between arms and across time (P=0.001). SAS (Depression): Depression between arms and across time were NS.	None	–
In both the CTC and the FEV arms, the patients were treated with tamoxifen (40 mg periorally once/day) for 2 years	EORTC QLQ-C30 (Fatigue)[i]: CTC reported being ↑ fatigued than patients in the control (P=0.025). EORTC QLQ-C30 (Sleep Disturbance): No significant difference between arms or across time (NS). HSCL-25 (Depression)[i]: CTC had significantly elevated scores on the depression subscale in comparison with the patients in the control (P=0.041).	ND	+
Participants met for 4 × 3 hr wkly lessons. Between meetings, they met to train assessment and techniques. FU discussions were held at termination and 5 mons later	EORTC QLQ-C30 (Insomnia)[i]: Both intervention arms improved significantly more than the UC arm regarding insomnia (P<0.01). There were significant differences between arms with INS having the greatest ↓ in insomnia, followed by IPS and UC arm (P<0.05). EORTC QLQ-C30 (Fatigue): No differences in fatigue between INS, IPS and control arms (NS). HADS (Depression): No differences in depression between INS, IPS and control arms (NS); no differences across time (NS).	ND	+
Participants met for 8 × 90 min wkly sessions offered in groups of 4–6 patients for 8 wks total; FU carried out 3, 6, and 12 mons after the treatment	ISI, Sleep Diary, Insomnia Interview Schedule (Insomnia)[i]: CBT arm showed great improvement compared to control on total sleep time (P<0.001), sleep onset latency (P<0.05), wake after sleep onset (P<0.001), and ISI (P<0.05); pooled analyses show a significant improvement from pre to EoT on all sleep variables (P<0.01); improvements were maintained from EoT to FU for all variables except total sleep time (P<0.05) and ISI (filled out by significant other; P<0.05) which showed further improvement. HADS (Depression)[i]: Depression ↓ over time only in the CBT arm (P<0.01); pooled analyses showed a significant improvement in depression scores from pre to EoT (P<0.001); improvements were maintained from EoT to FU (NS). MFI (Fatigue)[i]: No differences between arms (NS); pooled analyses showed a significant improvement in fatigue scores from pre to EoT (P<0.001); improvements were maintained from EoT to FU (NS).	ND	+
Estradiol in combinations with different progestogens for 1 year	HADS (Depression)[i]: No significant results between arms (NS); depression ↓ for all women across time (P<0.001). EORTC QLQ-C30 (Fatigue)[i]: No significant results between arms (NS); fatigue ↓ for all women across time (P<0.05). EORTC QLQ-C30 (Insomnia)[i]: Insomnia ↓ more and at a faster rate in the HT arm than the control (P<0.001); insomnia scores ↓ for all women across time (P<0.01).	ND	–
Low dose: 37.5 mg of venlafaxine daily for 6 wks High dose: 1 wk of 37.5 mg of venlafaxine daily plus 4 wks of 75 mg of venlafaxine daily plus 1 wk of 37.5 mg of venlafaxine daily	Negative affect index (Negative Affect): No significant differences between treatment and placebo (NS), with minimal effect size for low (0.06) and high dose (0.02) treatments, POMS (fatigue): No significant differences between treatment and placebo (NS), with minimal effect sizes for low (0.03) and high (–0.03) dose treatments, PSQI (Sleep Quality): No significant differences between treatment and placebo (NS), but notable effect sizes for low (0.29) and high (0.22) dose treatments.	Hypertension	+

(*Continued*)

Table 2 (*Continued*)

Citation	Population description	Description of intervention	Description of control
CAM			
Carson et al[61]	37 female breast cancer survivors (≤ Stage IIB) with a mean age of 53.9±9.0 (T) and 54.9±6.2 (C) years	Yoga awareness (YA): Group classes led by a certified yoga teacher; each class included gentle stretching poses, breathing techniques, meditation, study of pertinent topics, group discussion; participants encouraged to spend time practicing yoga at home with the aid of CD recording and illustrated handbooks Assessment time points: baseline, EoT (2 mons), and FU: 3 mons	Wait list: Participants invited to participate in yoga after 3 mons assessment

