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Multidisciplinary Rehabilitation in Women with Breast Cancer: a Systematic Review

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Abstract

Background: With improved survival rates in breast cancer (BC), there are implications for longer-term impact on disability, psychological function and quality of life, which may be amenable to rehabilitation. Rehabilitation is an expensive resource and the evidence to support its justification is urgently needed. The aim of this systematic review is to present an evidence-based overview of the effectiveness of multidisciplinary (MD) rehabilitation interventions in women with BC and the outcomes that are affected.

Methods: A search of the literature was conducted using medical and health science electronic databases (Medline, EMBASE, CINAHL, AMED, PEDro, LILACS and the Cochrane Library) up to May 2013 for studies reporting outcomes of BC patients following MD rehabilitation that addressed functional restoration and improved participation. Two reviewers applied the inclusion criteria to select potential studies and independently extracted data and assessed the methodological quality. Included studies were critically appraised using Grades of Recommendation, Assessment, Development and Evaluation (GRADE) methodological quality approach.

Results: Seven studies (two randomised controlled trials (RCTs), one controlled clinical trial (CCT) and 4 prospective observational studies) for MD rehabilitation programmes for women with BC were evaluated for the "best" evidence to date. There is 'moderate level evidence' (2 RCTS and 2 cohort studies) for the effectiveness of MD ambulatory rehabilitation in reducing disability, improving participation and quality of life in women with BC in the later stages, compared with lesser intensity rehabilitation intervention for up to 12 months. Further, one CCT and two observational studies demonstrated 'low level evidence' for inpatient MD rehabilitation for improved participation (up to 12 months); and 'very low level evidence' for longer term reduction in disability (6-12 months).

Conclusion: This review found 'moderate' quality evidence for ambulatory (outpatient) and 'low' quality evidence for inpatient MD rehabilitation in women with BC. The gaps in existing research should not be interpreted as ineffectiveness of MD rehabilitation in this population. Further research is needed with appropriate study designs, outcome measurement, and type of modalities and cost-effectiveness of these interventions.

Keywords: Breast cancer; Rehabilitation; Disability; Participation; Outcome

Introduction

Breast cancer (BC) is the most common malignancy in women and leading cause of morbidity and mortality, affecting approximately 1.38 million new cases (23% of all cancers) worldwide [1]. It is the main cause of cancer-related death amongst women with 458,000 deaths worldwide and over 2500 deaths in Australia annually [1,2]. The incidence of BC is on rise [3], with almost 11000 new cases each year in Australia [2]. It is estimated that by 2015, one in 9 Australian women will be affected from BC [2]. With early detection and therapeutic advances in BC management, mortality rates have declined significantly and majority of women after BC treatment now make good functional recovery [4]. However, patients still have to deal with severe short or long-term treatment side effects/complications and psychological distress related to the disease and treatment (such as pain, decreased shoulder range of movement (ROM), lymphoedema, fatigue, menopause, weight gain, seroma formation, neuropathy, mood disorder etc.) [5,6]. A range of neuropsychological sequelae can occur (such as anxiety, depression, fear of recurrence, sexual dysfunction, body dysmorphism etc.) and as disease progresses various other concerns arise (such as bone metastases, tumour infiltration causing plexopathy etc.) [7,8]. Further, various adjustment issues may surface in the transitional period in the community, such as the increased care needs, inability to drive and return to work, financial constraints, marital stress, limitation in societal participation, perceptions of self worth, self image and role reversal within the family. These long-term physical and psychological morbidity associated with BC treatment can be underestimated [9].

The World Health Organisation (WHO) promotes BC management control within national cancer control programmes integrating: prevention, early detection, diagnosis, treatment, rehabilitation and palliative care [3,10]. Acute treatment options may include; surgery, radiotherapy, chemotherapy and/or hormonal therapy [11]. Rehabilitation is integral part of BC management and is involves in all time periods, that is, early postoperative period, whilst going through all adjuvant therapies, late phases of care and long-term care continuum in the community [12]. It includes use of different interventions and involvement of various disciplines and maximizes patient function, promotes independence and adaptation, and improves patients quality of life (QoL) [13].

Multidisciplinary (MD) rehabilitation is a coordinated delivery of intervention by two or more disciplines with input from medical specialist [14]. It is designed to be patient-centred, time-based, functionally-oriented and aims to maximise activity and participation

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(social integration) using a biopsychosocial model within the structured framework outlined by the WHO International Classification of Functioning, Disability and Health (ICF) [15].

A number of systematic reviews have been conducted to support rehabilitation input for women with BC. These include mainly uni-disciplinary interventions: exercise therapy [6,16]; and physical therapy in managing lymphoedema [17]; psychological interventions (psychotherapy, cognitive behaviour training) [18]. Other reports have discussed the role of rehabilitation in cancer generally [7,19]. One systematic review of MD care for BC patients [14] reported 'weak evidence' for inpatient MD rehabilitation in producing short-term gains at the levels of impairment (shoulder range of movement), psychosocial adjustment and QoL after BC treatment. There was no evidence available on long-term functional gains at the levels of impairment, psychosocial adjustment and QoL. This review included only one randomized and one controlled clinical trial (RCT, CCT) of 'poor methodological quality'. There are several major challenges in conducting a RCT in a rehabilitation setting, including in the BC cohort : such as blinding, attrition (especially control group), heterogeneous patient characteristics, multilayered treatments, interdependent components, individual interventions and ethical considerations [20]. These factors tend to confound traditional RCT designs [21] and it is increasingly recognized that RCT/CCT cannot be applied in certain circumstances to address all the research questions that need to be answered [22]. Other methods have been developed for assimilating published literature to include a broader range of 'evidence', which encompass qualitative studies and different evaluation techniques [21]. Therefore, the aim of this systematic review is to assess the effectiveness of MD rehabilitation in persons after BC treatment by including both qualitative (observational studies) and quantitative studies (RCTs, CCTs) to provide the broader picture of currently available 'evidence' in addition to controlled experimental data.

