CRITICALLY APPRAISED TOPIC

FOCUSED CLINICAL QUESTION

In a 52 yo F with breast cancer, is regular physical exercise beneficial in decreasing severity of the negative side-effects (i.e. fatigue, nausea, loss of appetite, chronic pain, and myalgia) of chemotherapy and radiation treatment, versus traditional symptom management (i.e. medication, rest, "usual care")?

AUTHOR

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CLINICAL SCENARIO

At UNC Hospital, I worked with several patients in the acute setting who had undergone lumpectomies and mastectomies after diagnosis of breast cancer. On a personal and more recent note, my mother was diagnosed with breast cancer last year and is now experiencing upper extremity dysfunction after surgery, a decreased quality of life, and intense physical fatigue (resultant of chemotherapy). According to breastcancer.org, an estimated 246,660 women are expected to be diagnosed with invasive breast cancer in 2016, as well as another 61,000 cases of in-situ breast cancer.[1] With such a large number of individuals undergoing treatments, physical therapy has a role to play in the prevention and management of undesirable chemotherapy side-effects, as well as the biomechanical upper extremity limitations that arise from surgical intervention. Furthermore, different methods to staving off these effects provides an alternative to pharmaceuticals alone for patients whose quality of life and independent function have been affected by chemotherapy treatment. The goal of this critically appraised topic was to amass literature that examines exercise as one of these alternatives to alleviating chemo symptoms.

1. US Breast Cancer Statistice. *Breastcancer.org*. http://www.breastcancer.org/symptoms/understand_bc/statistics Published June 23, 2016. Accessed September 5, 2016.

2. Treatment & Side Effects. Breastcancer.org. http://www.breastcancer.org/treatment/side_effects Published May 15, 2013. Accessed September 5, 2016.

SUMMARY OF SEARCH

[Best evidence appraised and key findings]

- 10 studies were included in the final critical appraisal, selected due to their eligibility with inclusion criteria and their RCT, systematic review, or meta-analysis designs.
- Strength training and/or aerobic training positively influences physical fatigue from adjuvant chemotherapy, as well as some dimensions of mental, cognitive, and emotional fatigue.
- Exercise is found to generally influence short-term levels of fatigue during chemo, but return to baseline levels of physical activity and fatigue are common.
- Group exercise is not necessarily a confounding factor in the positive benefits attained by physical exercise programs for fatigue reduction, though level of physical activity, or lack thereof, prior to chemotherapy may influence its overall effect during actual chemo treatment.
- Key points for future research include examination of longer-term results after exercise intervention, consideration of pre-chemo physical activity levels, and influence of subject age on fatigue and activity.

CLINICAL BOTTOM LINE

An aerobic and/or strength-building exercise program is effective at reducing short-term physical function limitations and physical fatigue in individuals undergoing chemotherapeutic intervention for breast cancer. Exercise has beneficial effects beyond those found in a group-only exercise intervention, though both solo and group physical activities are ultimately beneficial. Furthermore, physical exercise has beneficial influence on other dimensions of fatigue and quality of life, including: mental and affective fatigue, motivation, and general levels of activity.

This critically appraised topic has been individually prepared as part of a course requirement and has been peer-reviewed by one other independent course instructor

SEARCH STRATEGY

Terms used to guide the search strategy			
Patient/Client Group	**I**ntervention (or Assessment)	**C**omparison	**O**utcome(s)
female* Post-menopause Post-menopausal Older female* Breast cancer	Exercise* Physical activity Submaximal exercise Workout* Train*	Pharmaceutical Anti-nausea Medication* Drug* Pharmacological	Nausea Fatigue symptoms

Final search strategy:

1. Breast cancer (MeSH Term)
2. (Female* OR older female* post-menopaus*) AND "breast cancer"
3. Exercise* OR physical activity OR submaximal exercise OR workout* OR train*
4. Pharmaceutical OR anti-nausea OR medication* OR drug* OR pharmacological
5. nausea OR fatigue OR symptoms
6. #1 AND #2 AND #3 AND #4 AND #5
7. #2 AND #3 AND #4 AND #5
8. (#1 OR #2) AND #3 OR AND #5
9. (#1 OR #2) AND #4 AND #5
10. #8 OR #9

Databases and Sites Searched	**Number of results**	**Limits applied, revised number of results (if applicable)**
PubMed	**306**	**Included only RCT, Meta-Analysis, and Systematic Reviews: narrowed to 56**
Cinahl	**78**	**"Breast cancer (MeSH Term)" and "adjuvant or standard care" were removed from search: narrowed to 43**
Web of Science	**13**	

INCLUSION and EXCLUSION CRITERIA

Inclusion Criteria
• Control group should have no exercise counsel or intervention applied • Control must include traditional methods of chemotherapy side-effect management; namely, pharmaceutical intervention • Subjects must be female • Published in English
Exclusion Criteria
• Subjects with other cancer diagnoses (i.e. ovarian or cervical cancer) • Subjects with neurologic and cardiopulmonary conditions

- Case studies, case series, narrative reviews, position statements

RESULTS OF SEARCH

Summary of articles retrieved that met inclusion and exclusion criteria

Author (Year)	Study quality score	Level of Evidence	Study design
Husebo et al. 2013	**6 -Pedro**	**2b**	**RCT**
Ligibel et al. 2016	**6 - Pedro**	**2b**	**RCT**
Mock et al. 2001	**7 - Pedro**	**2c**	**RCT**
Payne et al. 2008	**2 - Pedro**	**4**	**RCT**
Schmidt, M. et al. 2014	**7 - Pedro**	**2a**	**RCT**
Schmidt, T., et al. 2015	**8 - Pedro**	**2b**	**RCT**
Schwartz et al. 2001	**13 –D&B**	**4**	**One-group pretest-posttest design—no control.**
Travier et al. 2015	**8 - Pedro**	**2a**	**RCT**
van Vulpen et al. 2016	**10/11-AMSTAR**	**1a**	**Meta-Analysis**
Wu et al. 2008	**17 –D&B**	**4**	**Secondary data analysis**

