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Title: Are psychological interventions effective on anxiety in cancer patients? A systematic review and meta-analyses

Short running title: Psychological interventions on anxiety in cancer

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Abstract

Objective

The aim of this meta-analysis was to estimate the overall effect size (ES) of psychological interventions on anxiety in patients with cancer; and extract sample and intervention characteristics that influence effectiveness.

Methods

PubMed, Scopus, PsycINFO, Embase, Medline and CINAHL were searched using Medical Subject Heading keywords- *'cancer' AND 'anxiety' AND 'psychological intervention' AND 'counselling' AND 'psycho*' AND 'psychotherapy' AND 'psychosocial' AND 'therapy'* between January 1993- June 2017.

Results

Seventy-one studies were eligible for the systematic review; among them 51 studies were included in the meta-analysis calculations. The overall ES was -0.21 (95% confidence interval; -0.30 to -0.13) in favour the intervention. From sub-group analyses, studies conducted in Asia; enrolling inpatients; focussing on relaxation; of <6-week intervention duration; <30-minute intervention dose per session; and <4-hour of total time of intervention showed moderate ESs ranging from -0.40 to -0.55. Only two studies restricted enrolment to pre-screened patients with clinically elevated level of anxiety and showed moderate ES of -0.58.

Conclusions

Low psychological distress at baseline and non-evidence based interventions were the main factors identified for low effectiveness. Screening and assessment to determine clinical levels of anxiety in patients with cancer should be considered in future trials as an inclusion criterion before providing psychological interventions.

Systematic review registration: PROSPERO: International prospective register of systematic reviews: CRD42017056132

Keywords

Anxiety, cancer, intervention, meta-analysis, psychology, randomised controlled trials, systematic review

Background

People face many challenges to their psychological wellbeing after a diagnosis of cancer.¹ Despite this, many people with cancer cope well themselves without further support, while the coping capacity of some may be overwhelmed requiring supportive care and treatment.^{2,3} Anxiety is a common psychological problem in patients with cancer, often an early sign of distress originating from being overwhelmed by the diagnosis, diagnostic tests, treatments or side effects.⁴⁻⁸ Common symptoms of anxiety are excessive worry, restlessness, and insomnia.⁹ Phobia, generalized anxiety disorders, panic, fear of recurrence, post-traumatic stress disorder and obsessive-compulsive disorders are all considered part of anxiety disorders.^{7,10,11} Taken together, anxiety disorders are highly prevalent among cancer patients. Kuhnt et al¹² (2016) reported a 12-month and lifetime prevalence of any anxiety disorder of 15.8% and 24.1%, respectively. This was higher than the four-week prevalence (11.5%) reported earlier from the same cohort.¹³

Psychological interventions can reduce anxiety in patients with cancer and provide benefits for both psychological and physical health outcomes such as improved quality of life¹⁴⁻¹⁶, health behaviour^{17,18} and emotional function,^{14,16,18} and decreased insomnia¹⁶ and cancer treatment side-effects^{15,19,20} e.g. fatigue, pain, nausea, vomiting. Evidence for their effectiveness was summarised in one early meta-analysis by Sheard and Maguire²¹ (1999) which found that they had a moderate effect compared to standard care control (number of study, n=19, sample size, N=1023, ES: 0.42; 95% Confidence Interval, CI: 0.08 to 0.74). The ES was larger when the analysis was restricted to interventions providing group psycho-education (n=3, ES=1.59), of at least 8+ hours duration (n=4, ES=1.01), or when patients were only included after fulfilling predetermined criteria for significant distress (n=3, ES=0.85). The overall ES estimated was lower when two extreme outliers were removed (n=17,

ES=0.27).¹⁴ Later, Faller et al²² (2013) showed similar benefit of psychologic interventions in alleviating anxiety (n=74, ES: 0.38, 95% CI: 0.29 to 0.46) and the ES was increased for psychotherapy interventions delivered to screen-selected patients (n=8, ES: 0.56). Two meta-analyses conducted in China reported large ESs (ES: >0.8) in reducing symptoms of anxiety, however, these studies may not be representative of the patient experience elsewhere.^{23,24} Other meta-analyses focused on differences in effectiveness according to cancer stage, type or intervention methods (psychoeducation, psychosocial, behavioural) and reported widely ranging ESs.²⁵⁻³² Previous analyses did not apply strict inclusion criteria which may have contributed to the large differences in ESs. It is therefore important to consider the real benefits of psychological interventions for anxiety in patients diagnosed with cancer; and patient and intervention treatment characteristics associated with better success to guide future psychological interventions.