Methods

An integrated approach was employed, which included a comprehensive review of literature (peer review and grey literature) documenting interventions currently used in BC rehabilitation. A search of the literature was conducted using medical and health science electronic databases: Medline, Embase, AMED, CINHAL, PsycINFO, Cochrane Library databases. The literature search identified MD interventions used in BC rehabilitation clinical studies. Bibliographies of identified articles and manual search of relevant journals for additional references was conducted. Authors and known experts in the field were contacted. Grey literature search was conducted using different internet search engines and websites: such as System for Information on Grey Literature in Europe; New York Academy of Medicine Grey Literature Collection, National Quality Measures Clearinghouse and Google Scholar. In addition, various healthcare institutions; and governmental and non-governmental organisations associated with management of individuals with BC were also explored for relevant studies.

The same principle was used to search each database, which included all terms and phrases describing BC (breast cancer (neoplasm/tumor/tumour), mastectomy, axillary dissection, sentinel node dissection, adhesive capsulitis, cording, axillary web syndrome); rehabilitation (rehabilitation, ambulatory care, hospitalization, home care services, hospital-based, inpatients, outpatients, multidisciplinary, interdisciplinary, integrated, multimodal, physical therapy (physiotherapy), exercise(s), stretching, mobilization, physical activity (exertion), cognitive or psychological therapy, behaviour therapy, occupational therapy, social work, dietetics, dietary services, counselling) and outcomes (ROM, strength, lymphoedema, pain, QoL, psychosocial, activities), which was combined using the Boolean "OR". These terms then were grouped with the Boolean operator "AND" and the final search of the articles was performed from the displayed results. Medical subject heading (MeSH) search terms was used for all databases and a keyword search was used if the MeSH term was not available (Details available from authors). Publication bias was minimized by sourcing unpublished data where possible [23].

Inclusion and exclusion criteria

MD rehabilitation interventions and programmes have no definite classification, and can be broadly described in terms of settings and content [24]. For this review, MD rehabilitation was defined as '*any* intervention delivered by two or more disciplines (e.g. nursing, physiotherapy (PT), occupational therapy (OT), dietetics/nutrition, social work (SW), psychology or neuropsychology) referred by a medical specialist (surgeon, oncologist, rehabilitation physician)' [14]. All studies that assessed the effectiveness of organised MD rehabilitation (fulfilled the above definition) for women with BC with either routinely available local services or lower levels of intervention (such as medical or nursing care only), in different settings (inpatient, ambulatory/outpatient or home-based settings) or at different levels of intensity, irrespective of study designs were included. Study exclusion criteria included: studies that assessed the effect of therapy from a single discipline (for example, physiotherapy only) or any uni-disciplinary intervention or modality (for example, physical exercise, gym, stretching programme); non-English studies, theses, narrative reviews, editorials, case reports, economic evaluation, conference proceedings, studies conducted in paediatric population (<18 years) and studies with sample size of less than 10 patients. Studies that involved participants with other types of cancers or other diagnoses where data were specifically provided for women with BC were also included.

Study selection and data extraction

Both reviewers (FK, BA) independently screened all abstracts and titles of studies identified by the search strategy for inclusion and appropriateness based on the selection criteria. Once all potentially appropriate studies were obtained, each study was independently evaluated for inclusion. Any differences regarding study inclusion were resolved by discussion and consensus agreement. Data were extracted from studies that met the eligibility criteria using a standard performa, which included: study characteristics (publication date and country, study type, sample characteristics, outcome measures, follow-up period) and intervention characteristics (type, intensity, domains, settings and duration). Further information about the complete description of MD rehabilitation from the trial lists was obtained, where necessary. Any discrepancies were resolved by re-reviewing the study by both authors.

Both authors (FK, BA) critically appraised all included trials independently, based on Grades of Recommendation, Assessment, Development and Evaluation (GRADE) methodological quality from the domains: sequence generation, allocation concealment, blinding of participants, therapists and outcome assessors, incomplete outcome data and selective outcome reporting [25]. A '*yes*' indicates a low risk of bias, while '*no*' a high risk of bias, and '*unclear*' an unclear or unknown risk of bias. Studies were considered to be of 'high methodological quality' if the risk of bias for all domains was low. Studies were rated as 'low methodological quality' if there was unclear or high risk of bias for one or more domains [25]. All outcomes were categorised according

to the ICF [15] into those that focus on: *impairment* (e.g., muscle strength, pain); *limitation in activity* (e.g., self care, mobility) and *restriction in participation* (e.g., psychosocial function, relationships, social integration, QoL).