BEST EVIDENCE

The following 3 studies were identified as the 'best' evidence and selected for critical appraisal. Reasons for selecting these studies were:

- **van Vulpen et al. 2016:** This meta-analysis had a good design and was very specific to the topics I am searching for with my PICO question. It scored a 10/11 on the AMSTAR.
- **Schmidt, M., et al. 2014:** This scored a 7 on the Pedro scale and but had a good level of evidence with good patient follow-up. It explains results clearly and has an applicable topic to my question.
- **Travier et al. 2015: Th**is study explores many facets of function and QOL, with good statistical analysis and a longitudinal design, which would be more applicable to a real patient scenario, where the clinician treats over a period of time (rather than one-treatment-only approach).

SUMMARY OF BEST EVIDENCE

(1) Description and appraisal of "Effects of resistance exercise on fatigue and quality of life in breast cancer patients undergoing adjuvant chemotherapy: A randomized controlled trial" by Schmidt, M. et al, 2014

Aim/Objective of the Study/Systematic Review:
This randomized controlled trial set forth to examine the effects of group-based resistance training exercise on chemotherapy-related fatigue in patients with breast cancer, and to distinguish the exercise effects from the psychosocial effects of being in a group.
Study Design [e.g., systematic review, cohort, randomised controlled trial, qualitative study, grounded theory. Includes information about study characteristics such as blinding and allocation concealment. When were outcomes measured, if relevant] Note: For systematic review, use headings 'search strategy', 'selection criteria', 'methods' etc. For qualitative studies, identify data collection/analyses methods.

This was a randomised controlled trial. Allocation was performed by a biostatistician who was not involved in the recruitment process, using predetermined lists with random block size, stratified by age and baseline physical fatigue. There is no mention of blinding in subjects nor researchers and can therefore be assumed to have not occurred.

Outcomes were measured at baseline and at Week 13, after the 12-week intervention period.

Setting

[e.g., locations such as hospital, community; rural; metropolitan; country]

This study took place in Heidelberg, Germany, and the surrounding metropolitan areas in an outpatient setting, as all subjects were receiving chemotherapy after lumpectomy or mastectomy. All training sessions took place at the Institute of Sports and Sports Science at the University of Heidelberg.

Participants

[N, diagnosis, eligibility criteria, how recruited, type of sample (e.g., purposive, random), key demographics such as mean age, gender, duration of illness/disease, and if groups in an RCT were comparable at baseline on key demographic variables; number of dropouts if relevant, number available for follow-up]

Note: This is not a list of the inclusion and exclusion criteria. This is a description of the actual sample that participated in the study. You can find this descriptive information in the text and tables in the article.

All subjects had confirmed primary breast cancer *after lumpectomy or mastectomy*, and were scheduled for chemotherapy, and were capable of attending biweekly exercise sessions in specific facilities. 97 patients were eligible for the study, but 2 had to be excluded from statistical analysis because they started chemotherapy after baseline. 95 female participants were included in this study and pre-/post-intervention analysis.

Mean age of participants was 52.7 +/- 10.0. Average BMI was 26.0 +/- 4.8. At the onset of intervention, subjects were an average of 56.0 +/- 23.4 days out of surgery and an average of 18.8 +/- 23.4 days since commencing chemotherapy.

Most of the subjects had early-stages I-III breast cancer, while two were in stage IV with metastases.

Subjects were recruited through notification of the study during chemotherapy visits, as well as through flyers, posters, and physicians.

Thyroxin, a thyroid hormone, was being used by 22% of the exercise intervention subjects and 28% of the relaxation-control subjects. A total of 17 subjects were diagnosed with depression at baseline.

Intervention Investigated

[Provide details of methods, who provided treatment, when and where, how many hours of treatment provided]

Control: Relaxation Group Therapy

The control group met as a group and performed relaxation exercises without any physical activity. These sessions were well-supervised, according to the authors, though no specific parameters are detailed in the paper regarding what specific relaxation activities were included. Control group subjects met for 60 minutes, 2x/week, over a 12-week period.

Experimental: Resistance Group Exercise

The intervention involved 8 machine-based progressive resistance exercises (3 sets, 8-12 repetitions at 60-80% of a 1 rep. max.). All sessions were supervised and "well-defined," according to the authors; however, no specific machines nor exercises were detailed in the paper. It can be assumed that resistance exercises were applied to both the upper and lower extremities. Intervention group subjects met for 60 minutes, 2x/week, over a 12-week period.

Outcome Measures (Primary and Secondary)

[Give details of each measure, maximum possible score and range for each measure, administered by whom, where]

Fatigue was the primary outcome measure assessed in this study, using the self-assessment Fatigue Assessment Questionnaire (FAQ). Scoring was on a 0-100 scale, with a higher score indicating worse fatigue.

Quality of Life was self-assessed with the European Organization for Research and Treatment of Cancer Quality

of Life Questionnaire—EORTC QLQ-C30 (ver. 3.0). Scoring ranged from 0-100. On the global scale, a higher score indicated better quality of life, while a higher score in the subcategories (including the breast cancer-specific module), indicated poorer quality of life.

Depression was self-assessed using the Center for Epidemiologic Studies Depression scale (CES-D). The scores were rescaled to a 0-100 scale, which a higher score indicating higher depression. A score >38 on the 0-100 scale indicated potentially serious depressive conditions.