This study aimed to determine from randomised controlled trials the overall ES of psychological interventions to improve anxiety in patients with cancer. Sub group analyses were used to estimate sample or intervention characteristics associated with greater effectiveness. Lastly, we assessed whether or not treatment for anxiety was beneficial for patients with clinical level of anxiety. We considered for inclusion studies published after January 1993, since Sheard and Maguire's review (1999) already summarised reports before that time.²¹

Methods

Search strategy

This systematic literature review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) methods³³. Six databases (PubMed, Scopus, PsycINFO, Embase, Medline and CINAHL) were searched by SS and MJ to identify studies testing interventions for anxiety in

patients with cancer. The Medical Subject Heading (MeSH) terms used were 'cancer' AND 'anxiety' AND 'psychological intervention' AND 'counselling' AND 'psycho*' AND 'psychotherapy' AND 'psychosocial' AND 'therapy'. Searches were limited for publication dates between January 1993 (to exclude those studies already reviewed by Sheard and Maguire) to June 2017. In addition to using MeSH Heading searches as detailed above, any reports that cited Sheard and Maguire's (1999) study²¹ as well as the bibliographical references of retrieved articles, reviews, meta-analyses were screened manually and assessed whether they contained the relevant keywords for inclusion. The protocol was registered with PROSPERO (CRD42017056132).³⁴ The search strategy is presented in Figure 1.

Study inclusion and exclusion criteria

Participants: Studies were eligible for inclusion if they enrolled patients 18 years or older diagnosed with any type or stage of cancer; delivered a psychological intervention to ameliorate anxiety; focused on cancer patients. Studies that aimed to provide interventions to other participants besides cancer patients such as family members, friends, caregivers or couples were excluded.

Interventions: Stand-alone or combination interventions were eligible for inclusion: individual or group counselling described using terms such as psychological or psycho-social treatment, relaxation, cognitive behavioural therapy (CBT), psycho-education, psychotherapy, counselling or any supportive therapy aimed to improve psychological or emotional distress or mood specifically mentioning anxiety. Interventions that solely focused on mindfulness, imagery, visualisation or meditation were excluded. There were no restrictions as to who provided the intervention (e.g. oncologist, psychologist, psychiatrist, general practitioner, social worker, nurse, volunteer or other),

mode of intervention (e.g. face-to-face, telephone, online or other), length of intervention or length of follow-up.

Comparator: The presence of a control group that either received a minimal or alternative intervention, usual care or wait-list was another main inclusion criterion of this review. Single group pre-post comparisons were excluded.

Outcome: Eligible outcomes were the effects of psychological interventions on anxiety or emotional or psychological distress. Anxiety or distress could be determined by any standardised screening or diagnostic measure but to be included the studies needed to provide a separate score for anxiety outcomes. Studies that only present composite results of anxiety and depression or overall distress where anxiety symptoms could not be separated were excluded. Studies that used psychological interventions with the aim of reducing physical symptoms, prolonging survival, or impacting on biomarkers rather than ameliorating anxiety were also excluded.

Study design: Random allocation of treatment was another main criterion of this systematic review. Studies published in English were included. Studies with a sample size of less than 40 participants were excluded to reduce the potential influence of publication bias and inflated ES common in small studies.^{21,35} Non-full text sources such as abstracts, editorial materials, letters, case reports, unpublished materials or unpublished theses were excluded.

Study selection

All articles were retrieved by one reviewer (SS) using electronic and manual searches. After removing duplicate articles, titles and abstracts were screened for fulfilling the study inclusion and exclusion criteria (SS). All potential full-text articles were retrieved and evaluated against the

eligibility criteria. Two reviewers (SS, MJ) then independently assessed the eligibility of full text articles to be included in the qualitative and quantitative synthesis. Any disagreements were resolved by discussion.

Data extraction

Data were extracted from the final included studies following the pre-determined criteria of this systematic review.³⁴ Initially five studies were used as a pilot set to formulate the final data extraction criteria. The following major characteristics were extracted: study characteristics, patient characteristics, eligibility criteria of participants in the study, intervention characteristics and main outcomes measures.

This included total sample size, average age (range), gender, type and stage of cancer, eligibility criteria, type and method of intervention received by control and intervention groups, delivery mode (group or single), provider type, total intervention time, follow-up, types of screening tools to measure anxiety, and outcomes. Outcomes of anxiety (increased, no change or reduced) were determined from the change in mean score before and after the intervention period for quantitative analysis. If the mean score was unavailable in the study, outcomes were determined from mean differences, reductions in proportion diagnosed with anxiety from baseline to post-intervention from graphical presentations. e.g. box-and-whisker or line plots.

Data synthesis

For the quantitative analysis, post-intervention average mean and standard deviation values of anxiety determined by screening tools were extracted. If standard error or confidence intervals were reported, these were converted to standard deviation using the formula provided in the Cochrane

Handbook of Systematic Review using RevMan 5.3.³⁶ Median values were used as means in the meta-analysis.³⁷ If studies used more than one screening tool to measure anxiety, data from the tool most commonly used across the reviewed studies were extracted.