Notes: 33% of studies did not have sufficient statistical power, and 33% of studies did not report a power calculation: [a]patients receiving surgery; [b]patients receiving chemotherapy; [c]patients receiving radiation; [d]patients receiving surgery, chemotherapy, and radiation; [e]patients receiving surgery and chemotherapy; [f]patients receiving chemotherapy and radiation; [g]patients receiving hormone therapy; [h]treatment received not described; [i]effect size not reported; [***]Negative affect index was calculated as the combination of standardized scores on four questionnaires: the POMS-Short Form total mood disturbance score (excluding fatigue), the negative affect subscale of the PANAS, the CES-D, and the Ham-D.

Abbreviations: 95% CI, 95% Confidence Interval; BFI, Brief Fatigue Inventory; BSF, Berlin Mood Questionnaire; C, control group; CBT, Cognitive Behavioral Therapy; BDI, Beck Depression Inventory; CES-D, Center for Epidemiological Studies-Depression Scale; CFS, Chalder Fatigue Scale; CHT, chemotherapy; CRF, Case Report Form; EORTC QLC-C30, European Organization for Research and Treatment of Cancer Health Related Quality of Life Questionnaire; EoT, end of treatment; FACIT-F, Functional Assessment of Chronic Illness Therapy; FACT-A, Functional Assessment of Cancer Therapy-Anemia; FSCL, Fatigue Symptom Checklist; FSI, Fatigue Symptom Inventory; FU, follow-up; GBB, Geissen Complaints Inventory; GHQ, General Health Questionnaire; HADS, Hospital Anxiety Depression Score; HDRS, Hamilton Depression Rating Scale; HR, hour; HSCL-25, Hopkins Symptom Checklist-25; ISI, Insomnia Severity Index; MAF, Multidimensional Assessment of Fatigue; MD, mean difference; MDA BFI, Anderson Brief Fatigue Inventory; MFI, Multidimensional Fatigue Inventory; Min, minutes; Mon(s), month(s); MSQ, Mini Sleep Questionnaire; NCI-CTC, National Cancer Institute Common Toxicity Criteria; ND, not described; NFQ, Norwegian Fatigue Questionnaire; NS, not significant; PANAS, Positive and Negative Affect Scale; PFS, Piper Revised Fatigue Scale; POMS-DD, Monopolar Profile of Mood States; POMS, Profile of Mood States; PSQI, Pittsburgh Sleep Quality Index; QOL, quality of life; RT, radiation therapy; reps, repetitions; SAS, Self-rating Anxiety Scale; SCD, Self Care Diary; SD, standard deviation; SE, side effect; SIGN, Scottish Intercollegiate Guidelines Network; T, treatment group; UC, usual care; VDBP, van den Borne and Pruyn; Wk(s), week(s).

measurement as some other scales that focus solely on those respective symptoms.

Our systematic evaluation of the literature concerning quality using the SIGN 50 checklist suggested that overall, studies were of high quality, with over a quarter (n=12) of studies being of poor quality and only a few (n=4) being of very high quality. Studies could generally improve in their reporting of randomization and allocation concealment, as well as ensuring that the reliability and validity of outcomes reported are referenced appropriately. While it is not common practice that subscales of self-report questionnaires are referenced in terms of their reliability and validity, if analyses are conducted and conclusions are to be drawn by authors based on subscale results, we suggest that authors of studies should make reference to the reliability and validity of subscales that they examine. We also note that many studies were limited in their sample size.