Cognitive function was estimated using the "trail-making-test," in which a subject is timed on her ability to connect numbers and letters in a logical order. Greater time required to finish the test indicates worse cognitive function.

Clinical parameters like dates and types of chemotherapy were found in medical charts. Medications were assessed in personal interviews. Physical parameters like weight and BMI were also recorded. Isometric and isokinetic strength were measured using the IsoMed 2000, while endurance was measured with VO_{2peak}.

Main Findings

[Provide summary of mean scores/mean differences/treatment effect, 95% confidence intervals and p-values etc., where provided; you may calculate your own values if necessary/applicable]

An a priori analysis was performed on the three different fatigue dimension, and the study designed to detect a mean standardized effect size of .5, with a power of 80% and significance level at $p<0.05$.

Baseline medical characteristics, fatigue, and quality of life were similarly distributed between both intervention groups, with no statistically significant difference. However, there was a significant difference between groups for depression, which was significantly more common in the control group than the exercise group (p=0.0098).

Fatigue:

In the parameter of total fatigue in subjects *with and without depression*, between-group difference from pre- to post-intervention was -5.8 points (95% CI of -12.6, 1.1) and p=.098, with indication of beneficial effects in the intervention group versus the control. Physical fatigue in particular had a p=.052.

In individuals *without depression only*, there was a statistically significant between-group difference in total fatigue of -8.1 points (95% CI of -15.7, -0.4), p=0.039, and effect size of 0.47. Furthermore, there was a statistically significant between-group difference in physical fatigue, with a -10.2 point (?) difference (95% CI -19.7, -0.8), p=0.034, and effect size of 0.31.

Patients *with depression* had higher levels of fatigue at baseline, with levels remaining high or decreasing through treatment with no statistically significant between-group differences. Between-group difference of total fatigue was 7.0 (95% CI of -14.3, 28.2) and non-statistically significant p=0.49.

Quality of Life:

In the realm of quality of life on the EORTC-QLQ 30 scale, there was a statistically significant difference between groups in the realm of "role function" (14.7 point difference with a 95% CI of 1.0, 28.3; p=0.035, ES=0.48) and "social function" (12.6 points with 95% CI of 02, 24.9; p=0.46, ES=0.44). Both indicate beneficial effect of the exercise intervention group. It should be noted that this analysis only included patients *without baseline depression*. Any statistical analysis for subjects with depression is not shown in the paper, but the authors state that the 17 subjects with baseline depression presented with "substantially lower" QoL functional scores compared to patients without baseline depression, and there were no statistically significant effects of intervention versus control.

Depression and Cognitive Function:

Depression scores remained unchanged in both groups, with an effect size of 0.07.

Cognitive performance improvement significantly in the intervention group (-10.2 points, 95% CI -16.3, -4.2) but there was no statistically significant between-group difference.

Thyroxin users:

There was a subset of patients using Thyroxin during treatment: 22% of subjects in the exercise intervention group and 28% in the relaxation control group. Total fatigue in the relaxation control group increased significantly (-19.3 points, 95% CI -34.4, -4.1; p=0.016). Physical fatigue also significantly increased in this group (-27.3 points, 95% CI -48.6, -5.9; p=0.015, ES=1.31), as well as affective fatigue (-13.7 points, 95% CI -26.3, 20.3; p=0.027, ES=1.12).

Original Authors' Conclusions

[Paraphrase as required. If providing a direct quote, add page number]

The authors point out that this study indicated a beneficial effect of resistance exercise on physical fatigue and

quality of life in breast cancer patients undergoing chemotherapy. Furthermore, they conclude that resistance exercise has "significant and clinically relevant benefits…*over and above the psychosocial effects* on fatigue and important QoL scales during chemotherapy." (497) In other words, this study indicates that the effects of the exercise intervention group were not confounded due to the group/social nature of intervention, but truly from exercise itself, since the control group also experienced a group setting.

Critical Appraisal

Validity

[Identify the strengths and limitations of the study, including potential sources of bias. Comment on the overall methodological quality (including the score) as you determined from your assessment of the article. Comment on anything you believe was missing in the paper.]

Strengths: Strengths of this study include a well-defined control group that accounted for the potential impact of group-centered interventions. Additionally, there was a fair adherence rate of 71%. An a priori analysis was conducted, as well as fairly thorough statistical analysis of the between group differences. Randomized allocation was also sufficiently conducted. Another strength of the study was highly supervised and regulated sessions in both the intervention and control groups.

Limitations:

One limitation to the study was the lack of blinding; while this can be inherently difficult to do in a study that involves exercise as intervention, attempts could have been made or at least an explanation could have been offered by the authors.

Another limitation was variability between the two groups; in particular, some patients were taking Thyroxin for hypothyroidism during chemotherapy, which strongly influenced levels of fatigue. Fortunately, the authors did analyze results separately for this group, but it could have been used earlier on in the recruitment process as an inclusion or exclusion criterion. Another issue regarding variability was the inclusion of patients with depression, especially in the control group where they significantly outnumbered patients with depression in the intervention group. Again, this could have been used earlier in the recruitment process as part of inclusion or exclusion for the study. It should be noted that too much variability in subjects could have led to a decreased overall statistical power of the results.

Another limiting aspect of the study was the omission of baseline and post-intervention strength scores. This might have been good information to include to further emphasize statistical significance of improvements in the exercise group.

Recruitment for the study was also a limitation in that it resulted in a sample of convenience from one location. A broader search over a greater geographic area may have resulted in a more generalizable population sample that could be applied to a wider variety of patients in a clinically applicable sense. Furthermore, a larger sample size may have been helpful in boosting the statistical power of results.