Meta-analyses modelling

Random effect modelling was used to calculate the overall and subgroup ESs using RevMan 5.3³⁶ as a standardised mean difference (SMD) (Cohen's d).³⁷ The interpretation of the ES was <0.2 (small), 0.21 to 0.5 (medium) and >0.8 (large) (two-tailed *p* value of <0.05).³⁸ Heterogeneity was denoted by *Q* and *I*² values which were categorised into low (25%), moderate (50%) or high (75%).³⁷ Forest plots were used to display the number of participants, mean and standard deviation anxiety score values for intervention and control groups after completion of the intervention phase, and weight in %, which indicated the influence of the study on the overall pooled ES. Sub-group analyses were conducted to determine which sample or intervention characteristics influenced the ES. Sensitivity analyses were conducted by excluding the studies with the highest ES observed for the intervention and control groups, respectively, and in addition by excluding the study with the smallest sample size at post-intervention.

Risk of bias (RoB)

RoB analysis was conducted by two reviewers independently (MJ and SS). The RoB 2.0 tool to assess RoB in randomised trial was used.³⁹ Five domains were assessed-

1. Bias arising from the randomisation process including allocation of random sequence and concealment until recruitment, baseline imbalances of sample group size;

2. Bias due to deviations from intended interventions including awareness of assigned intervention by participants, carers or trial personnel and approach of 'intention-to-treat' analysis;
3. Bias due to missing outcome data including not using analysis of 'intention-to-treat' for all data or excluding missing data;
4. Bias in measurement of the outcome including whether outcome assessors were blinded to treatment allocation; and
5. Bias in selection of the reported result including whether it followed the protocol or statistical analysis plan.

For each domain, the RoB was categorised into– 'yes', 'probably yes', 'no', 'probably no' or 'no information'. Based on the summary score, each individual domain was then denoted as 'low risk', 'some concerns' or 'high risk'. Summarising across domains resulted in an overall rating of low risk (across all domains), some concerns (in at least one domain) or high risk (high risk in least one domain). Ratings of each study by the two reviewers were compared and any disagreement was resolved by discussion.

Results

Study selection

Study screening and extraction outcomes are presented in Figure 1. Overall, 1,539 studies were retrieved from electronic (n=1,203) and other sources (n=336). Of these, 177 studies were considered in full-text after excluding duplicates (n=344) and studies not matching inclusion criteria (n=1,021), and 71 studies were selected for the systematic review. The main reasons for exclusion of

studies at full-text stage were not reporting anxiety outcomes (n=40), non-randomized studies or no control group (n=16), no psychological intervention (n=14), or small (N= <40) sample size (n=8).

Characteristics of included studies

Characteristics of each study are presented in Supplementary Table 1.^{5,14-20,40-102} More than half of the included studies (n=38/71) were published after 2010. The majority of studies were conducted in Europe (n=29/71) or North America (n=19/71). A total of 13,098 patients with cancer were enrolled in the clinical trials with a median of 155 per study (minimum, N=40 and maximum, N=803). Around three-quarters of participants were female (N=9,773/13,098). The mean age of participants was 55 years. The majority of the studies (n=55/71) included patients newly diagnosed with cancer (n=19/71) or undergoing active treatment (n=36/71). Only three studies included patients with <6-month life expectancy. More than half of the studies (n=39/71) provided interventions for female patients diagnosed with breast (n=36/39) or gynaecological cancer (n=3/39). Only two studies (n=2/71) delivered interventions to male patients diagnosed with prostate or testicular cancer, the remaining 29 studies included mixed gender samples.

Cognitive behavioural therapy (CBT) (n=14/71), relaxation (n=12/71) and psychosocial therapy (n=9/71) were the most commonly delivered interventions. Thirteen studies delivered supportive care interventions. Only three studies delivered stepped-care interventions. Interventions were delivered in group (n=35/71) or individual settings (n=34/71) using face-to-face, telephone, online, self-delivery or combination delivery modes. Most common delivery was by psychologists (n=33/71), nurses (n=23/71), psychiatrists (n=11/71), or social workers (n=11/71), by one (n=31/71) or multiple (n=27/71) providers. Involvement of pharmacists (n= 2/71) was common in recently conducted studies to provide education about side effects of chemotherapeutic agents to the patients. Besides

health care professionals, trained cancer survivors were involved in 2/71 studies in the delivery of psycho-educational interventions. The duration of the interventions ranged widely from just 4 days to 1 year. Fifty studies monitored patients at fixed time intervals, with a minimal follow-up of 3-month to more than 2 years, while the remaining the studies reported immediate post intervention outcomes.

Different outcome assessment tools were used to measure anxiety, most commonly the Hospital Anxiety and Depression Scale (HADS) (n=38/71), State-Trait Anxiety Inventory (n=10/71), or Profile of Mood States (n=8/71). Overall, 87% (n=61/71) studies reported a reduction in anxiety scores from baseline to after the intervention. The remaining studies showed either no change (n=2/71) or an increase (n=7/71) in mean anxiety scores.

