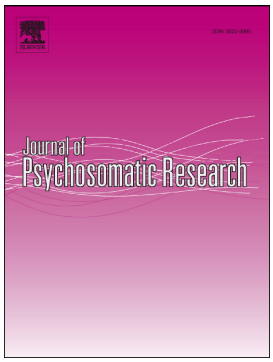

A systematic review of the quality of randomized controlled trials of psychological treatments for emotional distress in breast cancer

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PII: S0022-3999(17)31125-X
DOI: doi:10.1016/j.jpsychores.2018.02.013
Reference: PSR 9491

To appear in: *Journal of Psychosomatic Research*

Received date: 8 November 2017
Revised date: 31 January 2018
Accepted date: 23 February 2018

Please cite this article as: James Temple, Peter Salmon, Catrin Tudur-Smith, Christopher D. Huntley, Peter L. Fisher , A systematic review of the quality of randomized controlled trials of psychological treatments for emotional distress in breast cancer. The address for the corresponding author was captured as affiliation for all authors. Please check if appropriate. Psr(2017), doi:10.1016/j.jpsychores.2018.02.013

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Running head: Quality of psychological treatment trials in breast cancer

Acknowledgments of research support for the study: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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ABSTRACT

Objective

Meta-analyses of trials of psychological treatments for emotional distress in breast cancer (BCa) conclude that efficacious treatments exist. Subsequently, their implementation in routine care is widely promoted by health policy. However, the methodological quality of these trials has not been systematically evaluated. The present review investigates this issue.

Method

A systematic search identified randomised controlled trials of psychological treatments for emotional distress in BCa. The Psychotherapy Outcome Study Methodology Rating Form was used to assess the quality of trials. Generic design elements, including representativeness of sample, control of concomitant treatments, reporting clinical significance outcomes, and design elements specific to psychotherapy trials, including manualisation, therapist training, and therapist adherence and competence were evaluated.

Results

91 trials were eligible. Overall, methodological quality was low. Generic design elements were limited in most trials: 15% specified as an inclusion criterion that participants were distressed; 10% controlled for concomitant treatments; and 11% reported the clinical significance of findings. Design elements specific to psychotherapy trials were also implemented poorly: 51% used treatment manuals; 8% used certified trained therapists; and monitoring of adherence and competence occurred in 15% and 4%, respectively.

Conclusion

to be adequately empirically informed, trials of greater methodological rigour are essential. Trials should include participants with clinical levels of distress, control for concomitant treatments and report the clinical significance of findings. Trialists must also consider the specific requirements of psychotherapy trials.

Keywords: Breast Cancer; Emotional Distress; Methodological Quality; Psychological Treatments; Randomised Controlled Trials

Improvement in detection methods and advances in treatment have increased survival in breast cancer (BCa), with an estimated 3.5 million BCa survivors in the United States[1]. Around half of all newly diagnosed BCa patients report clinical levels of anxiety and/or depression based on either diagnostic criteria or cut-off points reflecting caseness on self-report or clinician administered questionnaires[2-4]. For most, distress naturally diminishes over time. However, some patients continue to experience distress. According to DSM III-R criteria[5], around 25% of patients experience clinical levels of anxiety and/or depression in each of the second, third, and fourth years, and 15% in the fifth year after diagnosis[3]. Emotional distress in BCa reduces quality of life, limits daily functioning, increases economic burden on health care systems, and decreases adjuvant treatment compliance[6-9].

Many randomised controlled trials (RCTs) have therefore examined the efficacy of psychological treatments for emotional distress in BCa across the disease trajectory (i.e. shortly after diagnosis, during treatment, and survivorship). Two Cochrane reviews and several additional meta-analyses of RCTs evaluating the efficacy of psychological treatments compared to controls produce small to modest effect sizes, with most concluding that efficacious treatments exist[10-17]. Health care policies in the United States, England, and Canada have therefore specified that psychological treatments should be available to BCa patients as part of their routine care. However, the methodological quality of RCTs for BCa patients experiencing emotional distress have yet to be comprehensively evaluated. In the present review, this limitation is addressed.

It is widely recognised that poor quality trials often overestimate treatment effects[18-23]. For example, meta-analysis report larger effect sizes in RCTs that do not use intention to treat analyses[21, 23-25], adequate randomization[21, 24], and blind outcome assessors[21, 26].Whilst many meta-analyses highlight that poor quality RCTs overestimate treatment effects, an additional concern is that poor quality undermines the confidence in the conclusions that can be drawn from RCTs[27-29]. For example, if concomitant treatments are not controlled for, it is difficult to determine the

psychometrically valid outcome measures are not used, researchers cannot be confident that intended outcomes were measured.

It is therefore crucial that the quality of trials of psychological treatments is known if policymakers and clinicians are to make informed decisions about the implementation of, and referral to, psychological treatments in clinical services. Assessing the methodological quality of RCTs has been fundamental to advancing the scientific credibility and reporting standards of psychotherapy outcome trials in mental health settings[21, 27-29]. For example, it appears that as the quality of psychotherapy trials for depression have improved, the magnitude of treatment effects have diminished[23, 30].