Finally, a significant limitation in the article was lack of detail in explaining the intervention and control protocols. The authors reference two prior studies upon which the protocols were based (for both exercise intervention and relaxation control), but this required further research and reading to understand what exactly was applied to the groups. Vague detail was given for both groups.

This study scored 7 on the PEDRO scale. This is due to the lack of blinding of subjects, therapists, and assessors. I originally scored this study a 2a for level of evidence, but believe I should have given it a 2b upon more detailed reflection of the study. This is because there was a 71% adherence rate, quality of intervention explanations (and therefore repeatability of the study) was lacking, and no blinding occurred, potentially leading to bias.

Interpretation of Results

[This is YOUR interpretation of the results taking into consideration the strengths and limitations as you discussed above. Please comment on clinical significance of effect size / study findings. Describe in your own words what the results mean.]

These results indicate that machine resistance exercise can be a beneficial tool in mitigating some of the negative effects of chemotherapy in patients with breast cancer, including fatigue, quality of life, and potentially depression. However, this effect must be limited only to females with breast cancer who have already undergone surgical removal of tumors. Furthermore, the subjects were from a small sampling of women in the Heidelberg, Germany area; thus, it cannot be assumed that these results will directly translate to American patients.

Another factor in interpreting these results is that both control and intervention groups received their respective "treatment" in a group setting. While the study was designed to eliminate any muddling effect that an intervention-only group-oriented treatment would have, it does cause me to question if a one-on-one resistance

training exercise program would have similar effects to that of this group-based study.

The resistance exercise protocol was vague, there are no details about what type of machine resistance exercises were used, so replicating the intervention in clinical practice would be difficult

Statistical analysis was performed with an analysis of covariance (ANCOVA). Regarding the effect size of exercise intervention on level of total fatigue in subjects without depression, there was a statistically significant difference between intervention and control groups with a large effect size of .47. Physical fatigue in this group had a minimal to moderate to large effect of .31. Quality of life in the realms of "role function" and "social function" also had large effect sizes of .48 and .44, respectively.

Physical function in the QoL scale had the largest effect size of all outcome measures in the study, at .55 and favoring the intervention group. However, the results were not statistically significant which may have been due to lack of power (perhaps from too much in-group variance or a small sample size).

(2) Description and appraisal of Effects of an 18-weel exercise programme started early during breast cancer treatment: a randomised controlled trial by Travier, et al., 2015.

Aim/Objective of the Study/Systematic Review:

This randomized controlled trial examined the effects of aerobic and resistance exercise on the negative effects of chemotherapy. Its main goal was to investigate influence of exercise on fatigue as the primary outcome measure.

Study Design

[e.g., systematic review, cohort, randomised controlled trial, qualitative study, grounded theory. Includes information about study characteristics such as blinding and allocation concealment. When were outcomes measured, if relevant]

Note: For systematic review, use headings 'search strategy', 'selection criteria', 'methods' etc. For qualitative studies, identify data collection/analyses methods.

This was a two-arm randomized controlled trial. Concealed randomization was performed by a computer, with stratification based on age, use of a tissue expander after surgery, and adjuvant treatment.

Blinding of participants was "not possible," according to the authors, due to the nature of intervention. However, outcome measures were assessed by researchers not involved with the subjects.

Outcomes were assessed at baseline, 18 weeks (post-intervention), and 36 weeks.

Setting

[e.g., locations such as hospital, community; rural; metropolitan; country]

This study took place throughout the Netherlands across various hospital systems in metropolitan areas. The main institution overseeing ethical concerns for this study was the University Medical Center Utrecht. The authors are vague on location of intervention sessions, but do mention in their discussion that much of the study took place in the subjects' respective treatment hospitals.

Participants

[N, diagnosis, eligibility criteria, how recruited, type of sample (e.g., purposive, random), key demographics such as mean age, gender, duration of illness/disease, and if groups in an RCT were comparable at baseline on key demographic variables; number of dropouts if relevant, number available for follow-up]

Note: This is not a list of the inclusion and exclusion criteria. This is a description of the actual sample that participated in the study. You can find this descriptive information in the text and tables in the article.

Participants were recruited through a convenience sampling, by simple invitation from their clinician or nurse during normal outpatient visits. All subjects were required to have a breast cancer diagnosis of less than 6 weeks, no distant metastases (stage M0), plans for chemotherapeutic intervention, and having no contraindications for physical activity.

Participants were aged 25 to 75 years old, with a mean age of 49.7 +/- 8.2 in the intervention group and a mean age of 49.5 +/- 7.9 in the usual care group. All subjects were female.

After recruitment, 204 individuals signed consent forms and were randomized to groups. However, 40 individuals were lost to follow-up throughout the study, for various reasons. Thus, n=164 subjects were ultimately included in statistical analyses.

Interestingly, level of physical activity prior to the study was not considered nor utilized as criteria for participation in the study. Furthermore, type of medication and adjuvant chemotherapy was not considered in inclusion/exclusion.

Intervention Investigated

[Provide details of methods, who provided treatment, when and where, how many hours of treatment provided]

Control: Usual Care Group

Patients randomized the usual care group simply maintained normal daily activities and their regular physical activity. They did not receive any guided physical activity intervention.

It should be noted that after the last week of intervention (week 18) the control group was allowed to participate in guided exercise programs, due to the common practice of providing exercise programs to cancer patients after primary treatment in the Netherlands.

Experimental: Exercise Intervention

The intervention group received guided physical activity intervention over the 18 week study period, in addition to their usual cancer care. Classes met 2 times/week in 60 minute sessions. They included a warmup, aerobic and muscle strength training, and cool downs.

Aerobic intervention included interval training of alternating intensities.

Strength training was performed for all major muscle groups, with weight assigned at 65% of the subject's 1 rep max.