Overall effect size

Of the 71 studies, 51 studies (N=8,283) were included in the meta-analysis. The remaining studies (n=20) were excluded due to reporting insufficient details on anxiety outcomes (Figure 1). The proportion of participants lost to post-intervention was 10.5% and the final sample size included in the meta-analysis was 7,491.

The overall ES for reduction in anxiety was small (-0.21; 95%CI: -0.30 to -0.13) (Figure 2). The meta-analysis showed moderate heterogeneity among the studies ($Q = 155.16$, $P < 0.00001$; $I^2 = 68\%$). Only five studies showed a large ES ranging between -0.80 to -1.43, while seven studies reported medium ESs ranging between -0.53 to -0.75. Factors which characterised studies with moderate to large ES were recruiting patients with high level of anxiety symptoms,^{19,67} intervention method well-matched to patients' needs,⁴¹ recruiting patients who were undergoing highly stressful cancer treatments,^{14,16,76} and specifically targeting anxiety treatments.^{18,60,64,76,85,101}

For sensitivity analyses, studies with the highest ES favouring the intervention (ES: -1.43)⁶⁴ or control groups (ES: 0.47)⁷⁰ were excluded, but this resulted in minimal (ES of -0.19 and ES of -0.22, respectively) change in overall ES. After excluding the two studies with the smallest sample size at post-intervention, the overall ES remained unchanged.^{43,92}

Sub-group analyses

Sub-group analyses are presented in Table 1. Studies conducted in Asia (n=11; ES: -0.46), those including patients with mixed types of cancer (n=16; ES: -0.30) and intervening on inpatients (n=20; ES: -0.40) showed higher than average ES. A moderate ES (n=2; ES: -0.58) was also identified in two studies which screened participants for anxiety before including them into the study.^{67,72}

Sub-group analysis stratified by intervention characteristics showed that studies that provided relaxation training (n=12; ES: -0.53), individual delivery (n=24; ES: -0.32), face-to-face with self-delivery mode (n=7; ES: -0.35), or deliver by multiple providers (psychologist and psychiatrist, n=2; ES: -0.40) resulted in higher ESs. Interventions of short duration (1-7 days, n=7; ES: -0.55 and <6 weeks, n=7; ES: -0.48) showed moderate ES. Higher ESs were identified for interventions that were provided at lower dose per session (<30 minutes, n=8; ES: -0.42 & 30-60 minutes; n=14; ES: -0.35). Short programs with smaller number of session (<4 hours, n=12; ES: -0.44 and 1-3 sessions, n=9; ES: -0.43) had higher ESs more intense or long programs.

Is treatment for anxiety more beneficial for patients with clinical level of anxiety?

Nine studies used formal screening for presence of anxiety or distress symptoms more broadly as part of the enrolment procedures (Table 2). Only one pilot study used a minimal cut-off score specifically for anxiety (Hamilton Anxiety Rating Scale, HAM-A; ≥ 14 score) as a formal inclusion

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criterion. This study delivered CBT, an appropriate evidence-based treatment for anxiety symptoms, and showed a large ES of 0.80.¹⁵

Five other studies (n=5/9) (Table 2) screened participants using the overall HADS score (such as ≥ 8 , ≥ 11 , ≥ 12 and ≥ 14), but not specifically their anxiety score.^{67,75,79,80,97} Among them Moorey et al (1998 and 2009)^{79,80} delivered CBT for patients with HADS scores ≥ 8 . Two studies^{67,97} used psychological interventions for elevated level of anxiety and/or depression (HADS score, ≥ 11). Only one study (n=1/9) delivered a stepped-care treatment following clinical practice guidelines to patients with head, neck and lung cancer and diagnosed with anxiety and/or depression symptoms (HADS-A > 7 , or HADS-total > 14) and resulted in an ES of -0.38.⁷⁹ In two studies (n=2/9), the structured clinical interview (Diagnostic and Statistical Manual of Mental Disorders, DSM III) was used to determine evidence-based anxiety symptoms (insomnia) in patients with cancer before delivering CBT, but not as an inclusion criterion.^{59,89} Owen et al (2017) delivered online psychological interventions to patients diagnosed with distress determined by the distress thermometer (minimum score of 4 to 10).⁸²

Four studies screened for distress using patient or provider self-report. Patients who self-reported respiratory distress symptoms (breathlessness, cough, or fatigue) or psychological complaint (such as anxiety) were included in two studies.^{93,102} Another two studies considered provider-reported anxiety and depression as well as psychological needs as reliable sources of sample inclusion criteria and delivered progressive muscle relaxation and CBT, respectively (n=2, ES: -0.40) (Table 1).^{19,95} However, these four studies did not use a standard screening tool to determine anxiety symptoms.