Results

The electronic database searches retrieved 879 published titles and abstracts. After removal of duplicates overall 801 tiles and abstracts were screened. Forty-four articles met the abstract inclusion criteria and were selected for closer scrutiny. Full texts of these articles were retrieved and both reviewers performed the final selection. One article that met the inclusion criteria were identified from the bibliographies of relevant articles. Of these 7 studies (2 RCTs, 1 CCT and 4 cohort studies) examining different rehabilitation interventions fulfilled the inclusion criteria for this review. All relevant studies were critiqued qualitatively using GRADE approach [25] to evaluate the quality of evidence. The study selection process is summarised in the PRISMA flow diagram shown in Figure 1.

The characteristics of the 7 included studies are summarised in Table 1. The included studies were conducted in various countries: two in Australia [20,26], and one each in Germany [27], South Korea [28], Sweden [29], Austria [30] and Brazil [31]. The participants of studies in this review included 956 women (846 completers) with BC. These women had confirmed diagnosis of BC and had undergone surgical procedures followed by chemotherapy or radiotherapy or both. The details of the surgical procedure and adjuvant treatments

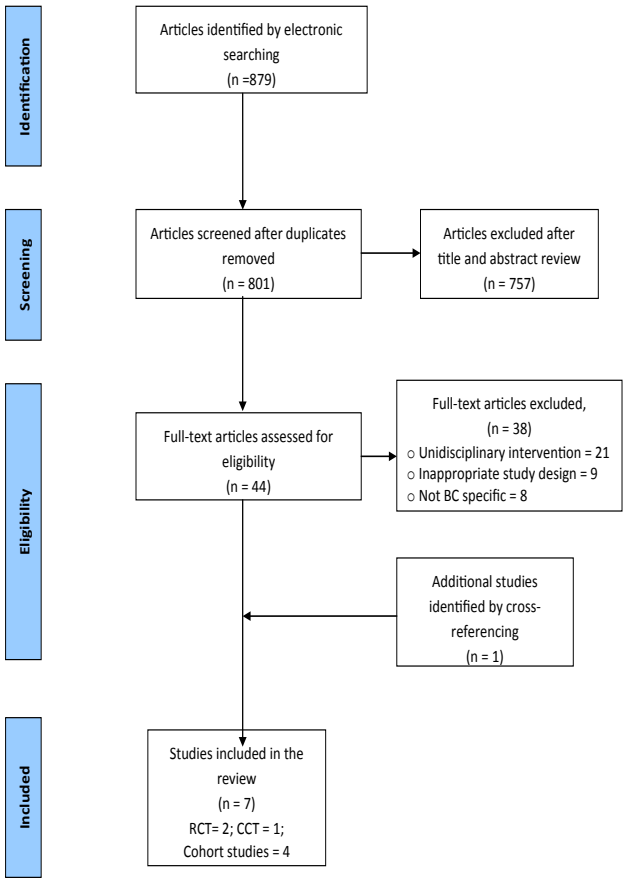

Figure 1: PRISMA flow diagram showing selection of article review.

were not provided in most of the studies. All studies included women older than 18 years. Majority of the studies recruited participants at sub-acute stage at least 12 months after completion of their definitive BC treatment [20,27,28,30], while one study recruited participants at diagnosis stage [29], and one at acute stage (at time of surgery) [31].

Multidisciplinary rehabilitation intervention characteristics

The MD rehabilitation programme used in the included studies varied: 3 studies evaluated inpatient MD programmes [27,30,31], while 4 studies evaluated outpatient MD programmes [20,26,28,29]. All MD programmes comprised physical activity and psycho-educational components. The control groups also varied amongst the studies, and included patients in wait-list, with no treatment or usual care only and different clinical subgroups. The follow-up periods ranged from 10 weeks [28] to 12 months post intervention [26,27,29] (Table 1).

Risk of bias in included studies: The methodological quality assessment details of the included studies are provided in Table 2. The methodological quality of the included trials varied and in general, most appeared to be of 'moderate' to 'poor' quality. Most studies were under powered with small convenience sample of women with BC, limited to single facility. Only one RCT [20] was of 'moderate' quality, with few methodological issues, which included: participant blinding and attrition (especially control group). All other trials had substantial flaws in their methodological design with a high risk of bias related to their group allocation procedure, blinding of patients, therapists and outcome assessors, heterogeneous patient characteristics, multilayered treatments, reporting of co-interventions and outcome analysis. The randomisation procedure was unclear in Hartman et al. [27]; the study was redefined midway as a prospective exploratory feasibility study due to 'missing knowledge', though was initially designed as a RCT. Outcome measurements used also varied amongst included studies and in some studies [20,28] measures used were not validated in the BC population. Pooling of data from these studies was confounded by above mentioned reasons and all included studies were critiqued qualitatively rather than attempting a meta-analysis.