Participants were also educated on the benefits of physical activity and encouraged to be active for at least 30 minutes on 3 days per week.

All sessions were supervised by a physical therapist and incorporated behavioral principles of Bandura's cognitive theory. This is not detailed by the authors.

Outcome Measures (Primary and Secondary)

[Give details of each measure, maximum possible score and range for each measure, administered by whom, where]

Fatigue was the primary outcome measure in this study, self-assessed through the Multidimensional Fatigue Inventory (MFI) and the Fatigue Quality List (FQL). Scores on the MFI range from 4-20, with a higher score indicating more fatigue. Scores on the FQL were grouped in subscores, based on 28 adjectives used to describe perception of fatigue.

Secondary Measures:

Quality of Life was self-assessed using the European Organization for Research and Treatment Cancer Quality of Life Questionnaire and the Short Form Health Survey. This was scored from 0-100 with a higher score indicating higher quality of life. Anxiety and depression were assessed with the Hospital Anxiety and Depression Scale. This is scored from 0-21, with a higher score indicating increased anxiety and depression.

Aerobic capacity was measured through a cardiopulmonary exercise test with continuous breathing gas analysis. Cycling workload was increased until the subject hit either physiologic exhaustion or symptom limitation. Exhaustion was classified by a peak heart rate of >85% of age-predicted max HR and a respiratory exchange ratio >1.10.

Thigh muscle strength was assessed by use of a Cybex dynamometer at angular velocities of 60 deg/s and 180 deg/s. After three repetitions, the highest peak torque was calculated.

Handgrip strength was measured by taking the best of two attempts using a handgrip dynamometer.

Body weight and height were measured to the nearest .5 kg and .5 cm.

Physical activity level was self-assessed through the Short QUestionnaire to ASess Health (SQUASH). The questionnaire covers activity domains in commuting, leisure-time, sport, household, and at work. The authors calculated and focused on weekly minutes of moderate-high intensity physical activity, as well as leisure and sport activity.

Main Findings

[Provide summary of mean scores/mean differences/treatment effect, 95% confidence intervals and p-values etc., where provided; you may calculate your own values if necessary/applicable]

An a priori analysis found that the study needed 75 participants in both the intervention and control groups, with the study designed to detect a between-group change in fatigue of +/- 4 SD, with a power of 80% and $p<0.05$.

Baseline physical and medical characteristics were evenly dispersed between both groups, with the exception that women in the intervention group were more highly educated, had higher incidence of triple negative breast cancer, and were post-menopausal.

Fatigue: Primary Outcome:

Both groups reported significant increases in physical fatigue from baseline to the end of the 18 week study. However, the intervention group had statistically significantly less fatigue than the control group at 18 weeks, with a between group difference of -1.3 points (95% CI, -2.5 to -0.1, ES -0.30). However, differences in general and mental fatigue were not statistically significant between groups.

At the 36-week follow-up, no significant differences were found between the two groups. In fact, reported fatigue was similar to that at baseline, except for mental fatigue with a difference of +1 point (95% CI, 0.1 to 1.9).

Quality of Life:

Both groups reported significant decreases in their quality of life, as well as presenting with increases in depression scores. On the Short Form Health Survey at 18 weeks, a significant between group difference was found for "change in health" with a mean difference of 11.3 points in favor of the intervention group (95% CI, 3.4 to 19.1, with an effect size of 0.47). At the 36-week followup, both groups reported higher scores for their mental health but the improvement was markedly lower in the intervention group, with a mean difference of -4.0 points (95% CI, -7.8 to -0.1, ES -0.26).

Muscle Strength, Aerobic Capacity, and Body Weight:

Surprisingly, no significant between-group differences were found in $VO2_{peak}$ and peak power output. Aerobic capacity did not significantly differ between the groups at 36 weeks.

However, muscle strength in the intervention group was significantly higher for knee flexion and extension at 18 weeks. Left knee extensor torque had a mean 10.1 point difference in favor of the intervention group (95% CI, 3.2 to 16.9, ES= .45). Right knee flexor torque had a mean 9. 1 difference in favor of the intervention group (95% CI, 3.6 to 14.6, ES= .42).

Original Authors' Conclusions

[Paraphrase as required. If providing a direct quote, add page number]

Travier et al conclude that an exercise program offered early in a breast cancer treatment protocol (specifically in individuals undergoing chemotherapy) has potential to reduce "short-term physical fatigue and diminishment of cardiorespiratory fitness," as well as improving muscular strength (10). In general, exercise is a positive intervention that reduces chemotherapy-related fatigue.

Critical Appraisal

Validity

[Identify the strengths and limitations of the study, including potential sources of bias. Comment on the overall methodological quality (including the score) as you determined from your assessment of the article. Comment

on anything you believe was missing in the paper.]

This study was scored at an 8 on the Pedro scale and give a level 2a of evidence. It was scored an 8/10 due to its lack of blinding of subjects and assessors.

Strengths:

Strengths of the study include its large sample size and the high adherence (83%) to intervention treatment. Additionally, its criteria of only including subjects <6 weeks after diagnosis ensured that all subjects were receiving chemotherapy at some point during the study, increasing its construct validity.

Another strength of this study is the specific description of the exercise interventions, making this trial repeatable and easier to understand from a clinical perspective.

Limitations:

Unfortunately, ethical regulations required that the control group be permitted to participate in exercise programs after the 18 week trial period. After the 18 week intervention, 56% of the control subjects were reporting high levels of physical activity, which may have confounded the true effects of the treatment group at the 36-week followup.

Another limitation was the lack of regulation in pre-diagnosis physical activity level in both groups. There was no inclusion/exclusion criteria about exercise levels prior to assignment to control or intervention group, which may have underestimated the actual effect of the exercise intervention at both the 18- and 36-week marks.