In BCa, there have been two Cochrane reviews that assessed the risk of bias (RoB) of individual trials[10, 11] using the Cochrane RoB tool[31] (random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, complete outcome data, and selective outcome reporting) and both found that, in most trials, the RoB was unknown. In addition, two meta-analyses[13, 14] assessed the risk of bias using the Jadad scale[32] (random sequence generation, blinding of participants and personnel, and complete outcome data). One reported that 87% of trials were of high quality[13] while the other reported that only 29% were of high quality[14]. A further meta-analysis[12] assessed two RoB elements (random sequence generation and complete outcome data) and two other design features (adequacy of sample size and control for patient demoralisation) essential to high quality RCTs and reported that 44% of trials were of high methodological quality. However, all five failed to assess many other generic design features that are equally essential to high quality RCTs (including clarity of sample description, representativeness of the sample, specificity of outcome measures, reliability and validity of outcome measures, nature of control conditions, length of follow-up, control of concomitant treatments, statistical methods, and reporting of clinical significance). Available meta-analyses therefore provide only a partial assessment of trial quality in BCa.

from RCTs that inadequately specify the nature of the intervention being evaluated are of limited value and also negate replication[33]. Therefore, treatment manuals are crucial to standardising psychological treatment and to discriminating between alternative treatments. Furthermore, to be confident that treatment was carried out as designed, it should be delivered by certified therapists trained in the treatment being investigated[34, 35], and treatment must be monitored for therapist adherence (faithfulness to the prescribed treatment) and competence (skilfulness with which the treatment is delivered)[36, 37]. Ideally, treatment should be delivered by more than one therapist and therapists should be included as a random design factor in analysis to avoid confounding between therapist and treatment[28]. Lastly, the conclusions that can be drawn from a psychotherapy trial depend on whether the duration and intensity of treatment conditions was matched. Only two meta-analyses in BCa reported on psychotherapy-specific design elements, and in a limited manner[11, 12]: Naaman and colleagues[12] assessed treatment fidelity and manualisation, and Mustafa and colleagues[11] provided information on therapist training.

Available meta-analyses have therefore inadequately assessed the methodological quality of RCTs in BCa. To overcome the limitations of previous assessments of trial quality, we used the Psychotherapy Outcome Study Methodology Rating Form (POMRF), which was explicitly designed to assess both generic design elements and those specific to psychotherapy trials[38]. The POMRF has been used to assess the quality of psychological treatment trials for mental health populations in four reviews. The first examined the quality of cognitive behavioural therapy (CBT) trials for depression in children[39], the second examined the quality of CBT trials for obsessive compulsive disorder in adults[28], and the third examined the quality of acceptance and commitment therapy trials across a range of mental and physical health conditions[40]. The final review, also across a range of mental and physical health conditions, compared the quality of CBT trials to those using third wave CBT approaches and found that the quality of CBT trials were more methodologically rigorous[38].

the overall quality of RCTs of psychological treatments for emotional distress in BCa, considering both generic design elements and those specific to psychotherapy trials; (2) evaluate specific design elements that have previously been inadequately evaluated in meta-analyses or are poorly implemented in clinical trials; (3) assess the quality of RCTs in this population against the benchmark of RCTs in mental health populations; (4) assess whether the quality of RCTs differ depending on the type of treatment being tested; and (5) determine whether methodological quality has improved over time.

METHOD

This review is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[41]. All analyses used SPSS version 22.0.0.1.

Eligibility criteria

Eligibility criteria are detailed according to the PICOS framework[41].

Participants. The participants of the studies included in the present review were exclusively adults aged 18 years or older with a histologically confirmed diagnosis of BCa. Participants across all stages of the BCa disease trajectory (i.e. shortly after diagnosis, during medical treatment, and survivorship) were included.

Interventions. As the term "psychological treatment" is poorly defined in the literature[10], we used a generic definition: treatments using psychological or behavioural techniques not based solely on impersonal media (i.e. written or visual material distributed on-line or by electronic or printed media).

treatments without the use of a control condition were also included.

Outcomes. The primary and/or secondary outcome was emotional distress, defined as anxiety, depression, general mood, or global emotional distress. This definition was chosen to be as inclusive as possible as it matches the inclusion criteria used in previous meta-analyses[10-13, 15].

Studies. Only RCTs published in English in a peer-reviewed journal.

Search strategy

PubMed, PsycINFO, Web of science, Scopus, PsycARTICLE, and AMED were searched from their inception until October 2016 using Medical Subject Headings (MeSH) terms and keywords to identify psychological treatment trials for emotional distress in BCa. Combinations of terms associated with psychological treatments, emotional distress, and BCa were used. An English language filter was also used. The final search strategy used for PubMed, which is available in Appendix Table A1 (see online), was adapted for each electronic database. To ensure a comprehensive search, reference lists and relevant meta-analyses were hand-searched for additional studies.

