Psycho-Oncology
Psycho-Oncology **25:** 400–411 (2016)
Published online 6 August 2015 in Wiley Online Library (wileyonlinelibrary.com). **DOI**: 10.1002/pon.3925

Psychological interventions for distress in adults undergoing haematopoietic stem cell transplantation: a systematic review with meta-analysis†

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†Research sponsored by Health Education East Midlands via the Trent Doctorate Programme in Clinical Psychology. The authors report no conflicts of interest.

Abstract

***Objectives*: To investigate the characteristics, methodology, quality, and efficacy of psychological interventions for distress in adult patients undergoing haematopoietic stem cell transplantation (HSCT).**

***Methods*: A systematic review of relevant studies was conducted using six databases with supplementary hand searching. Included studies employed an experimental or quasi-experimental design, interventions included at least one psychological component, and outcomes involved psychological distress in affective terms. Data were abstracted, and study quality was assessed using Cochrane Foundation criteria amended to include confounder and common factors control. Data were examined and synthesised using a narrative approach and meta-analysis.**

***Results*: Eleven articles for nine interventions met the inclusion criteria out of 11 741 abstracts. The studies varied in quality, general, intervention, and methodological characteristics while findings were mixed. Interventions tended to show better efficacy when incorporating a major psychological component involving cognitive behavioural or emotional processing methods with substantial interventionist input. However, this was also associated with methodological limitations and threats to internal validity such as poor confounder and common factors control. A meta-analysis yielded a small but significant pooled effect size estimate in favour of interventions with inconsequential heterogeneity. Risk of bias remained a concern.**

***Conclusions*: Psychological interventions may provide some benefit in alleviating distress in HSCT but conclusions remain tentative in light of methodological limitations and risk of bias. Further research is needed to evidence the individual contribution of intervention components and mechanism of change together with improving intervention efficiency and methodological quality.**

Received: 10 April 2015
Revised: 13 June 2015
Accepted: 7 July 2015

Background

Haematopoietic stem cell transplantation (HSCT) is a complex procedure aimed at a range of haematological and autoimmune illnesses and involves transfer of haematopoietic stem cells harvested either from the patient (autologous) or a matched donor (allogeneic) [1]. Over 45 000 individuals worldwide undergo the procedure annually often resulting in substantial benefits but the procedure is very intensive [1]. The initial stages often involve high doses of chemotherapy sometimes with radiation aiming at severe depletion of bone marrow cells and suppression of the immune system in preparation for stem cell infusion to restore haematological and immune systems [1]. The process can last several weeks involving very high levels of toxicity often in addition to previous chemotherapy, prolonged periods of isolation, and a range of debilitating side effects [1–3]. Physical side effects are often multiple with the greatest impact during the first 30 days and can include fatigue, disturbed sleep, weakness, nausea, pain, graft-versus-host disease (GVHD where donor immune cells attacks the patient's organs), and even death [1–3]. Long-term complications are also a concern such as elevated risk of mortality [4] and chronic health conditions with 20% of patients experiencing severe complications [5–7].

Psychological distress in HSCT and its sequelae

In light of the physical burden, it is not surprising that patients experience considerable psychological distress. Patients report a consuming effort to prepare and an ongoing struggle, describing the procedure as 'walk to hell and back' or 'really, really hard' [8, p. 404]. Studies in adult HSCT have observed considerable psychological distress, particularly during hospitalisation, with up to a quarter of patients meeting clinical criteria for anxiety and/or depression [3,9–13]. Following transplantation, psychological distress improves but can persist with up to 40% of patients experiencing depression and up to 30% anxiety even one year later [14].

Apart from psychological well-being, distress also appears to affect physical well-being and recovery although

research remains limited and correlational. Studies have observed associations between psychological distress and worse treatment adherence, reduced pain and symptom tolerance, longer hospital stay, and higher mortality [11,12,15]. In addition, stress has been associated with greater subsequent incidence of illness, harmful physiological changes, greater pain perception, suppression of the immune system, and higher risk of infections more generally [16]. In a procedure such as HSCT, which involves pain and substantial immune system recovery [1], distress may increase patients' vulnerability and impede the process.

The contribution of psychological intervention

The above research findings highlight the potential benefits of psychological intervention in alleviating distress in HSCT and supporting recovery. Research in the psychological needs of HSCT patients has indicated potential areas for intervention. Findings suggest that pretransplant avoidance, lack of professional emotional and informational input, and a threatening perception of the illness and future together with loss of agency often present in HSCT patients can predict higher distress and physical symptoms [17–22]. Conversely, optimism and self-efficacy have predicted improved physical and emotional functioning following HSCT [23]. These findings are also in line with the wider theoretical literature suggesting that illness appraisals and coping can play an important part in adjusting to health-related difficulties [24,25].