Blinding was not performed on subjects nor assessors, which may have led to bias. While the nature of intervention may have prevented complete blinding of the subjects, more effort could have been made to blind assessors in order to reduce chances of bias and potentially skewed results.

The term "usual care" was very vague and not well-defined. As this term and potential protocol for "usual care" is so broad, its lack of description and specific criterion are a limitation to the study and its potential repeatability.

Finally, despite the authors' assertion that the groups were very similar at baseline, the intervention group had a notably higher level of overall education and were all post-menopausal. This presents an obvious age difference between the two groups that could have confounded results. Additionally, level of education is certainly important when considering a patient's health literacy, and that higher overall level of education in the intervention group could certainly have influenced the level of adherence, as well as the end results.

Interpretation of Results

[This is YOUR interpretation of the results taking into consideration the strengths and limitations as you discussed above. Please comment on clinical significance of effect size / study findings. Describe in your own words what the results mean.]

These results indicate that patients with breast cancer who are undergoing chemotherapy may positively benefit from aerobic and strengthening exercise throughout their course of treatment. However, this interpretation must be limited to females who have a diagnosis less than 6 weeks old and no metastases, as the study only examined an exercise regimen that begins early in breast cancer treatment.

Furthermore, this study took place in the Netherlands where diagnosis and treatment are likely similar to that of standard US protocol. However, the Netherlands provides exercise programs to individuals after their primary treatment; this protocol resulted in control group subjects increasing their physical activity after 18 weeks, which may have confounded results. Thus, interpretation of 36-week follow-up results should be read with caution and awareness of these resources available to patients.

The study also did not rule out subjects based on prior levels of physical activity, or lack thereof. Therefore, patients who may opt to participate in an exercise program to reduce chemo-related fatigue should be appropriately assessed for readiness to be physically active and to be assigned safe and appropriate exercise interventions.

Regarding the effect size of intervention on physical fatigue, there was a small difference (ES= -0.30) between groups with significantly less fatigue in the intervention group. Effect size of knee flexion and extension strength was small to moderate (ES=.45).

Fortunately, the intervention group description was specific enough that a PT could replicate it in the clinic. Usual care was not specific and should be interpreted with a grain of salt. Individual application of these results would require individualized review of medical history, type of cancer, and type of "usual care" the patient is receiving.

(3) Description and appraisal of "Effects of physical exercise during adjuvant breast cancer treatment on physical and psychological dimensions of cancer-related fatigue: a meta-analysis" by van Vulpen et al, 2016.

Aim/Objective of the Study/Systematic Review:

The objective of this meta-analysis was to examine the effects of exercise during breast cancer treatment on physical fatigue and psychological fatigue. The analysis was accomplished through systematic searches in PubMed, Embase, and the Cochrane Library.

Study Design

[e.g., systematic review, cohort, randomised controlled trial, qualitative study, grounded theory. Includes information about study characteristics such as blinding and allocation concealment. When were outcomes measured, if relevant]

Note: For systematic review, use headings 'search strategy', 'selection criteria', 'methods' etc. For qualitative studies, identify data collection/analyses methods.

This paper was a meta-analysis, conducted within PRISMA guidelines.

Search Strategy:

Literature was found through a search of PubMed, Embase, and the Cochrane Library during June of 2015.

Searches were comprised of combinations of the following terms: breast neoplasms, breast, mammary, carcinoma, cancer, malignan, neoplasm, tumor, exercise, fatigue, physical activity, aerobic, strength, resistance.

Inclusion Criteria:

Only randomized controlled trials were included in this search. Further criteria included: a study population of breast cancer patients undergoing either chemotherapy and/or radiation therapy; evaluation of an exercise program (aerobic and/or resistance) as intervention; a control group receiving "usual care" or a placebo intervention; assessment of fatigue through a multidimensional questionnaire; reporting on various dimensions of fatigue.

Data Extraction and Quality Assessment:

Inclusion eligibility was reviewed independently by two investigators.

Relevant information was collected from studies using a pre-made data extraction form.

Quality of outcome level for every study was assessed independently by two authors using the "risk of bias tool," provided by Cochrane. Risk of bias was assessed based on a study's allocation of concealment, blinding of participants and assessors, completeness of the reported data, and any selective reporting. Since all interventions in the five studies were unable to blind participants, simply due to the nature of the intervention, all studies scored "high risk of bias" on the Cochrane tool. Furthermore, no studies blinded outcomes assessment, due to use of self-reported and subjective questionnaires as outcome measures.

Publication bias was further assessed using Egger's and Begg's tests.

Statistical Analysis:

Meta-analyses were performed for each dimension of fatigue, using SPSS Statistics 21 and R Studio 3.1.1. Weighting of the effect size was used in consideration of the study size.

Results of the various fatigue dimensions were visually presented with forest plots.

The I^2 statistic was used for assessment of heterogeneity, with 25%, 50%, and 75% representing low, medium, and high heterogeneity, respectively. Statistical heterogeneity for all dimensions after analysis was low (I^2=1.0%)

Setting

[e.g., locations such as hospital, community; rural; metropolitan; country]

The authors are not specific about the exact setting of the included papers in this analysis. However, they do note that intervention exercise programs took place in supervised settings or in home-based settings. Funding for the meta-analysis was provided by the World Cancer Research Fund, The Netherlands. The authors were based in London, UK, and Utrecht, The Netherlands.

Participants

[N, diagnosis, eligibility criteria, how recruited, type of sample (e.g., purposive, random), key demographics such as mean age, gender, duration of illness/disease, and if groups in an RCT were comparable at baseline on key demographic variables; number of dropouts if relevant, number available for follow-up]

Note: This is not a list of the inclusion and exclusion criteria. This is a description of the actual sample that participated in the study. You can find this descriptive information in the text and tables in the article.