Overall GRADE results suggest that, out of the three symptoms we reviewed, the one most likely to improve with treatment is sleep disturbance, with many studies reporting a significant effect on sleep disturbance, regardless of type of intervention. In these studies, sleep disturbance was generally reflected by reduced insomnia, and was generally measured using self-report questionnaires such as the Pittsburgh Sleep Quality Index (PSQI), the Insomnia Severity Index (ISI), and the EORTC-QLQ-30 insomnia subscale. Interventions were generally applied post-surgery, and during the active course of breast cancer treatment (examples are chemotherapy and/or radiation), with duration of treatments ranging from 3 weeks to 2 years, and generally being of about 6 weeks. It is interesting to note that only one study included in the GRADE analysis[58] utilized an intervention that specifically targeted insomnia. This suggests that self-reported sleep disturbance is a more easily modifiable target in breast cancer patients undergoing active treatment, regardless of the type of intervention. Breast cancer patients report high levels of sleep disturbance at all stages of the breast cancer experience: before diagnosis, after diagnosis and before cancer treatment, during cancer treatment, and even years after the end of cancer treatment.[62] Persistent and pervasive sleep problems are debilitating, exacerbate physical pain and psychological distress, and have been shown to impair the immune system; disrupting inflammation signaling and the hypothalamic-pituitary-adrenal axis (HPA) stress response.[63] Hence targeting sleep disturbance might be the fastest way to improve quality of life and health in breast cancer patients, ultimately decreasing recurrence and hence increasing longevity. Future research should test the validity of these hypotheses.

Our GRADE results indicated mixed findings for interventions on improving fatigue, and little support for depression. These results suggest that while the clustering of sleep disturbance, fatigue, and depression is common, the successful treatment of one symptom does not necessarily result into adequate treatment of related symptoms.

Intervention duration	Relevant outcomes assessed/results	Adverse events	Quality
YA: 8 × 120 min/wk group classes for 8 wks total – gentle stretching poses (40 min) – breathing techniques (10 min) – meditation (25 min) – study of pertinent topics (20 min) – group discussion (25 min)	Daily diary (Fatigue)[i]: YA arm showed greater ↓ in fatigue compared to the control at EoT ($P<0.01$) and FU ($P<0.01$). Daily diary (Negative Mood)[i]: No differences in negative mood between arms at EoT (NS) but YA showed greater improvement compared to control at FU ($P<0.001$). Daily diary (Sleep Disturbance)[i]: YA showed greater ↓ in sleep disturbance compared to control at EoT ($P<0.01$) but not at FU (NS).	ND	+

Findings suggested that reduction of fatigue sometimes, but not always, followed successful reduction of insomnia in breast cancer patients. The strong co-morbidity of fatigue and sleep disturbance has been previously noted in terms of its occurrence prior to, during, and after active treatment for cancer, [2,64,65] with some studies suggesting some commonality in dysregulation of inflammatory pathways[9,66,67] associated with fatigue and sleep disturbance during treatment. However, persistent fatigue is also associated with HPA axis dysregulation,[7] which may require other forms of