Effectiveness of outpatient multidisciplinary rehabilitation: The four studies (2 RCTs and 2 prospective studies) addressing the efficacy of outpatient MD rehabilitation [20,26,28,29] recruited a total of 521 patients (482 completers). Khan et al. in a RCT [20] evaluated the effectiveness of comprehensive individualized ambulatory MD rehabilitation programme (3 one-hour sessions of interrupted therapy/ week, for 8 weeks), which included: PT for strengthening and shoulder ROM, lymphoedema care, OT for energy conservation and task re-acquisition strategies to improve everyday function (domestic, community tasks), driving and return to work; and clinical psychology for counselling, coping and supportive strategies. Another RCT with a wait-list control group [28] reported effectiveness of an MD intervention including a group-based programme at a tertiary care centre (3 episodes per week for 10 weeks), together with a home-based exercise programme. The intervention included: psychology based education, exercise, peer support group activity, medical, dietician and image consultant input, and a fitness instructor [28]. A prospective study [26] assessed the effectiveness of two outpatient low-technology, rehabilitation programmes with common and key goal of restoration of upper-body strength and flexibility, with additional general support programmes. Another prospective study [29] examined the effects of outpatient MD educational programme led by a specialist nurse, with PT, SW, a physician and BC patients' advocacy group member.

Impairment: Changes at the level of impairment were reported in only one study [28]. The authors found increased ROM of the affected

Study, Year, Country	Study design	Participants	Intervention	Outcomes	Assessment time points	Results	Author's conclusion
Khan et al., 2012 Australia	RCT	N = 85. treatment group = 43 and control = 42 (loss to follow-up 6) *Inclusion criteria*: aged >18 years; confirm BC diagnosis, currently disease free and assessed by a surgeon/oncologist *Exclusion*: survival less than 4 months, severe disease and unable to participate in the programme.	*Treatment group* – ambulatory individualized high intensity MD programme (Social, Psychology, OT, PT and medicine) 3 one-hour sessions of interrupted therapy/ week, for 8 weeks *Control group* – usual activity at home (local gym, yoga, community activities) and received fortnightly phone calls	DASS, PIPP, CARES-SF, FIM	Pre-intervention (baseline) and 4 months post intervention	• Significant difference between both groups in improved at 4 months for DASS Depression scores (p=0.006) (moderate effect size, r>0.3), PIPP Mobility (p=0.05) and Participation (p=0.04) scales, and CARES-SF Global score (p=0.02) (small effect size, r< 0.3). • Treatment group, compared with control group, showed significant improvement in the DASS Depression scores: 22/42 (52.4%) versus 12/37 (32.4%) (p=0.02). • No difference between groups was noted in the FIM scale.	Rehabilitation can benefit participation in BC survivors. Evidence for specific rehabilitation interventions is needed. Integrated cancer programmes allow opportunities to evaluate patients in various settings, but require outcome research to develop service models for survivorship issues.
Cho et al., 2006 South Korea	RCT	N = 65. treatment group = 34 and control = 31 *Inclusion criteria*: histologically confirmed stages of BC, no current progressive disease; within 2 years after the mastectomy; completion of chemotherapy and/ or radiotherapy with or without current hormone therapy *Exclusion:* any mental disease or systemic disease	*Treatment group* - ambulatory MD rehabilitation programme (psychology based education, exercise, peer- support group activity, medical input, dietician, image consultant, fitness instructor) for 3 episodes/sessions per week for 10 weeks *Control group* – wait-list no treatment (offered treatment post study)	ROM shoulder, Psychological Adjustment Scale, and a local quality-of life measure	Pre-intervention (baseline) and 10 weeks post intervention	At 10 weeks follow-up: • Affected shoulder joint ROM significantly increased in the intervention group (11.5 % vs. 1.3%, p=0.000). • Significant increase in the flexion in both intervention and control group. • Compared to the control group, there was significant differences in extension, abduction, external rotation, and internal rotation after the test in the intervention group (p=0.000, p=0.011, p=0.006, p=0.000, respectively). • Psychosocial adjustment in the intervention group increased by 2.9 points while it decreased in the control group by 3.0 points (p=0.000). • QoL in the intervention group increased by 0.9 points while it decreased in the control group by 0.1 points (p=0.002).	A comprehensive group rehabilitation programme, comprised of psychology-based education, exercise and peer support group activity promote the recovery of the affected shoulder joint ROM, alleviate physical symptoms, and improve psychological adjustment and the QoL for early breast cancer patients.
Hartman et al., 2007 Germany	CCT	N = 197; Treatment group = 98, control group = 99 *Inclusion:* Histologically confirmed BC <5 yrs; age 25 – 75; speaks sufficient German. *Exclusion:* Psychiatric disease; life expectancy <1 year; history of another cancer within last 5 years; inpatient treatment or breast recondition during study; lack of compliance.	*Treatment group* - 3 week step-by-step inpatient and outpatient MD rehabilitation programme (physician input, psychology, physiotherapy), plus at 4 & 8 months later – a one week rehabilitation programme each time *Control group* - only one 4 week step-by-step inpatient and outpatient MD rehabilitation programme	EORTC-QLQ-C30	Pre-intervention (baseline), end of 3 or 4 week programme, 12 months	• Compared with the control group, the treatment group showed a improvement in gQoL, emotional function and cognitive function after 4 weeks, however, this was not statistically significant (gQoL 16 vs 12.6 p = 0.098, EF 30.7 vs. 23.7 p = 0.066, CF 11 vs. 4.5 p = 0.13). • Mean changes of physical function were similar in both groups (4.5 vs. 4.2, p=0.7) • At 12-month follow up intervention group improved their cognitive function by 2.3 whereas it decreased in control group by -5.5 this difference between groups became significant (p=0.0098) • Changes of other dimensions of QoL showed no difference	Step by Step rehabilitation programme was shown to be superior to the conventional rehabilitation programme with regard to the QoL.