Study selection

First, titles and abstracts were screened by one reviewer (JT) to remove clearly irrelevant reports. Next, full-text of all potentially relevant papers was retrieved and assessed for inclusion by the same reviewer (JT). Uncertainties were discussed with a second reviewer (PF). When a single trial was published more than once, we evaluated the report that most thoroughly presented the methods and findings. Therefore, each paper represented a unique trial.

Data extraction

extracted from trials included year of publication; country of origin; number of participants randomly assigned to condition; mean age; tumour stage; treatment status; outcome measures; treatment type; treatment format; duration of treatment; number of sessions; and type of control condition. Disagreements were resolved by discussion. The data extraction form is available on request from the first author.

Aim 1: Overall quality of trials

Methodological quality was rated using the POMRF (see online, Appendix Table A2). It consists of 22 items, each scored 0 (poor), 1 (fair), or 2 (good), producing a total score ranging from 0 to 44, with higher scores indicating greater quality. Three items relating to psychiatric diagnoses (items 2, 4, & 8), irrelevant to this review, were disregarded; therefore, in this study, the maximum possible score was 38.

A minimum cut-off score to determine adequate methodological quality on the POMRF has not been established. However, a review[27] which used the Randomized Controlled Trial Psychotherapy Quality Rating Scale (RCT-PQRS)[42] to evaluate the quality of psychodynamic trials provided a suitable benchmark. In that review, a cut off score of at least 50% of the maximum possible score on the RCT-PQRS was used. Thus, in this review a total score of 19 out of 38 was chosen as the criterion for minimum adequate quality. To compare quality on generic and specific items, we allocated POMRF items to two subscales: "*generic design elements"* (Table 1: maximum possible score of 26) and *"psychotherapy-specific design elements"* (Table 1: maximum possible score of 12). To allow comparison between the two subscales, total subscale scores were transformed into percentages of the maximum possible.

Each trial was rated independently by two reviewers (JT & CH). To determine consistency of quality scores between the reviewers, inter-rater reliability was assessed using the intra-class correlation coefficient (ICC) for total quality scores, and the weighted kappa statistic for individual item scores. The ICC for total quality scores was 0.95 (95% CI, 0.92-0.97) and kappa for individual items ranged from 0.73 to 0.93, with mean

discussion and consensus between both reviewers (JT & CH).

Aim 2: Quality of specific design elements

We descriptively evaluated all design elements specific to psychotherapy trials (Table 1) and generic ones that were particularly poorly implemented (i.e. a score of zero in at least 75% of trials).

Table 1

Subscale 1: Generic design elements (maximum possible score of 26)	**Subscale 2: Psychotherapy-specific design elements (maximum possible score of 12)**
1. Clarity of sample description	13. Manualised, replicable, specific treatment programs
3. Representativeness of sample	14. Number of therapists
5. Specificity of outcome measures	15. Therapist training/experience
6. Reliability and validity of outcome measures	16. Checks for treatment adherence
7. Use of blind evaluators	17. Checks for therapist competence
9. Assignment to treatment	22. Equality of therapy hours
10. Design	
11. Power analysis	
12. Assessment points	
18. Control of concomitant treatments	
19. Handling of attrition	
20. Statistical analyses and presentation of results	
21. Clinical significance	

[Table 1. Items in the Psychotherapy outcome study methodology rating form]

To locate meta-analyses and systematic reviews evaluating the quality of RCTs using the POMRF in mental health populations, all papers citing the study in which the POMRF was devised were identified by searching Google Scholar. Potentially relevant papers were retrieved and assessed for eligibility. To compare the quality of RCTs in BCa with RCTs in mental health populations, for which the full 22-item scale was reported, scores were transformed into percentages of the maximum possible score on the scale, as well as on the two subscales.

Aim 4: Quality comparison by treatment type

Trials were stratified according to type of psychological treatment, grouped in five categories:

Cognitive-behavioural based treatments were defined as those targeting specific thoughts or behaviours using cognitive, behavioural, or cognitive behavioural techniques. Procedures included cognitive restructuring, relaxation training, behavioural activation, and problem solving. *Mindfulness based* treatments were those focusing on guided meditation, visualisation, and present-moment awareness. *Psychoeducation* primarily provided health education. *Support based* treatments were focused on creating a supportive environment by providing emotional or social support. *Peer-led* treatments included any treatment that was delivered by non-professional peers. *Other* treatments did not fit a defined category or combined different approaches without emphasizing any one.