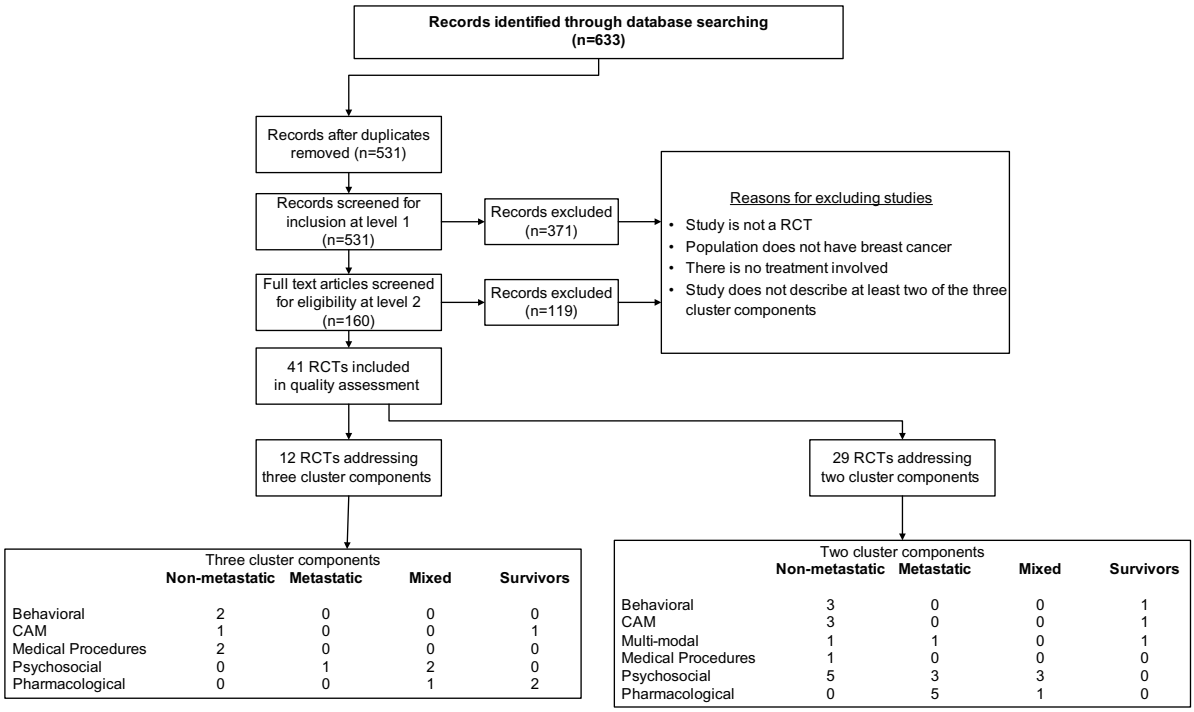

Figure 2 Flow chart.
Abbreviations: CAM, complementary/alternative medicine; RCT, randomized controlled trial.

Table 3 GRADE analysis: quality of the overall literature pool by population/intervention type for studies assessing three cluster components

Condition	Number of participants completed (number of studies)	Confidence in estimate of effect GRADE	Magnitude of estimate of effect GRADE	Safety GRADE	GRADE recommendation	Comments
Metastatic (n=1)						
Psychosocial*	–	–	–	–	–	–
Non-metastatic (n=5)						
Behavioral	70 (2)	C	ND	0	No recommendation	Some promise for sleep, mixed for fatigue, neither statistically significant on depression. Both poor quality (–,–) studies and under-powered.
Pharmacological	558 (2)	B	ND	0	Weak recommendation in favor	Promising for sleep, mixed for fatigue, and neither statistically significant for depression. Mixed quality studies (+,–).
CAM*	–	–	–	–	–	–
Mixed (n=3)						
Psychosocial	237 (2)	B	ND	0	Weak recommendation in favor	Promising for sleep, mixed for depression and not statistically significant for fatigue. Adequate quality studies (+,+).
Pharmacological*	–	–	–	–	–	–
Survivors (n=3)						
Pharmacological	145 (2)	B	ND	0	No recommendation	Promising for sleep, no evidence for depression or fatigue. Mixed quality studies (+,–).
CAM*	–	–	–	–	–	–

Notes: *Due to the small number of studies in these categories, four studies[35,40,42,43] were not assessed via the GRADE; There are four major domains that comprise the core of the modified GRADE methodology: (1) confidence in the estimate of the effect was categorized into the following groups using pre-defined criteria: A) High: further research is very unlikely to change confidence in the estimate of effect; several high quality RCTs with consistent results or in special cases, or one large, high quality, multi-center RCT; B) Moderate: further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate; one high quality RCT or several RCTs with some limitations; C) Low: further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate; one or more RCTs with severe limitations; D) Very Low: any estimate of effect is very uncertain; expert opinion, no direct research evidence or one or more RCTs with severe limitations. (2) magnitude of the effect was categorized into five levels of none (<0.2), small (0.2–0.5), moderate (0.5–0.8), large (> 0.8), or not described (authors did not describe or report effect size for this review's outcomes of interest due to the lack of author reporting). (3) safety grade is dependent on the frequency and severity of adverse events and interactions. Safety was categorized into one of the following grades: +2, appears safe with infrequent adverse events and interactions; +1, appears relatively safe but with frequent but not serious adverse events and interactions; 0, safety not well understood or conflicting; –1, appears to have safety concerns that include infrequent but serious adverse events and/or interactions or; –2, has serious safety concerns that include frequent and serious adverse events and/or interactions. (4) strength of the recommendation can be determined using the following categories and criteria: strong recommendation in favor of or against – very certain that benefits do, or do not, outweigh risks and burdens; no recommendation – no recommendations can be made or; weak recommendation in favor of or against – benefits and risks and burdens are finely balanced, or appreciable uncertainty exists about the magnitude of benefits and risks.