Gordon et al., 2005 Australia	Prospective cohort study	n=275 Intervention = 67 (group 1 = 36, group 2 = 31), control = 208 *Inclusion:* confirm diagnosis with primary BC, with unilateral disease, able to speak English, with no cognitive problems; aged 25–74 years. *Exclusion*: very ill, if previously attended one of the two interventions	*Treatment groups*: two outpatient low-technology, rehabilitation programmes with common and key goal of restoration of upper-body strength and flexibility and general support– early home-based physiotherapy intervention (Domiciliary Allied Health and Acute Care Rehabilitation Team 'DAART') or a group-based exercise and psychosocial intervention (Strength Through Recreation Exercise Togetherness Care Health 'STRETCH') programmes *Control*: women with BC from another project, with no intervention.	FACT-B, DASH	Pre-intervention (baseline), post-intervention, 6- and 12-months from the date of diagnosis	• Comparing pre/post-intervention measures, benefits were evident for functional well-being, including reductions in arm morbidity and upper-body disability for participants completing the DAART service at 1-2 months. In contrast, minimal changes were for the STRETCH group at approximately 4-months post-diagnosis. • Overall, mean HRQoL scores improved across all groups from 6- to 12-months and no differences were found, however, this obscured declining HRQoL scores for 20–40% of women at 12 months post-diagnosis, despite receiving supportive care services. • Social and emotional well-being scores showed no statistical significant differences over time 6–12 months post-diagnosis ($p = 0.88$ and $p = 0.41$, respectively). • Sub-group analyses of proportions of women with declined, unchanged or improved HRQoL scores; at 12-months post-diagnosis, participants in the unchanged group had high scores, which were very similar to scores of participants in the improved group and substantially higher than those participants in the declined group; all were statistically significantly different ($p < 0.05$), except for DAART women for FACT-G, FACT-B & DASH scores	Professionally led group exercise therapy with psychosocial care appears to have a neutral effect on upper-body recovery and improving HRQoL. However, it provides advantages for attendees in the form of peer-support, education, a holistic focus and the potential for addressing previously unrecognised psychological problems in a caring and acceptable environment.
Koinberg et al., 2006 Sweden	Prospective cohort study	N = 96 Intervention = 50, control = 46 (1 loss to follow-up) *Inclusion*: BC classified as stage I or II, ability to speak Swedish and psychologically capable of participating *Exclusion:* not provided	*Treatment group:* outpatient MD educational programme led by a specialist nurse, with PT, SW, a physician and BC patients' advocacy group member, 4 sessions for 4 weeks, 2 – 6 months post surgery *Control:* traditional follow-up to a physician programme (2 times a year)	FACT-G, SCA, SOC	At diagnosis (1 month following surgery-pre-intervention) and 12-months	• The women in the MD educational programme increased their physical and functional well-being (P<0:01). • No differences either between groups or within groups with regard to coping ability, participation in decision-making and knowledge about the disease at baseline or the 1-year follow-up • The women in traditional follow-up by a physician increased their functional well-being while social/ family well-being (P<0:01) decreased over time. • Women in the traditional follow-up by a physician scored statistically significant lower in the area of sense of coherence in 1 year (mean = 74.4, SD = 12.4 and mean = 67.7, SD = 11.4, for baseline and 1-year follow up, respectively; P<0:001).	A MD educational programme may be an alternative to traditional follow-up by a physician after breast cancer surgery, but more research is needed about the financial benefits and effectiveness of such a programme.

Strauss-Blasche et al., 2005 Austria	Pre-post design	N = 149 (33 patients drop out) *Inclusion*: all patients who had had BC surgery within the last 72 months *Exclusion*: not specified.	*Treatment group:* inpatient MD rehabilitation programme incorporating manual lymph drainage, exercise therapy, massage, psychological counselling, relaxation training, balenotherapy (carbon dioxide baths, and mud packs) *Control:* for Mud packs therapy only N= 25, No mud packs N = 50 (matched control)	EORTC QLQC30, HADS, serological marker CA 15-3, GICQ	Pre-intervention (2 weeks before), at the end of the programme (3 weeks), and 6 months post programme	• QoL, including function, physical complaints, and mental wellbeing, improved significantly from 2-weeks before rehabilitation to the end of rehabilitation (mean ES =0.49). The greatest short-term improvements found for mood-related aspects of QoL. • Mean ES for to 6 months follow-up=0.31, the largest sustained improvement found for social functioning, pain and fatigue, followed by emotional functioning and depression. • Older patients, non-obese patients, patients with a greater lymphoedema and patients with an active coping style showed slightly greater improvements. • The tumour marker CA 15-3 declined significantly to follow-up in those receiving mud packs.	Inpatient rehabilitation, in combination with spa therapy, can be seen as a promising measure for improving QoL in BC patients.
Pinto e Silva et al., 2008 Brazil	Prospective cohort study	N = 89 (9 patients drop out) Intervention groups = 61: 2 groups (sentinel node biopsy (SNB) = 30; complete axillary lymph node dissection (ALND) = 31. Control group = 28 randomly allocated from SNB group. *Inclusion*: women treated for stages I and early II BC, undergoing quadrantectomy or simple mastectomy without distant metastases and prior malignancy *Exclusion*: not specified.	*Treatment group:* inpatient postoperative MD rehabilitation programme provided by PT, SW, nurses & psychologists. *Control:* (only the SNB group) clinical follow-up	FACT-G, FACT-B, TOI, EWB, BCS	Pre-intervention (baseline), at the end of the programme 30 days postoperative, and 6 months	• Women undergoing ALND had a better QoL within 30 days of surgery on the FACT-B (P = .0117), FACT-G (P = .0425), TOI (P = .0104), EWB (P = .0003), and BCS (P = .001). • Improvement remained significant 6 months after surgery only on the EWB subscale (P = .0204). • Women undergoing SNB had a better QoL only on the EWB subscale, which was significant 6 months after surgery in the group with rehabilitation (p = .03) and 30 days after surgery in the group without rehabilitation (p = .04) • Chemotherapy did not interfere with QoL in all groups. • Comparing the mean FACT-B and its diverse subscales among the different groups at the three time periods evaluated, there was no difference in QoL among the groups at any time period studied. • EWB subscale improved significantly (P = .0041) for all groups with time.	Women undergoing ALND benefited from a rehabilitation programme and had a better QoL. Women undergoing SNB, regardless of rehabilitation, showed improvement in QoL for the emotional well-being subscale only.