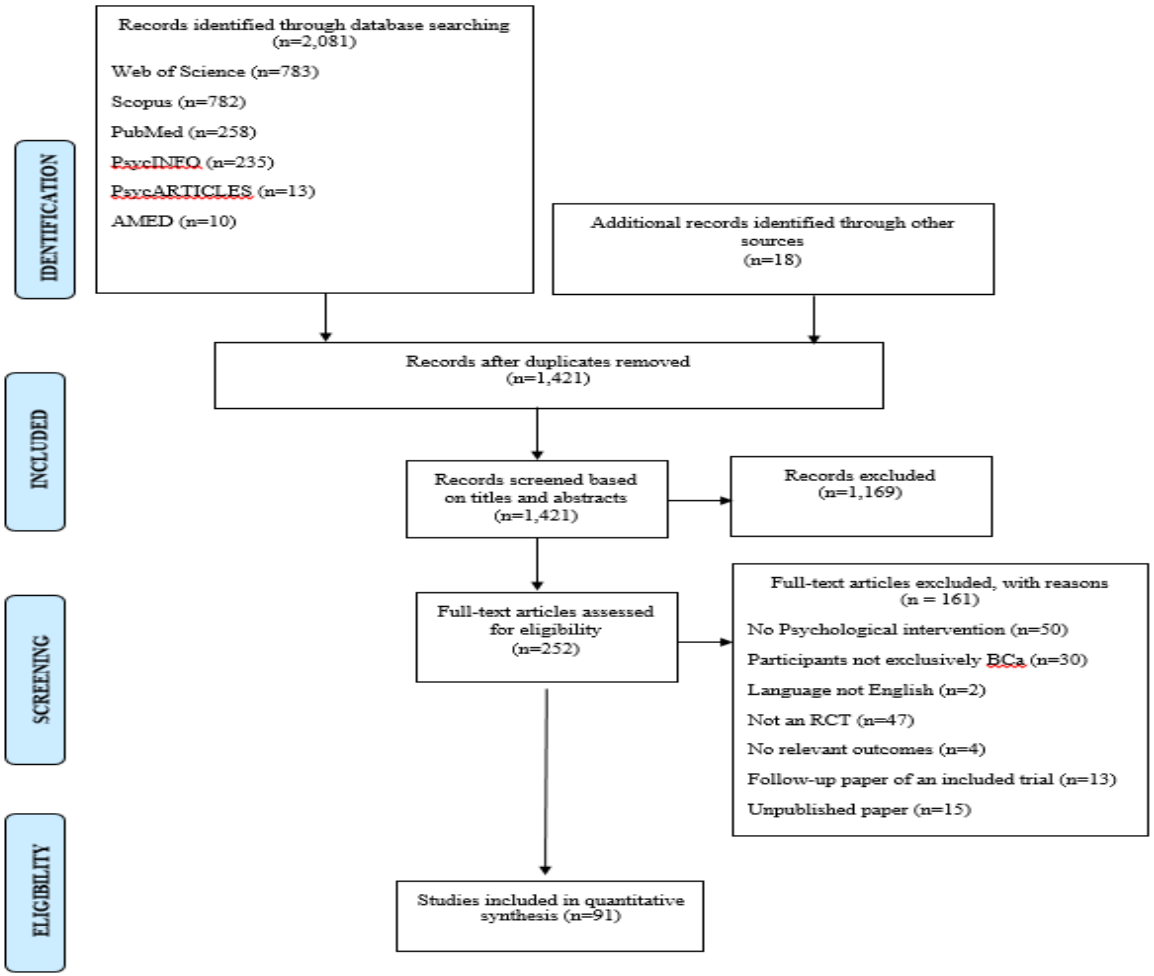
One-way ANOVAs were used to compare trial quality between these categories. Total POMRF scores and the two subscales scores distinguishing generic and psychotherapy design elements were evaluated. *Post hoc* Tukey HSD tests followed significant effects to identify which treatment types differed.

Spearman correlation was calculated for year of study publication with total POMRF scores and the two subscale scores distinguishing generic and psychotherapy design elements.

RESULTS

The search retrieved 2,081 citations (Figure 1); 18 more were identified through hand searching. After removal of duplicates, 1,412 remained for screening based on title and abstract. Of these, 1,169 clearly did not meet the inclusion criteria. The full text articles of the remaining 252 citations were retrieved and assessed. Ninety-one articles published from 1980 through October 2016 were eligible and included. A complete list of references of the included RCTs can be found in the Appendix online.

Table 2 summarises trial characteristics. Most trials exclusively included non-metastatic BCa patients and were conducted in the United States. The treatment approach used most frequently was CBT and most treatments were delivered in group format. Appendix Table A3 (see online) provides a complete description of each trials' characteristics.



[Figure 1: PRISMA flow chart showing trial identification and selection]

			Treatment format						Treatment type											
	Total sample		Individual		Group		Couples		CBT		Mindfulness		Psychoedu		Support		Peer-led		Other	
	(n=91)		(n=37)		(n=48)		(n=6)		(n=40)		(n=5)		(n=6)		(n=21)		(n=6)		(n=13)	
Variable	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Population																				
Patients																				
Total No. of patients	13,553		5,553		7,334		666		4,809		922		1,102		3913		1234		1573	
Mean sample size per study	149		150		153		111		120		184		184		186		205		121	
Median sample size per study	117		120		119		46		100		172		162		152		198		87	
Minimum sample size	14		25		32		14		14		71		66		46		104		40	
Maximum sample size	558		558		382		302		355		366		367		558		305		382	
Mean age, years	52		53		52		50		52		52		49		54		52		52	
Median age, years	52		54		51		52		53		50		50		53		51		53	
Stage of disease																				
Non-metastatic	59	65%	23	62%	31	65%	5	83%	28	70%	5	100%	5	83%	11	52%	3	50%	7	54%
Metastatic	7	8%	1	3%	6	13%			3	8%					4	19%			3	23%
Both	15	16%	9	24%	5	10%	1	17%	6	15%					4	19%	2	33%		
Not reported	10	11%	4	11%	6	13%			3	8%			1	17%	2	10%	1	17%	3	23%
Country																				