After screening of 63 articles, 5 RCT studies were ultimately included in the meta-analysis.

Four studies included 100%, while one study had 98% female subjects due to the inclusion of n=2 men.

Mean age of participants ranged from 50 to 56 years old.

All studies required subjects to have definitive diagnosis of breast cancer. Four studies had subjects undergoing chemotherapy, radiation, or both; one study had subjects only undergoing radiation therapy.

Intervention Investigated

[Provide details of methods, who provided treatment, when and where, how many hours of treatment provided]

Control: Relaxation program or usual care

All studies employed a control group that had no guided physical exercise intervention:

Two studies simply utilized "usual care" for the control group, indicating no exercise nor any programmed activity provided to the control.

Three studies utilized "sham" interventions with no physical exercise: two studies provided supervised relaxation programs to the control group, while one study incorporated a flexibility and relaxation program for the control group.

Further detail on the control groups' details ("usual care," the supervised relaxation programs, and the flexibility/relaxation program) are vague and unspecific in this meta-analysis.

Experimental: Exercise Intervention

Three of the studies provided only supervised group exercise intervention to the experimental subjects. One study provided only home-based exercise intervention. Finally, one study provided both supervised group exercise and home-based exercise intervention.

Initiation of intervention ranged from the 1st or 2nd cycle of chemotherapy to within 6 weeks of diagnosis.

All exercise programs ranged from 30 to 60 minutes in duration, 2-5x/week.

All five studies had progressive resistance training incorporated into the intervention protocol. Three studies had both aerobic training and resistance training.

Adherence to the exercise programs ranged from 71% - 83%.

Outcome Measures (Primary and Secondary)

[Give details of each measure, maximum possible score and range for each measure, administered by whom, where]

Fatigue was assessed in all studies through two multidimensional fatigue surveys, both with higher scores indicating greater fatigue:

The Fatigue Assessment Questionnaire (FAQ)- a 20-item survey covering physical, affective, and mental fatigue states. Scored on a 0-100 scale, with a higher score indicating higher level of fatigue.

Multidimensional Fatigue Inventory (MFI)- a 20-item questionnaire measuring general, mental, and physical fatigue, as well as "reduced activity" and "reduced motivation." Scored from 4-20, with a higher score

indicating greater fatigue.

Main Findings

[Provide summary of mean scores/mean differences/treatment effect, 95% confidence intervals and p-values etc., where provided; you may calculate your own values if necessary/applicable]

Presentation of statistical findings were visually displayed through forest plots. All studies' showed reductions in fatigue that generally favored the physical exercise interventions.

Results of the analysis of all five studies showed that physical exercise had statistically significant effects on:

- General fatigue: 95% CI -0.38 to -0.05; ES= -0.22
- Physical fatigue: 95% CI -0.49 to -0.21; ES= -0.35
- "reduced activity" on the MFI: 95% CI -0.38 to -0.05; ES= -0.22
- "reduced motivation" on the MFI: 95% CI -0.35 to -0.01; ES= -0.18

The studies that provided supervised group physical activity interventions only (n=4) had slightly larger beneficial effect sizes on:

- general fatigue: 95% CI -0.47 to -0.04; ES= -0.25
- physical fatigue: 95% CI -0.56 to -0.23; ES= -0.39

However, the effect on "reduced activity" and "reduced motivation" was not similarly larger when analyzing just the supervised group interventions.

As seen in the results above, effect sizes were largest in the dimension of physical fatigue.

Statistically significant effects were not found on mental or affective fatigue.

Original Authors' Conclusions

[Paraphrase as required. If providing a direct quote, add page number]

The authors conclude that physical exercise during adjuvant breast cancer treatment has beneficial influence on general and physical fatigue, as well as positive influence in decreasing "reduced activity" and "reduced motivation." The authors also conclude that due to the largest effect size being in the dimension of physical fatigue, physical fatigue is most sensitive to physical exercise intervention.

Critical Appraisal

Validity

[Identify the strengths and limitations of the study, including potential sources of bias. Comment on the overall methodological quality (including the score) as you determined from your assessment of the article. Comment on anything you believe was missing in the paper.]

<u>Strengths:</u>

This study had very clear inclusion and exclusion criteria. It also had very clear outcome measures for assessment, making results easy to read and understand from a clinical perspective. It also utilized two independent reviewers when amassing potential articles for inclusion, reducing risk of bias and sloppy work. Finally, it presents results in clear forest plots that make "readability" of the meta-analysis much better, thus making the results easier to understand from a clinical perspective.

It should also be noted that heterogeneity of the studies was very low (I^2=1.0%), indicating low variation between the studies' subjects and characteristics.

<u>Weaknesses:</u>

The meta-analysis had a very limited number of studies (n=5) included in the final analysis, which meant that not all possible exercise programs/interventions that are published could be included. This limited the results and overall influence of exercise on the various fatigue dimensions. Furthermore, though it had very clear outcome measures, the authors used only two questionnaires, which further limited inclusion of other potentially valid studies. In addition, these questionnaires were self-reported, decreasing overall objectivity of findings due the subjective nature of a self-reported measure.

<u>Potential Sources of Bias:</u>

The authors claim no conflict of interest in this meta-analysis and no sources of bias. However, they do state

that all five studies included scored a "high risk of bias" on the Cochrane tool due to their lack of blinding of subjects. Bias may also have resulted

This study was scored a 10/11 on the AMSTAR. This is because it did not include a list of all the studies resulting from their search, but rather just the studies that met inclusion criteria.

Interpretation of Results

[This is YOUR interpretation of the results taking into consideration the strengths and limitations as you discussed above. Please comment on clinical significance of effect size / study findings. Describe in your own words what the results mean.]