BC = breast cancer, BCS = Breast Concern Subscale, CARES-SF = Cancer Rehabilitation and Evaluation System - short form, DASH = Disabilities of the Arm, Shoulder and Hand, DASS = Depression, Anxiety and Stress Scale, EORTC QLQC30 = European Organisation for Research and Treatment of Cancer (EORTC) for QoL Questionaries, EWB = emotional well-being, FACT-B = Functional Assessment of Cancer Therapy – Breast Cancer, FACT-G = Functional Assessment of Cancer Therapy-General, GICQ = German illness coping questionnaire, HADS = Hospital Anxiety and Depression Scale, N = total number, OT = Occupational therapists, PT = physiotherapist, PIPP = Perceived Impact of Problem Profile; QoL= quality of life, , SCA = Self-Care Aspects questionnaire, SOC = Sense of Coherence scale, , SW = social worker, TOI = Trial Outcome Index, ROM = Range of motion

Table 1: Summary of included studies.

shoulder joint in the intervention group (11.5 ± 7.8%) compared with the control group (1.3 ± 4.8%; p=0.000). The differences in improvement in shoulder extension, abduction, external rotation, and internal rotation after the intervention were significant in the intervention group compared with the controls (p<0.01 for all) [28]. Although shoulder flexion significantly improved in both groups, there was no statistical difference between groups (p=0.667).

Activity: Khan et al. [20] measured disability by change in FIM-motor scale and subscale scores at 4 months post intervention, and found no difference between groups (p >0.05 for all). The authors postulated that this may be due to high functioning BC participants in the community (ceiling effect) [20]. Gordon et al. [26] reported

Bias	Khan et al. 2012	Cho et al. 2006	Hartmann et al 2007	Gordon et al. 2007	Koinberg et al. 2006	Strauss-Blasche et al. 2005	Pinto e Silva et al. 2008
Random sequence generation (selection bias)	-	+	?	+	+	+	?
Allocation concealment (selection bias)	-	+	?	+	+	+	+
Blinding of participants and personnel (performance bias)	+	+	+	+	+	+	+
Blinding of outcome assessments (detection bias)	-	+	+	+	+	+	+
Incomplete outcome data (attrition bias)	-	+	+	+	+	-	+
Selective reporting (reporting bias)	-	-	+	+	+	+	+
Other bias	-	+	+	+	+	+	+
Study quality rating	moderate	Very low	Very low	Very low	Very low	Very low	Very low

+ = high risk; - = low risk; ? = unclear risk.
GRADE = Grades of Recommendation, Assessment, Development and Evaluation

Table 2: Levels of quality of individual studies (GRADE* approach[25]).

that benefits from intensive MD ambulatory (Domiciliary Allied Health and Acute Care Rehabilitation Team) service were evident for functional well-being, including reductions in arm morbidity and upper-body disability at 1-2 months. Though, these differences were statistically not significant (p>0.05 for all except for arm morbidity) they were considered as clinically important. In contrast, minimal changes were found in participants completing group therapy provided by the exercise psychologist [26]. Koinberg et al. [29] in another prospective study found that women in the MD programme increased their physical and functional well-being during the 1 year follow-up (p<0:01). Cho et al. [28] did not report changes at the level of disability.