(continued on following page)

			Treatment format						Treatment type											
	Total sample		Individual		Group		Couples		CBT		Mindfulness		Psychoedu		Support		Peer-led		Other	
	(n=91)		(n=37)		(n=48)		(n=6)		(n=40)		(n=5)		(n=6)		(n=21)		(n=6)		(n=13)	
Variable	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
USA	45	49%	20	54%	20	42%	5	83%	21	53%	3	60%	3	50%	10	48%	5	83%	3	23%
Canada	10	11%	4	11%	6	13%			6	15%			1	17%	2	10%			1	8%
Australia	7	8%	2	5%	5	10%			3	8%			1	17%	2	10%			1	8%
UK	4	4%	3	8%	1	2%					1	20%			3	14%				

Other	21	25%	5	14%	13	27%	1	17%	8	20%	1	20%	1	17%	3	14%	1	17%	7	54%
	China (2), Croatia (1), Denmark (2), France (2), Germany (1), Greece (2), Holland (1), Iran (2), Ireland (1), Israel (1), Italy (1), Japan (2), Korea (1), Norway (1), Romania (1)		Croatia (1), Germany (1), Italy (1), Korea (1), Romania (1), Greece (1)		China (2), Denmark (2), France (2), Holland (1), Iran (1), Ireland (2), Israel (1), Japan (2), Norway (1)		Greece (1)		China (1), Croatia (1), Denmark (1), France (1), Iran (1), Ireland (1), Israel (1), Italy (1)		Denmark (1)		Norway (1)		China (1), Japan (1), Romania (1)		Korea (1)		France (1), Germany (1), Greece (2), Holland (1), Iran (1), Japan (1),
Exclusively distressed patients																				
Yes	12	13%	7	19%	5	10%			8	20%					1	5%	1	17%	2	15%
No	79	87%	29	81%	43	90%	6	100%	32	80%	5	100%	6	100%	20	95%	5	83%	11	85%
Outcomes measures*																				
Anxiety	47	52%	22	60%	22	46%	3	50%	24	60%	3	60%	3	50%	9	43%	2	33%	6	46%
Depression	60	66%	29	78%	27	56%	4	67%	26	65%	4	80%	4	67%	12	57%	5	83%	9	69%
Mood/ global distress	44	48%	10	27%	30	63%	4	67%	21	53%	2	40%	3	50%	10	48%	2	33%	6	46%
Treatment (active treatment)																				
No. of sessions																				
Mean	8		7		9		6		9		8		5		7		7		9	

(continued on following page)

			Treatment format						Treatment type											
	Total sample		Individual		Group		Couples		CBT		Mindfulness		Psychoedu		Support		Peer-led		Other	
	(n=91)		(n=37)		(n=48)		(n=6)		(n=40)		(n=5)		(n=6)		(n=21)		(n=6)		(n=13)	
Variable	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Median	8		6		9		6													
Minimum	1		1		1		4		1		6		3		1		3		2	
Maximum	25		25		23		8		23		11		6		16		9		25	
Variable No. of sessions (trials)	9		4		5				2						5		2			

Length of sessions (hours)																				
Mean	1.5		0.75		1.75		0.75		1.5		2		1.5		1.25		1.25		1.5	
Median	1.5		0.75		2		1.5				2									
Minimum	0.25		0.25		1		0.5		0.5		2		0.25		0.5		1		0.5	
Maximum	3		1.5		3		1.5		3		2		2.5		2		1.5		2.5	
Variable no of sessions (trials)	12		6		6				4		3				3		2			
Not reported (trials)	14		8		4		2								3		1		4	
Treatment type																				
CBT	40	44%	14	38%	22	46%	4	67%												
Mindfulness	5	5%			5	10%														
Psychodu	6	7%	2	5%	4	8%														
Support	21	23%	11	30%	9	19%	1	17%												
Peer-led	6	7%	5	14%	1	2%														
Other	13	14%	5	14%	7	15%	1	17%												
Treatment Format																				
Individual	37	41%							14	35%			2	33%	11	52%	5	83%	5	39%
Group	48	53%							22	55%	5	100%	4	67%	9	43%	1	17%	7	54%
Couples	6	7%							4	10%					1	5%			1	8%

[Table 2. Descriptive summary of included studies by treatment type and format.

Abbreviations: No., number; CBT, cognitive behavioural therapy; Psychoedu, psychoeducation

Notes: * Because several trials used multiple outcome measures, the number of trials presented for the type of outcome measure exceeds the total number of trials]

Aim 1: Overall quality of trials

The mean total quality score on the POMRF was 13.3 out of 38 with median 13 and IQR 6 (i.e. 35% of the maximum possible score; median 34%, IQR 16%). Only 12 trials (13%) reached the criterion of 19, indicating that 79 trials (87%) were of inadequate quality. The mean total quality of *"generic design elements"* was 10.5 out of 26 with median 11 and IQR 3 (i.e. 40% of the maximum possible score; median 42%, IQR 12%), while the mean total quality of "psychotherapy-specific design elements" was 2.8 out of 12 with median 2 and IQR 3 (i.e. 23% of the maximum possible score; median 17%, IQR 25%). In general, therefore, quality was poor, particularly for design elements specific to psychotherapy trials.