In spite of evidence indicating the potential of psychological intervention in HSCT, relevant research remains limited compared to related clinical areas and particularly cancer [26,27]. For example, psychological therapies with educational, cognitive-behavioural, or coping skills components have been shown to facilitate physical and emotional functioning, improve immune function, and enhance survival in cancer patients [26–28]. Such reviews of the literature have also been helpful in highlighting limitations of existing research such as poor methodology in participant selection, limited use of blinding, and non-equivalent control interventions. This is important to not only guide clinical judgement but also identify future research needs. However, while psychological interventions have begun to emerge in HSCT [e.g., 29,30], such a resource does not exist at present. In light of marked discrepancies in outcomes and methods [e.g. 29,30] this can be problematic as lack of clarity can misguide and hinder both clinical and research progress. To address this need, the present project aims to conduct a systematic review of the literature and meta-analysis to answer the following questions:

1. What are the characteristics and efficacy of psychological interventions aiming at alleviating psychological distress in adult HSCT recipients?
2. What is the methodology and quality of the research evidence?
3. What participant, methodological, and intervention characteristics are common in studies demonstrating positive effects?

Methods

This review follows standardised guidelines of reporting systematic reviews and meta-analyses [31,32]. The review protocol was finalised following two peer review meetings undertaken within the department. Consistent with the aims of the review, the following eligibility criteria were applied:

- The target population included HSCT patients.
- Patients were at least 18 years old.
- Psychological interventions were those that had explicitly included at least one component relevant to psychological theory, for example, coping, emotional processing, appraisals, and so forth. This excluded solely physical (including relaxation), art, occupational, medical interventions, or hypnosis.
- Outcomes were evaluated using at least a quasi-experimental design. Uncontrolled designs such as pre and postintervention comparisons were not included because of lack of control for maturation and concurrent effects [33] including that of undergoing HSCT.
- Outcomes explicitly included psychological distress defined in affective terms (e.g. anxiety, depression, negative affect, etc.).

A computerised search of major psychological, medical, and nursing literature and doctoral theses databases with a moderate degree of overlap was conducted starting at 1959 where possible as the year of first transplantation [1,34,35]: PsycINFO (1959 to December Week 4, 2014), MEDLINE (1959 to December Week 4, 2014), EMBASE (1974 to 2014 Week 52), CINAHL (1982 to December 30, 2014), and ProQuest Theses (1959 to December 30, 2014). Search terms were identified from a range of sources including systematic reviews of psychological interventions and distress in HSCT and analogous populations [14,26–28] and during preliminary scoping of the literature [e.g. 29,36,37], and relevant subject headings via the databases. Details of the search strategy are available online in Appendix A.

Following database screening, the first 300 results of Google Scholar (until December 30, 2014, listed by relevance) were also examined together with hand searching tables of contents of the specialist journals Bone Marrow Transplantation, Psycho-Oncology, and Journal of Psychosocial Oncology for additional references. Reference

DOI: 10.1002/pon

lists of all identified publications were also screened. An attempt to trace further unpublished research was made by contacting authors of research identified by these means (e.g. indexed conference abstracts) and the European Group for Blood and Marrow Transplantation. Two of the authors undertook all screening procedures independently. A flowchart of the procedure is presented in Figure 1. Data relating to the research questions and study quality were extracted by two of the authors independently (details of abstracted data are available online in Appendix B).

As use of composite scales with overall study quality ratings has not been empirically supported [38], a component study quality assessment was employed consistent with Cochrane Foundation practice [39]. This examined selection (random assignment and allocation concealment), performance (blinding of participants and personnel), detection (blinding of outcome assessors), attrition (intention to treat analyses), and reporting biases (incomplete reporting of outcome data). Two further components were considered. Control for confounding variables was assessed via evidence that groups were comparable (particularly in smaller studies where randomisation may not have been successful) or appropriate statistical control. Influence of common factors (therapeutic relationship, increased contact, or other factors not specific to the intervention [40]) was assessed via the presence of some attentional equivalent in the control group. Two of the authors undertook the rating independently and discrepancies were resolved via consensus. Further details on adjustments to the Cochrane criteria are available online in Appendix B.