Participation: Khan et al. [20] reported that participants in MD rehabilitation programme showed significant improvement in 'participation' domains and QoL up to 4 months. The treatment group, compared with control group, showed significant improvement in Depression Anxiety Stress Scale (DASS) – 'depression' scores (p=0.006) (moderate effect size (ES), r>0.3); Perceived Impact of Problem Profile (PIPP) - 'mobility' (p=0.05) and 'participation' (p=0.04) scales; and Cancer Rehabilitation and Evaluation System - short form (CARES-SF) 'global' score (QoL) (p=0.02) (small effect size, r<0.3) [20]. Cho et al. ([28] reported significant improvement in participants after the rehabilitation programme: psychosocial adjustment improved in the intervention group by 2.9 ± 6.3 points while it decreased in the control group by 3.0 ± 6.3 points (p=0.000). Similarly, QoL improved in the intervention group while it decreased in the control group (p=0.002). The authors indicated that an alleviation of physical symptoms or impaired function may have contributed to improve QoL in the intervention group [28]. Gordon et al. [26] found improvement in mean HRQoL scores across all participants receiving MD rehabilitation from 6 to 12 months post-diagnosis, however, social and emotional well-being scores showed no statistical significant differences over time. In contrast, Koinberg et al. [29] in another prospective study did not find any beneficial effect of MD educational programme with regard to coping ability, participation in decision-making and knowledge about the disease at baseline or 1-year follow-up.

Effectiveness of inpatient multidisciplinary rehabilitation

Three studies evaluated the effectiveness of inpatient MD rehabilitation programmes. [27,30,31] and recruited a total of 435 subjects (364 completers). Hartmann et al. [27] in a CCT compared 2 types of inpatient MD rehabilitation programme (a 'step-by-step' model and 'single burst' model), to determine whether more prolonged intervention delivered over a period of several months could produce a more sustained improvement in QoL. The "step-by-step' model consisted of an initial 3-week programme incorporating medical input, psychology and PT, followed by two subsequent in-patient breaks of 1 week at 4 and 8 months. The control group received only one episode of the programme (single burst model) [27]. Two other prospective studies assessed different types of inpatient MD rehabilitation programmes. Strauss-Blasche et al. [30] evaluated programme incorporating manual lymph drainage, exercise therapy, massages, psychological counseling, relaxation training, balenotherapy (carbon dioxide baths, and mud packs), while Pinto e Silva et al. [31] assessed structured rehabilitation programme provided by PT, SW, nurses and psychologists. The studies did not provide details of the type of rehabilitation modalities (stretching, gym, task reacquisition, psychoeducation) used, nor the actual duration or intensity of specific interventions.

Impairment: None of the studies reported changes at the level of impairment.

Activity: Hartmann et al. [27] reported no changes (mean) in physical function between the treatment group receiving a structured MD rehabilitation programme and the control group (4.5 versus 4.2, p=0.7). Further, there were no significant differences between groups in physical function, in a sub-group analysis of those with musculoskeletal disease at baseline [27]. Strauss-Blasche et al. [30] and Pinto e Silva et al. [31] did not report any outcome in the level of activity.

Participation (Psychosocial outcomes and QoL): Hartmann et al. [27], reported that inpatient MD rehabilitation programme showed marked benefits for patients with cognitive impairment and QoL. Overall, the treatment group showed improved QoL, emotional and cognitive function after 4 weeks of receiving therapy compared with the control group. However, this was not statistically significant (p >0.05 for all). In a subgroup analysis of patients with impaired cognitive function at baseline, at the 12-month follow-up, the intervention group improved their cognitive function by 2.3 points, whereas it decreased in the control group by -5.5 (p=0.009) [27]. Similar favourable effect of the inpatient MD rehabilitation programme was reported in another study [30]. In this pre-post design study [30], the authors demonstrated that participants' QoL, including function, physical complaints, and mental wellbeing, improved significantly from 2-weeks before rehabilitation to the end of rehabilitation (mean ES =0.49, p<0.001) and this improvement was maintained at the 6-month follow-up (p ranged from <0.05 to <0.001, except for cognitive functioning p >0.05). The short-term improvements were for mood-related aspects of QoL, while sustained improvement was for social functioning, pain and fatigue, followed by emotional functioning and depression (mean ES at 6 months follow-up =0.31) [30]. Another prospective study [31] showed the beneficial effect of inpatient MD rehabilitation programme in early stage BC women undergoing surgery. The authors found that both

patient groups undergoing axillary lymph node dissection (ALND) or sentinel node biopsy (SNB) showed a better QoL within 30 days of surgery, however, patients in ALND group improved significantly in most aspects of QoL ($p<0.05$) and these improvements remained significant 6 months after surgery ($p=0.02$) [31].

Discussion

This systematic review provides an evidence-based overview of the effectiveness of MD rehabilitation in women with BC. It highlights the lack of robust, methodologically strong studies evaluating the effectiveness of MD rehabilitation intervention in this population. Consistent with another review in this area [14], most studies were of 'poor quality' due to multiple methodological flaws (such as unclear/lack of randomization procedure, concealed allocation and blinding procedures). Of the seven studies included only one was of 'moderate' quality. The MD programme evaluated in the included studies varied and included psychology-based education, PT, OT, peer support group activity, dietician, image consultant input; and a fitness instructor.

The findings from this review suggest that there is a '*moderate evidence*' for ambulatory MD rehabilitation in producing short-term gains at the levels of participation, psychosocial adjustment and QoL after BC treatment. There was no evidence available on functional gains at the level of activity and impairment. There is '*weak evidence*' for inpatient MD rehabilitation followed by ambulatory care in improving in terms of impairment, activity, psychosocial adjustment, and participation for short-term (up to 12 months). There was 'no evidence' for the longer term or cost-effectiveness of these programmes, nor best 'dose' of therapy (frequency and duration) or supremacy of one therapy over another.