Aim 2: Quality of specific design elements

Appendix Table A4 (see online) displays the individual item quality scores for each trial. Four generic design elements were particularly poorly implemented: representativeness of the sample (item 3), use of blind evaluators (item 7), control of concomitant treatments (item 18), and clinical significance (item 21). These are evaluated in detail below, followed by the elements specific to psychotherapy trials.

Generic design elements

Representativeness of the sample

Of the 74 trials in which emotional distress was the primary outcome, only 11 (15%) specified as an inclusion criterion that participants were distressed. Two of these, however, excluded participants with clinical levels of anxiety or depression. Of the 63 trials not specifying distress as an inclusion criterion, two excluded participants with clinical levels of emotional distress and two excluded participants with prior history of psychiatric treatment

Of the 17 trials in which emotional distress was the secondary outcome, only three (18%) specified that to be included participants must be experiencing the specific difficulty that the primary outcome measured; for example, requiring evidence of insomnia for inclusion in a trial in which the primary outcome was insomnia.

Use of blind evaluators

Only 16% of trials (n=14) reported using blind assessors, but none of these described ensuring that the assessor was unaware of the treatment condition.

Control of concomitant treatments

Only nine trials (10%) described controlling for concomitant treatments. Of these, two ensured that patients received no additional treatment (psychological or pharmacological); four excluded patients receiving additional psychological treatment (but not those receiving pharmacological treatment); the remaining three included patients taking anxiolytic or antidepressant medication provided the dose was stable.

Clinical significance

Only 10 trials (11%) reported the clinical significance of treatment effects. However, all 10 used a different operational definition of clinical significance preventing assessment of the absolute efficacy across different treatments and trials.

Psychotherapy-specific design elements

Manualised treatment

Only 46 trials (51%) used a manual to standardise treatment. Of these, 19 referenced a published manual; six referred to an unpublished manual available on request; and 21 referred to a *"manual"* or a *"manualised treatment"* without information on how to obtain it. An additional eight trials were ambiguous about whether a manual existed, for example reporting that treatment was *"based on"* or *"modelled after"* a specific manualised treatment.

Therapist training

Only 29 trials (32%) included therapists qualified to deliver psychotherapy, for example stating that therapists were *"clinical psychologists"*. Only seven of these (8% of trials) used therapists with specific training in the treatment being investigated. An additional 29 trials (32%) used therapists with training in the treatment being investigated, but these therapists either had little experience in psychotherapy, for example being *"master's level registered nurse therapists",* or their clinical background was not reported. Of the remaining trials, 14 used therapists with little experience and without training in the treatment being evaluated; in nine it was merely stated that therapists were "*trained*" or "*experienced*"; and 10 provided no information about therapist training.

Monitoring therapist adherence and competence

Only 17 trials (15%) monitored therapist adherence and only five (4%) monitored therapist competence. An additional 12 reported monitoring treatment delivery but without specifying what aspects were monitored.

Number of therapists

Most trials (67%) included more than one therapist to deliver treatment. However, of these, 16 (18% of all trials) did not specify the number of therapists, although using the plural 'therapists', and only six (7% of all trials) analysed the effect of therapist on outcome.

Equality of therapy hours

Eleven trials (12%) used only a wait-list control design. Of those using active treatment control conditions, only 19 (21% of all trials) equalized the number of treatment hours between conditions. Of the remaining 61 trials, 26 had more than a 20% difference in treatment hours between conditions, 30 did not report hours received in the control condition, and five did not report hours received by either condition.

Aim 3: Quality comparison with mental health populations

To assess the quality of RCTs in mental health populations relative to RCTs in BCa, we identified three meta-analyses using the POMRF addressing depression in children[39], obsessive compulsive disorder[28], and across several mental health populations (e.g. anxiety, depression, borderline personality disorder)[30]. Mean total quality scores ranged from 45 to 52% of the maximum possible, higher than the corresponding score in the present review (34% of the maximum, Table 3). Quality of generic and psychotherapy-specific design elements could not be compared because the mental health meta-analyses did not report individual item scores.

	Number of RCTs included	Mean total score	Maximum possible score	Maximum possible score as a %	Range of scores	Range of scores as a %
Emotional distress in BCa	91	13.3	38	35%	6-30	16-79%
Depression in children	10	22	44	50%	8-30	18-69%
Individuals with mental health conditions	31	20.3	44	46%	-	-
OCD in adults	37	23	44	52%	15-34	34-77%

Table 3

[Table 3. Comparison of total quality scores on the POMRF of RCTs in this population with RCTs in mental health populations.