Abbreviations: CAM, complementary/alternative medicine; GRADE, Grading of Recommendation Assessment, Development and Evaluation; RCT, randomized controlled trial.

intervention in addition to modifying sleep. Results for the concomitant modification of depression along with sleep were not promising. Interestingly, depression was more likely to improve with improvements in fatigue, although generally speaking, depression was the least likely symptom of the three to improve during the study period. This suggests that while depression often occurs with fatigue and sleep disturbance during cancer treatment, it may be harder to treat effectively, especially during the course of breast cancer therapy. These findings echo similar conclusions derived from meta-analyses of psychological and pharmacological therapies for depression, where evidence appears mixed for pharmacotherapy, and while somewhat promising for certain psychosocial approaches, is still relatively limited in certain cancer populations.[68,69]

We note that the majority of our studies generally focused on interventions of a single modality, such as a sole behavioral (exercise), psychosocial (psychotherapy), complementary medicine (herb), or pharmacological (drug) treatment. It is unknown, however, whether more integrative, multi-modal

treatments that focus on all aspects of the person and therefore address more than one symptom at once (ie, a multi-modal or "whole systems" approach) may show more promise in being able to effectively treat the symptom cluster to enable breast cancer patients to achieve and maintain a healthier and more regulated state during and after treatment. Multi-modal treatment options, as compared to single modality treatments, have emerged as an important option in the management of many disorders and have the potential to simultaneously address the dynamic nature of the disease process over time. It is the authors' recommendation that future studies consider more multi-modal or whole-systems approaches to addressing these types of symptom clusters associated with disease states.

There are limitations associated with this systematic review. First, because this is a Rapid Evidence Assessment of the Literature, the authors only examined the RCT study designs reported on in the English language to explore this research question. Second, due to the general lack of studies reporting examination of all three symptoms examined in the review, and the challenge of existing studies having inadequate power and lack of adverse events reporting, it is challenging to make recommendations about particular types of interventions for this symptom cluster. While we were able to extract data for the studies that included two of the three symptoms as outcomes, we were unable to conduct the GRADE on studies that reported only two of the three symptoms for this review, and this may be seen as a limitation. However, our primary objective was to determine the impact of interventions that addressed all three components of the targeted symptom cluster of depression, fatigue, and sleep disturbance. The information from this review may guide further reviews that may choose to examine more specifically the impact of interventions on two of the three symptoms (such as fatigue and sleep disturbance). We encourage researchers in the field to take into consideration where we have noted the quality of reporting can be improved in future studies and some of the interventions, outcomes, and symptom cluster relationships that we have discovered throughout this process to produce powerful results in future work.

Conclusion

In summary, results from our systematic review, using the REAL© process, suggest that among the clustered symptoms of fatigue, sleep disturbance, and depression, sleep disturbance appears to be the symptom that responds best to interventions currently studied, with some studies also showing promise for fatigue. It is unclear whether treatment of sleep disturbance will necessarily result in effective improvements in other symptoms. Results also suggest that compared to sleep disturbance and fatigue, depression may be more difficult to treat for breast cancer patients and that treatment of sleep disturbance and fatigue do not necessarily translate to adequate treatment of depression. We highly recommend that future studies examine the psychometric and clinical validity of the hypothesized relationship among the sleep/fatigue/depression symptom cluster in breast cancer patients, including examining the relationships of these symptoms over time. In addition we encourage the development and testing of new treatment modalities, including multi-modal treatments, which may prove to be more efficacious than those presently studied for this cluster of symptoms.

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Disclosure

The authors report no conflicts of interest in this work.

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