Rehabilitation approach for BC patients should include a wide spectrum of treatment and use of different interventions. It should provide a flexible service that caters to the changing needs of these individuals [14], optimize standard medical treatments (surgery, radiotherapy, chemotherapy), reduce complications and manage pain, promote exercise and psychosocial adjustment for participation. Improving or restoring physical and psychosocial abilities is a key issue in rehabilitation of BC patients, as they can be affected from a combination of motor (weakness), lymhoedema, sensory (pain), fatigue, and psychological impairments. However, 'best' evidence to date in literature is largely for uni-disciplinary rehabilitation interventions such as physical therapeutic modalities [16, 32-34], psychological interventions [18,35]. Many of these interventions have not yet carried into comprehensive MD rehabilitation programmes, and few studies show its implementation.

Rehabilitation is a complex intervention, defined as 'complex' where the active ingredient in the intervention is not easily identifiable [36]. There are many challenges in evaluating rehabilitation interventions in BC. Women following BC treatment can present with diverse clinical presentations with varying levels of disability requiring an individualized approach. The perspectives of patients (and/or caregivers), is often neglected and needs to be incorporated in rehabilitation programmes to facilitate communication and agreement amongst treating clinicians with respect to clinical approach [14]. The outcome measures used in the BC population need to reflect its complex constructs and focus on impairments, activity and restriction in participation, as advocated by WHO ICF [15]. Generic measures used in BC (and other cancer populations) in general rehabilitation settings (e.g. the Functional Independence Measure) may not be sufficiently sensitive to capture the relevant gains following intervention, and have floor/ceiling effects. In particular QoL is difficult to measure given the many factors can influence it. The BC specific measures can be comprehensive and varied [37-39]. For example the Cancer Rehabilitation Evaluation System Short Form (CARES-SF) [39] provides information about day to day problems and rehabilitation needs of these persons. With improved mortality following BC treatment more research is needed to gain consensus on a suitable battery of measures to capture change in physical ability (at the level of impairment and disability), as well as the longer-term outcomes relating to psychosocial adjustment and QoL.

The physical and psychological sequelae are common in this population and may need referral to specialized rehabilitation services. Although patients report satisfaction with treating specialists; the communication between MD treating team is perceived as problematic and greater emphasis on survivorship care plan and information needs is required [40]. Innovations that offer new paradigm shifts in the delivery of timely, cost-effective, patient-centred and transparent services are needed. A collaborative integrated long-term approach incorporating surgical/oncological and rehabilitation treating teams can address these and respond to public health priorities and access issues. Participatory limitations due to psychological issues, work, family and social re-integration need particular attention. This requires education and support for women with BC, and their treating MD teams.

This review included studies, with different research designs in the analysis of evidence for effectiveness of MD rehabilitation, rather than including only experimental designs. The evidence synthesis highlights the need for systematic data collection in the course of real life clinical practice, as well as long-term follow-up outcomes, by inclusion of research evidence beyond the restrictive experimental trials (RCTs or CCTs). Various authors have argued that though RCTs are appropriate to study effects of an intervention and considered 'gold standard' for high level evidence, they might be less appropriate in studying 'complex' interventions such as rehabilitation due to various issues, such as ethical consideration (withholding and/or delaying interventions or providing placebo); heterogeneous populations, interdependent components and contexts; and multifaceted, multilayered treatments [21,24,41,42].

Several limitations in the methodology and the completeness of the retrieved literature in this review cannot be ruled out. Despite the extended range of terms that were used to capture the widest possible selection of the relevant literature, the search strategy principally encompassed the cited literature. Further, search strategy included searching of reference lists only within the relevant papers for other possible articles missed in electronic searches, which may have introduce the reference bias and have missed some relevant articles, included negative and unpublished trials. Finally, though the GRADE approach used to appraise the studies is robust system for evaluating experimental trail-based evidence, its sensitivity for evaluating observational studies is still debatable [21]. As per the GRADE definition, most of these studies are likely to be rated as high risk (due to lack of sequence generation, allocation concealment and blinding). However, it is argued that, although the starting point for this type of research is at low-level evidence, the evidence can be upgraded if the findings are consistent and strong [21].

In conclusion, there is increasing awareness of MD rehabilitation in early and long-term management of women with BC. Although this review highlights the lack of 'high' quality studies evaluating effective MD rehabilitation in BC survivors (types of rehabilitation settings, components, modalities and duration of therapy; effective care pathways and the long-term functional outcomes (including societal reintegration); it adds to the existing evidence by providing

'moderate to low' quality evidence to support MD rehabilitation in this population. MD rehabilitation programmes (particularly in ambulatory settings) have shown to be beneficial in improving different aspects of activities, participation and QoL. Findings from existing studies are inconclusive and adequate descriptions of the content of MD rehabilitation were often lacking. Difficulties in assimilation of data are further compounded by the diversity of contents of MD programmes and outcome measures used. These conclusions are tentative, and while evidence for effectiveness of MD rehabilitation is limited, the gap in current research should not be interpreted as ineffectiveness of MD rehabilitation in women with BC. Rigorous research is needed for future research into appropriate outcome measures, optimal intensity, frequency and cost-effectiveness of MD rehabilitation therapy over a longer time period.

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