None of the studies used a diagnostic interview to determine anxiety disorder before sample enrolment. Four studies assessed clinical anxiety disorder using structured interview such as DSM III

as part of the baseline data collection procedure after enrolling patients into the study,^{50,74,91,94} but patients with or without anxiety disorder were included in these interventions.

RoB Assessment

Overall, around one-third of the trials (n=22/71) were judged to have high RoB on at least one criterion (Supplementary material 2). The remaining trials (n=49/71) presented only some concerns. The highest RoB was identified in the randomization process (n=17/71), with concealment of allocation sequence often not reported. Most studies had low risk of selective reporting of result (n=68/71), or missing outcome data (n=63/71). Most clinical trials were not blinded for intervention or outcome measurement. A high proportion of trials therefore scored high due to awareness of assigned intervention by participants as well trial personnel (n=66/71) and outcome assessors (n=64/71).

Discussion

Overall effectiveness of psychological interventions

This large review and meta-analysis systematically identified the sample and intervention characteristics associated with effective psychological interventions to improve anxiety in patients with cancer. Overall the interventions achieved only a low ES of -0.21 (95%CI; -0.30 to -0.13), lower compared to previously conducted meta-analyses.^{21-25,27,31,32} In contrast to these previous reports, our study applied much stricter inclusion criteria only extracting data from large and high quality studies. Our study further closely examined moderators of effectiveness.

Lack of distress or anxiety already at baseline was one common reason identified by study authors for low effectiveness of psychological interventions.^{46,48,49,51,53,55,57} Inclusion of an unscreened sample

was another reason.^{42,51,58} These issues have been raised previously with recommendations that evidence-based care should only be offered to patients for whom intervening in clinically indicated.^{7,21,22,27,32,103} A review of 14 meta-analyses looking at distress reduction more broadly, not specifically for anxiety, showed that the treatment benefit of psychological interventions was three times higher when screening was done compared to no screening.¹⁰⁴ Despite this, the majority of the clinical trials in this review included patients based on their status as a cancer patient receiving treatment, having symptoms from their cancer treatment or for the prevention of distress. In a recent study, Braamsee et al (2013) reported that patients (18.7%, N= 9/48) who dropped out of interventions did so stating that they felt they can cope well themselves.⁴⁶

Furthermore, studies reported that many patients from both intervention and control groups⁴² or only control groups,^{56,69} already received routine mental health support, psychological treatment^{45,81,93} or psychotropic medications.^{45,50,59,67,80} In some instances, patients even received both psychological and pharmacological treatment before being enrolled in the intervention studies. For example, 25%¹⁵ and 10.3%⁴⁶ of patients received support from a mental health professional and antidepressants, making it difficult to disentangle any independent intervention benefit. In another study, the proportion of participants taking antidepressants increased over time - from 29% at the baseline to 37% at 10 weeks of psychological intervention.⁸⁰ In that context, several studies deliberately excluded patients with severe distress (HADS score ≥ 20 followed by DSM IV interview),⁶³ high anxiety,⁷⁸ past depression,⁵⁸ regular psychotropic medication prescription,^{19,83,89} mood disorder, psychiatric disorder or major depressive disorder,^{18,40,60,68,83,90} or psychiatric comorbidity diagnosed by psychiatrist,⁶⁶ limiting the findings of many studies to patients with mild distress.

Besides receiving active off-trial treatment, control group participants may show improvements in their anxiety due to the Hawthorne effect. This was observed in the study of Dolbeault et al (2009) which used a wait-list control group design⁶⁰ as well in a study by Cheung et al (2003) who provided a minimal intervention to the control group.¹⁴ Randomisation may be a factor associated with non-uptake of potentially eligible patients.⁹⁵ Patients who have an expressed need to receive psychological interventions may decline to participate in a study where they may be assigned to a no-intervention control group.^{81,95}

Our subgroup analyses aimed to determine factors associated with low ES and found that patients assigned to group interventions, certain intervention methods, patients diagnosed with breast cancer or female patients, newly diagnosed patients, and intervention characteristics including high duration, large dose of intervention per session, number of session and total hours seemed to result in less benefit than others. One reason for why low dose interventions may have been more effective was that such interventions were commonly provided to inpatients or in crisis response settings. For example, Arakawas et al (1997) study provided relaxation training within 3-4 sessions which resulted in large ES and reduced anxiety symptoms during chemotherapy.⁴¹

Previous studies found that group therapy has similarly effective compared to individual therapy and more cost-effective.²¹ It is therefore not surprising that more than half of the studies reviewed used group setting, although many of these were designed to provide psychological support and not primarily to treat anxiety. However, the ES of group interventions was much smaller ($n=25$, ES: -0.13) than that of individual interventions ($n=24$, ES: -0.32). Given the infectious nature of anxiety, an individual treatment mode may be most desirable for anxiety disorders. Observing that others become unwell or die, feeling uncomfortable in presence of others, and less flexible scheduling were

previously identified as other possible barriers to group therapy.^{49,60-62,74,76,86,87} For example, in the Breitbart et al (2015) study, around one-third of the sample (N=81/253) never participated in the group intervention due to scheduling conflicts or deteriorating health (N=35/81 each).⁴⁹ In a study by Edmonds et al (1999), patients felt, 'the group setting too anxiety provoking',⁶² while some 'dislike group therapy' or 'did not want to meet other sick women with a poorer prognosis'.^{44,59}