Abbreviations: POMRF, psychotherapy outcome study methodology rating form; RCT, randomised controlled trial; BCa, breast cancer; OCD, obsessive compulsive disorder]

Aim 4: Quality comparison by treatment type

One-way ANOVAs revealed no significant difference in overall quality scores or generic subscale scores. A significant difference was seen for psychotherapy specific subscale scores (Table 4). Post-hoc testing showed that mindfulness trials were of better quality than support, peer and "other" treatment trials. However, mindfulness trials still only had a mean quality score of 5.4 out of 12 (i.e. 45% of the maximum possible score) on this subscale.

	CBT (n=40)	Mindfulness (n=5)	Psychoedu (n=6)	Support (n=21)	Other (n=13)	Peer-led (n=6)	All trials (n=91)	F-value
Total quality score	14.13 (4.61)	16.6 (2.7)	13.17 (0.75)	12.14 (3.86)	12 (3.96)	11.66 (3.14)	13.27	1.78
Subscale 1: Generic design elements	11.08 (3.2)	11.2 (1.3)	11 (1.26)	9.67 (2.31)	9.85 (2.76)	9.83 (2.64)	10.49	1.05
Subscale 2: Psychotherapy-specific design elements	3.05 (1.99)	5.4 (2.07)[a]	2.17 (0.75)	2.48 (2.18)[b]	2.15 (1.77)[b]	1.83 (1.17)[b]	2.78	2.81 *

Table 4

[Table 4. Means (SDs) and F-values for the items on the POMRF for different treatment types

Abbreviations: POMRF, psychotherapy outcome study methodology rating; psychoedu, psychoeducation *P<0.01, [a,b]Means with different superscript differs significantly]

Aim 5: Quality trends over time

The overall quality score modestly improved with year of publication (rho=0.4,p<0.001) (Figure 2). However, the mean total quality of the 30 trials published in the last five years was still only 14.7 with median 14.5 and IQR 7 (i.e. 38% of the maximum possible, median 34%, IQR 13%) and only six of these met our criterion for adequate quality. Generic design elements improved across publication year (rho = 0.48, p<0.001) but psychotherapy-specific design elements did not (rho = 0.15, p=0.15) (Figure 3).

[Figure 2. Scatterplot of total quality scores on the POMRF by year of publication. Abbreviations: POMRF, psychotherapy outcome study methodology rating form]

[Figure 3. Scatterplot of POMRF score on generic design elements and psychotherapy-specific design elements by year of publication. Abbreviations: POMRF, psychotherapy outcome study methodology rating form]

DISCUSSION

Our findings show that the methodological quality of RCTs for emotional distress in BCa is poor. Most RCTs were of inadequate quality and of lower quality than those in mental health. While quality modestly improved from 1980 to 2016, most of the more recently published RCTs were still poorly designed.

Quality was particularly poor for design elements specific to psychotherapy trials. Moreover, while implementation of generic design elements improved over time, that of psychotherapy-specific ones did not. Design elements specific to psychotherapy were lacking in most trials, thereby compromising the internal validity of such trials. Only around one in 20 monitored therapist competence or analysed the effect of therapist on outcome; only around one in 10 employed therapists who were adequately trained in the treatments or monitored therapists' adherence to them; only around one in five compared conditions with an equal number of treatment hours; and barely half used a manual to standardise treatment. The purpose of these design elements is to ensure that a psychological treatment is implemented correctly. Because none of the trials in this review adequately implemented all these elements, their findings provide unreliable information about the treatments the authors are claiming to evaluate.

Although, in general, generic design elements were not as poorly conducted as those specific to psychotherapy trials, important ones were still neglected, thereby further compromising trials' internal and external validity. Only around one in 10 trials controlled for concomitant treatments, blinded assessors, specified as an inclusion criterion that participants were distressed, or reported the clinical significance of treatment effects.

While all these areas represent significant deficits in the BCa literature, the latter two are particularly concerning. Consensus-based clinical practice guidelines specifically recommend the use of psychological treatments for BCa patients experiencing clinical levels of emotional distress[43, 44] and the standards by which a treatment is considered "evidence based"

recommend that trials provide an estimation of clinical significance[33, 45]. If trials do not target patients with emotional distress, findings cannot be generalised to the population of patients to whom the treatments would be offered in practice: i.e. those with clinical levels of emotional distress. Additionally, if trialists do not report the clinical significance of treatment effects, it is difficult for researchers, clinicians, service providers and policy-makers to assess the practical relevance of findings. Determining and applying standardised criteria for the clinical significance of treatment effects would advance psychotherapy outcome research in BCa. The most established method for determining clinical significance[46] is the approach developed by Jacobson and colleagues[47, 48]. There are two components to the approach, the first determines if the degree of change following treatment is statistically significant beyond the degree of change that could be an artefact of repeated measurement. The second determines if treated individuals are distinguishable from a representative normative population. To be classified as recovered, an individual must a) show a change larger than measurement error and b) be indistinguishable from a normative population following treatment.