These results clearly indicate that physical exercise has a significant effect on physical fatigue in patients undergoing breast cancer treatment (either chemotherapy, radiation, or both). Furthermore, a supervised group intervention may be more effective, based on the results. The effect sizes were all generally small; even the largest effect size (physical fatigue in supervised exercise interventions only) was small to moderate at -0.39. This indicates that the magnitude of the effect of physical activity intervention was small and is perhaps too small for a decisive conclusion regarding exercise's influence on fatigue.

The meta-analysis only included 5 studies, which allowed for very direct and easy-to-interpret results. However, it does mean that, overall, the analysis has a relatively small sampling of the literature that is published on breast cancer and exercise.

Overall, these results could be utilized in clinic with the expectation that a patient undergoing chemotherapy and performing physical exercise would likely benefit the most in the realm of physical fatigue. That individual might also have beneficial effects in mental and general fatigue.

EVIDENCE SYNTHESIS AND IMPLICATIONS

Appraisal of the articles:

All of the evidence in this critical appraisal showed that physical exercise has a generally positive effect on an undesirable side-effect of breast cancer treatment: namely, fatigue. The study by Schmidt, M., et al recognized that a confounding factor in exercise interventions could be the group dynamics, rather than exercise alone, contributing to reduced levels of fatigue. They did an excellent job of mitigating these confounding effects in their studies; results showed that physical activity does indeed positively influence fatigue. Both the study by Travier et al and the meta-analysis by van Vulpen et al agree with that finding.

In general, evidence points to positive benefits of physical activity for reduction of chemo-related fatigue in breast cancer patients. However, the quality of studies varied widely and presented statistical results that ranged from thorough to almost non-existent. Of all the studies reviewed in this appraisal, Schmidt, M., et al presented the most dynamic and integrated statistical analysis. Additionally, lack of blinding was a common issue in the studies, primarily due to the fact that exercise intervention is impossible to blind from the intervention subjects.

Clinical implications:

Considered as a whole, the papers amassed in this search resulted in findings generally suggesting that physical activity is a beneficial intervention for individuals undergoing breast cancer treatment. However, the studies varied in their intervention approaches and even their control group approaches. All studies employed some form of aerobic/endurance exercise, resistance training, or both in their intervention groups; this approach can certainly be employed in clinical practice through use of aerobic training and strength intervention. Control groups were also generally similar to each other, typically treated as "usual care" (meaning subjects went about daily lives and practices with no change in routine and receiving appropriate standards of care for their breast cancer diagnosis). However, the control group in the study by Schmidt et al received a group relaxation class, while the meta-analysis by van Vulpen et al pointed out one study's use of a flexibility and relaxation class for the control. This is mentioned simply to point out the findings that group intervention does not necessarily play a role in the benefits provided by physical exercise; whether performed alone or in a group, physical activity has been found to be beneficial in reducing fatigue during chemotherapy.

In practice, timing of exercise intervention may have an impact on the benefits a patient receives from physical activity on reduction of fatigue. Travier et al accurately pointed out that most breast cancer patients will commence either chemotherapy or radiation within 6 weeks of diagnosis. In order to receive the beneficial effects of exercise intervention, it logically must be performed at the same time that the fatigue-inducing chemotherapy is taking place; thus, administration of exercise protocols should be near or at the commencement of chemo.

In fact, level of physical activity prior to intervention may play a role in the patient's success with exercise and chemo-related fatigue. A paper published in the Journal of Strength and Conditioning Research (not included in

the final critical appraisal due to its case study design) found a reduction in fatigue levels in a patient who began exercise one week prior to chemotherapy and continued training throughout treatment.[1] Travier et al also more definitively found that exercise intervention subjects had significantly better reduction of fatigue, though the results may have been underestimated due to the high levels of physical activity in both control and intervention subjects prior to chemo. This indicates that patients who were active before chemotherapy may have increased likelihood of reduced fatigue during chemo than those who were not active but only recently started exercising. In practice, this means that patients may be encouraged to begin an exercise program prior to starting chemotherapy, in order to maximize its fatigue-reducing benefits.

Intensity of the intervention may also play a role. Schwartz et al found that supervised low- to moderate-intensity exercise had a significant influence on reducing chemo-related fatigue, whereas Mock et al found that a simple home-based walking program was effective in reducing fatigue. In general, the studies collected in this critical appraisal featured supervised interventions, with a few home-based programs; consideration of these results, therefore, should consider and employ the influence of a supervised intervention from an individual such as a PT.

Suggestions for future research:

Not surprisingly, long-term implications of the benefits of physical activity during chemo for breast cancer are limited. Travier and Schmidt et al both found results in which control and intervention subjects returned to baseline levels of fatigue within months of completing chemotherapy. Of course, chemo-related fatigue is a short-term symptom by nature, but it would be interesting to have greater follow-up with these subjects in order to discern the more long-term influence of an exercise intervention during breast cancer chemotherapy.

Another suggestion for future research would be to examine influence of physical activity levels prior to chemo in the reduction of fatigue symptoms. Though it is mentioned in some of the papers appraised here, the topic is not exclusively studied in a true randomized trial.

Finally, future research might consider influence of age on exercise-induced reductions of chemo-related fatigue. The studies here did not exclude subjects based on age, but it would be of clinical interest to examine how one's age influences their activity tolerance, response to chemotherapy, and overall levels of fatigue. Furthermore, influence of menopause on these symptoms would likely be included and would be of clinical significance.

1. De Paleville, D., Topp, R., Swank, A. Effects of aerobic training prior to and during chemotherapy in a breast cancer patient: a case study. *J Strength Cond Res*. 2007; 21(2): 635-637.

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