According to international clinical practice guidelines from the United States of America, Australia and Canada for the management of anxiety in patients with cancer, the type and severity of anxiety should be determined before providing psychological or pharmacological treatment.¹⁰⁵⁻¹⁰⁷ The Australian Clinical Pathway recommends a stepped care model whereby patients should receive the minimum level of psychological treatment that is effective in treating their anxiety, and more intensive psychological treatment in combination with pharmacological treatment should be reserved for patients with severe anxiety.¹⁰⁶ Recently, three studies specifically trialled stepped care treatments.^{46,75,86} However, the treatment was ineffective for anxiety in two studies. Braamsee et al (2016) attributed this to low intervention uptake or low psychological distress at baseline (prevalence of elevated anxiety symptoms at baseline was only 6.5%).⁴⁶ Rissanen et al (2015) mentioned that the intensity of the initial step intervention (stress management education) may have been too low or too similar to easily accessible online information.⁸⁶ Moreover, both studies did not screen patients for anxiety or distress. The stepped care approach was genuinely conducted by Krebber et al (2016) and resulted in moderate amelioration of anxiety symptoms (ES: -0.38).⁷⁵

Conclusions

Study strengths

This analysis has several strengths including stringent selection of randomised controlled trials, exclusion of studies with small sample size, and detailed systematic review evaluation of the bias of each study using the Cochrane Risk of Bias (RoB) 2.0 form (Supplementary material 2). Our study provided evidence for factors associated with low intervention effects, which should be considered when planning future clinical trials.

Study limitations

Limitations include difficulties to extracting data on anxiety outcomes specifically which many studies did not report separately from overall distress. This may have resulted in some potentially relevant studies being excluded from the review. Second, studies published in non-English languages and unpublished research were excluded. Third, we excluded interventions focusing on fear of recurrence, pre-existing conditions or comorbid conditions such as pain.⁷ Fourth, we only estimated the ES using the immediate post-intervention outcomes and did not estimate the ES at different time intervals during follow-up. Therefore, we could not determine whether the benefit of psychological interventions was sustained or not.

Clinical implications

In conclusion, this review has highlighted that many clinical trials have provided psychological interventions to patients with minimal level of anxiety symptoms rather than following evidence-based treatment guidelines or focussing on patients with clinically elevated anxiety. Although meta-analyses indicated that the interventions were effective, the absence of screening in the design of most trials, alongside a relative paucity of evaluation of stepped-care intervention models is likely to have contributed to smaller ESs than may have otherwise been achieved. Given that most health systems operate in the context of constrained resource environments, future studies should follow

appropriate screening and assignment procedures, and test appropriate interventions including stepped-care models that are likely to be both effective and cost-effective.

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Conflict of interest statement

The authors have declared no conflicts of interest.

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†List references included in the systematic review and meta-analysis are presented in the Supplementary material 3.

Table 1: Sub-group analysis (Negative values represent greater reduction in anxiety symptoms) †

	Number of studies	Effect size [95% CI]	Heterogeneity (I ²) (%)
Overall effect size	51	-0.21 [-0.30, -0.13]	68
Sample characteristics			
1. Origin of participants			
Asia	11	-0.46[-0.65, -0.26]	58
Europe	21	-0.25[-0.38, -0.11]	75
Australia	6	-0.10[-0.23, 0.03]	0
North America	12	-0.02[-0.16, 0.12]	34
International	1	0.1[-0.13, 0.32]	-
2. Gender			
Male and female	20	-0.25 [-0.40, -0.10]	76
Female only	30	-0.19[-0.31, -0.08]	62
Male only	1	-0.13[-0.34, 0.09]	-
3. Type of cancer			
Mixed ¹	16	-0.30[-0.48, -0.13]	80
Melanoma	2	-0.22[-0.51, 0.06]	0
Breast	28	-0.17[-0.29, -0.06]	63
Other ²	3	-0.15[-0.50, 0.21]	65
Lung	2	-0.12[-0.37, 0.13]	0
4. Inclusion criteria to participate in the study			
Inpatient treatment	20	-0.40[-0.57, -0.23]	78
After treatment	10	-0.19[-0.31, -0.06]	28
Any cancer patients	6	-0.07[-0.21, 0.06]	0
Newly diagnosed	11	-0.06[-0.21, 0.09]	47
Palliative treatment	3	0.04[-0.17, 0.24]	21
Advanced stage	1	0.16[-0.19, 0.51]	-
5. Screening to measure anxiety and other			
Measure anxiety and depression using HADS ³	2	-0.58[-1.01, -0.15]	63
Provider reported distress without using screening tool	2	-0.40[-1.26, 0.46]	91
No/Not reported	41	-0.21[-0.30, -0.12]	63
Patient self-reported distress	1	-0.09[-0.41, 0.22]	-
Measure anxiety symptom- insomnia using DSM III ³	2	-0.05[-0.78, 0.68]	78
Measure psychiatric disorder using DSM III ⁴	2	-0.00[-0.21, 0.20]	0
Measure distress using distress thermometer ³	1	0.08[-0.13-0.29]	-
Intervention characteristics			
1. Type of intervention			
Relaxation	12	-0.53[-0.79, -0.26]	78