The overall methodological quality of trials did not differ by type of treatment. For design elements specific to psychotherapy trials, quality did differ by type of treatment explored, with mindfulness treatment trials achieving better quality scores than support, peer, and "other" treatment trials However, trials evaluating mindfulness-based treatments were still of limited quality. Many of the trials provided insufficient details about treatment methods and procedures. Thus, it was not possible to categorise treatments by distinct treatment approaches, but only by broad categories of type of treatment. This highlights the importance of studies clearly reporting the type of treatment used with clear and unambiguous descriptions of the treatments being compared.

Although the methodological quality of trials modestly improved over time, the majority of the most recent RCTs were still of inadequate quality. Thus, there is clearly substantial room for improvement in the conduct of RCTs in this population.

This review has some important limitations. Our assessment of study quality was limited to what was included in the published reports. As most journals impose word limits, authors may have excluded important information. Thus, some trials may have implemented unreported design elements. We also relied on summary scores to quantify the overall quality of trials. Summary scores can be problematic as they can mask methodological strengths and weaknesses of a trial. Trials that differ in the conduct of individual design elements may still result in the same overall score. Finally, we did not evaluate whether methodological quality differed amongst trials including patients at different points in the BCa trajectory, because many trials included patients at multiple points in the disease trajectory.

In conclusion, the current view that efficacious psychological treatments exist for distress in BCa patients is based on poor quality RCTs. It does not follow that efficacious treatment do not exist, or that conclusions of previous reviews are wrong. However, with increasing investment in, and growing priority of, psychological treatments for emotional distress in BCa[10, 49], it is imperative that future psychological treatment trials are conducted with greater methodological rigour to make sure evidence based practice occurs in clinical settings. We urge researchers to ensure that the methodological issues presented in this review are adequately implemented in future trials. In particular, trials need to include participants with clinical levels of emotional distress, control for concurrent treatments and report the clinical significance of treatment outcomes. Trialists must also consider the methodological challenges specific to psychotherapy trials.

Disclaimer: The authors acknowledge no financial interest or benefit arising from the direct applications of their research

Conflicts of interest: The authors have no competing interests to report

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sDeclarations of interest: None. The authors have no competing interests to report

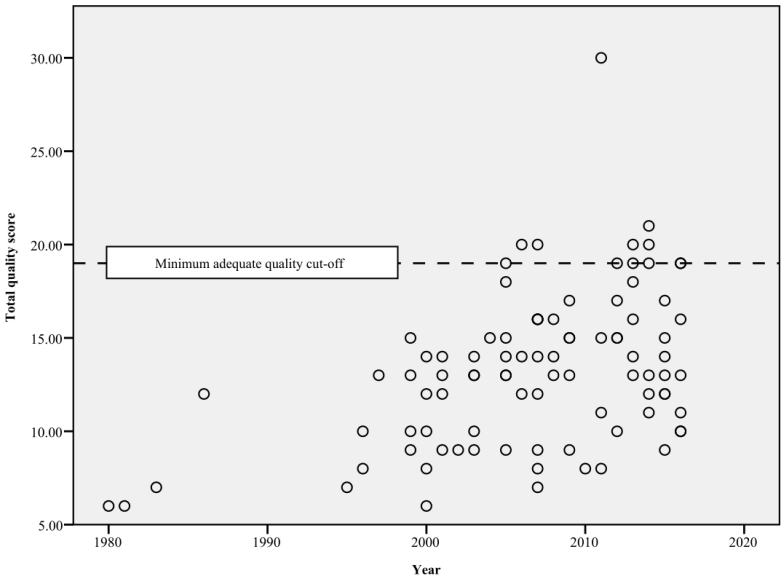

Fig 2

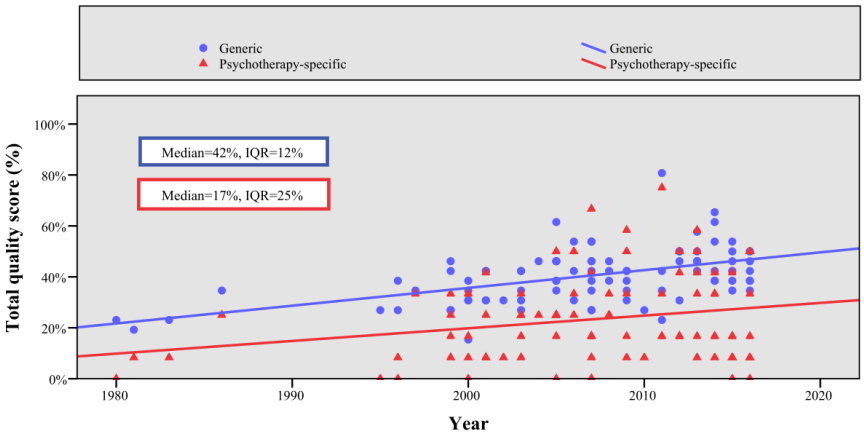

Fig 3

Highlights

- Anxiety and depression are common in Breast Cancer (BCa) patients
- Psychological treatment trials for emotional distress in BCa are of poor quality
- Components specific to psychological treatment trials are of poorest quality
- The overall methodological quality of trials does not differ by treatment type
- Methodological quality of psychological treatment trials is improving