Counselling & other	2	-0.25[-0.65, 0.14]	43
Psychological	6	-0.24[-0.51, 0.03]	77
Psychosocial	6	-0.20[-0.50, 0.10]	78
Psycho-education	5	-0.18[-0.36, -0.01]	42
Supportive expressive therapy	4	-0.16[-0.35, 0.03]	0
Stepped care	3	-0.08[-0.40, 0.25]	61
Cognitive behavioural therapy	9	-0.08[-0.20, 0.05]	14
Psychotherapy	4	0.07[-0.09, 0.23]	0
2. Group/individual			
Individual	24	-0.32[-0.47, -0.18]	75
Group	25	-0.13[-0.24, -0.03]	58
Both	2	-0.07[-0.25, 0.11]	0
3. Delivery mode			
Face-to-face & self-delivery	7	-0.35[-0.61, -0.08]	73
Face-to-face	25	-0.27[-0.40, -0.14]	71
Face-to-face & telephone	9	-0.21[-0.41, -0.00]	65
Face-to-face & online	2	-0.11[-0.67, 0.46]	79
Online	3	-0.00[-0.14, 0.13]	0
Telephone	4	0.05[-0.17, 0.28]	29
Individual	1	0.07[-0.52, 0.65]	-
4. Change of anxiety score			
No change	1	-0.30[-0.72, 0.11]	-
Reduced	45	-0.24[-0.33, -0.14]	70
Increased	5	0.04[-0.12, 0.20]	0
5. Follow-up			
No	17	-0.24[-0.40, -0.09]	68
Yes	34	-0.20[-0.30, -0.09]	68
6. Type of provider			
Not reported	7	-0.41[-0.68, -0.14]	62
Psychologist & psychiatrist	2	-0.40[-0.78, -0.02]	37
Other ⁵	5	-0.33[-0.66, -0.01]	76
Only psychologist	11	-0.24[-0.50, 0.01]	80
Psychologist & nurse	3	-0.21[-0.45, 0.04]	52
Only nurse	8	-0.20[-0.34, -0.06]	29
Group ⁶	10	-0.10[-0.28, 0.08]	73
Psychologist & social worker	2	-0.01[-0.28, 0.26]	0
Dual professional ⁷	3	0.03[-0.26, 0.31]	41
7. Duration			
1-7 days	7	-0.55[-0.75, -0.35]	16
Less than 6 weeks	7	-0.48[-0.82, -0.15]	83
Not reported	2	-0.34[-1.25, 0.57]	93
6-11 weeks	16	-0.13[-0.29, 0.03]	69
More than 12 weeks	19	-0.08[-0.15, -0.01]	0
8 Dose/session			
Less than 30 min	8	-0.42[-0.75, -0.09]	81

30-60 min	14	-0.35[-0.53, -0.17]	70
Not reported	10	-0.10[-0.23, 0.03]	28
More than 60 min	19	-0.10[-0.22, 0.02]	60
9 Number of sessions			
1-3	9	-0.43[-0.69, -0.16]	76
Not reported	6	-0.21[-0.51, 0.09]	71
More than 8	15	-0.18[-0.33, -0.03]	69
4-8	21	-0.17[-0.30, -0.04]	64
10. Total hours			
Less than 4 hours	12	-0.44[-0.64, -0.25]	55
4-7 hours	7	-0.26[-0.56, 0.05]	84
More than 8 hours	20	-0.15[-0.28, -0.02]	70
Not reported	12	-0.10[-0.21, 0.02]	25
11. Experience of provider			
Not reported	7	-0.41[-0.68, -0.14]	62
Not specified ⁸	24	-0.29[-0.42, -0.16]	70
Yes	19	-0.08[-0.21, 0.04]	63
No	1	0.06[-0.39, 0.51]	-
12. Training of provider			
No	4	-0.28[-0.65, 0.08]	62
Not reported	25	-0.23[-0.36, -0.09]	66
Yes	22	-0.19[-0.32, -0.07]	73
13. Manual used in intervention			
No	1	-0.82[-1.22, -0.41]	-
Other ⁹	13	-0.31[-0.53, -0.09]	72
Not reported	13	-0.28[-0.48, -0.09]	73
Yes	24	-0.12[-0.22, -0.02]	55
14. Control condition			
Standard care	30	-0.28[-0.41, -0.16]	74
Minimal/Alternate intervention ¹⁰	15	-0.12[-0.24, 0.00]	40
Waitlist	6	-0.08[-0.30, 0.14]	62

†Sample and intervention characteristics were presented according to the highest negative effect size for intervention favour to the highest positive effect size of control favour.

CI- Confidence Interval, DSM- Diagnostic and Statistical Manual of Mental Disorders, HADS- Hospital Anxiety and Depression Scale.

¹Included two or more different types of cancer.

²Included prostate, thyroid and blood cancer.

³Formally screened patients for the presence of anxiety and anxiety symptoms using standard tools

⁴Did not screen for anxiety, but assessed anxiety using structured clinical interview as a part of baseline data collection procedure.

⁵Included doctor, therapist, research assistant, psychotherapist, pharmacist individually.

⁶Included three or more health care professionals.

⁷Included nurse and volunteer, psychiatrist and nurse, psychologist and health visitor.

⁸Not informed the experience of provider.

⁹Written instruction, workbook, booklet, leaflet, handouts, reading materials or audiotape.

¹⁰Minimal or alternate intervention means that the patients in the control group received only a component of the full intervention or received a different intervention (for example exercise) from the intervention group.

Table 2: Anxiety screening, assessment tools, intervention type and dose delivered in patients with cancer

Screening	Variables	Tool	Study	Intervention type	Intervention dose	Effect size†
<i>Studies that formally screened patients for presence of anxiety using standard tool</i>						
Screening (n=9)	Anxiety	HAM-A	Greer et al 2012 ⁶⁴	CBT	6 therapies for 8-week	++
	Anxiety & depression	HADS, CIDI	Krebber et al 2016 ⁷²	SCI	10-15-minutes for 10-week, 45-60 min for 6-week	-0.38
			Goerling et al 2011 ⁶²	Psychological	-	-0.82
		HADS	White et al 2012 ⁹⁵	Psychological	3-week	+++
			Moorey et al 1998 ⁷⁷	Psychological therapy	8-week	+++
			Moorey et al 2009 ⁷⁸	CBT	16-week	+++
	Anxiety symptoms-insomnia	DSM-III	Dirksen & Epstein 2007 ⁵⁴	CBT	1-2 hour for 10-week	-0.41
			Savard eta al 2005 ⁸⁷	CBT	90-minute for 8-week	0.34
	Distress	Distress thermometer	Owen et al 2017 ⁸⁰	Psychological	12-week	0.08
<i>Studies that screened for distress according to patient and provider report</i>						
Patient self-reported (n=2)	Anxiety symptoms (Cough/fatigue/breathlessness)	Yes, No	Yorke et al 2015 ¹⁰²	Psycho-education, counselling	12-week	+++
	Psychological complaint, e.g. anxiety		van der Spek et al 2017 ⁹¹	Psychotherapy	2-hour for 8-week	-0.09
Provider reported (n=2)	Anxiety & depression		Charalambous et al 2015 ⁴⁷	PMR	27-minute for 4-week	-0.82
	Psychological needs		Watson et al 2017 ⁹³	CBT	8-session for 12-week	0.06
<i>Studies that did not screened for anxiety, but assessed anxiety disorder using structured clinical interview as a part of baseline data collection procedure after enrolling patients into the study</i>						
Structured interview (n=4)	Anxiety disorder	DSM-III	Burton et al 1995 ⁴³	Psychotherapy	45-60-minute for 3-week	+++
			Kissane et al 2003 ⁷¹	Relaxation	50-90-minute for 20-week	0.03

Walker et al 1999 ⁹²	Relaxation	18-week	-0.10
Simpson et al 2001 ⁸⁹	Psychotherapy	90-minute foe 6-week	+++

CIDI- Composite international diagnostic interview, HADS- Hospital Anxiety and Depression Scale, DSM- Diagnostic and Statistical Manual of Mental Disorders, HAM-A- Hamilton Anxiety Rating Scale, CBT- Cognitive behavioural therapy, SCI- Stepped care intervention

†ES originated from forest plot (Figure 2). ††Greer *et al.*, (2012) study showed large effect size for intervention (ES: 0.84). †††Did not include in the meta-analysis.

Figure 1: PRISMA flow diagram of systematic review and meta-analysis

Figure 2: Forest plot of the effects of psychological interventions on anxiety in cancer patients (negative values favour the intervention- representing greater reduction in anxiety).

Figure 1: PRISMA flow diagram of systematic review and meta-analysis

Figure 2: Forest plot of the effects of psychological interventions on anxiety in cancer patients (negative values favour the intervention- representing greater reduction in anxiety).

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