For the quantitative synthesis regarding efficacy, mean pre and postintervention mean change differences were calculated and standardised for each group. Signs were reversed so that a positive sign always reflected improvement. Where studies provided data for more than one relevant outcome, these were pooled to form a mean effect size per study. Data were then entered in a meta-analysis to estimate the overall weighted intervention effect of pre/post change difference between the two groups. Data were pooled using the generic inverse variance method with fixed effects where heterogeneity was not significant and Hedges' g representing standardised mean differences [35,41–43]. Where multiple postintervention data were available, data from the time point closest to the end of the intervention were entered first followed by sensitivity analysis using data from the final follow-up. Effect sizes were interpreted using Cohen's [44] guidelines with 0.2 considered small, 0.5 medium, and 0.8 large. Heterogeneity was examined visually and statistically (Chi^2 test [41]). The I^2 statistic quantified heterogeneity with values up to 40% representing relatively inconsequential, 30%–60% moderate, 50%–90% substantial, and 75%–100% considerable heterogeneity [41]. Publication bias, primarily because of underreported studies with null effects [35], was assessed via visual inspection of the funnel plot. Review Manager (Version 5.3) software [45] was employed with *alpha* level of significance set at 0.05 (0.10 for heterogeneity tests [35]).

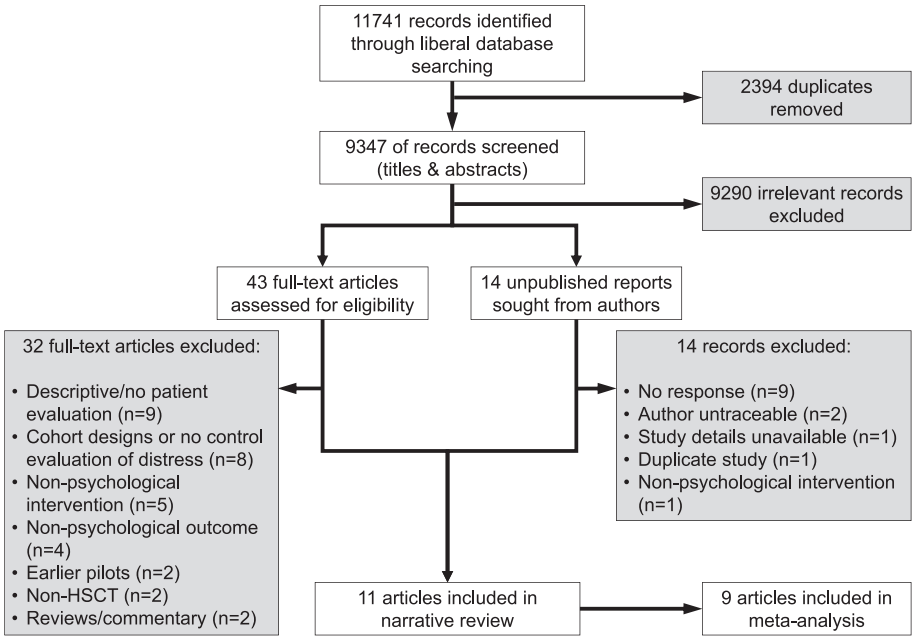


Figure 1. Flowchart of the selection of studies investigating psychological interventions in haematopoietic stem cell transplantation

DOI: 10.1002/pon

Results

Included studies

Eleven studies met the inclusion criteria (Figure 1). Of these, 10 were published in peer-reviewed journals [29,30,46–53], and another [54] was an unpublished doctoral thesis. One study was in Spanish [46] and translated by the authors. Details of included studies are presented in Table 1 with overall effects in Figure 2. Hand searching and contact with the European Group of Blood and Marrow Transplantation did not reveal any additional studies.

General characteristics

The 11 studies described and evaluated nine interventions since 1998. Seven studies (six interventions) were from the United States of America [29,48,49,51–54] and four (three interventions) were from European countries [30,46,47,50]. All samples consisted primarily of white participants. Haematological malignancies (lymphoma, myeloma, and leukaemia) were the most frequently targeted disease with only two interventions for breast cancer patients. Two thirds of the interventions did not discriminate between allogeneic and autologous transplant patients.

Intervention characteristics

Interventions varied in timing, intensity, delivery, content, and the extent to which they targeted solely psychological distress or additional areas of functioning. Seven intended to alleviate distress following transplantation of which three also targeted distress during the procedure. Another two focused on distress during transplantation only. Regarding outcomes, only two interventions [29,46] were aimed solely at psychological distress. The others had a broader scope also aiming at improving non-psychological functioning such as physical or social quality of life which were not in the focus of the present review.

Seven interventions incorporated Cognitive Behaviour Therapy (CBT) methods (see [55] for an overview of such methods) with emphasis on cognitive components and two [47,51] employed other approaches. CBT-based components included informational input or psychoeducation regarding various aspects of distress (e.g. stress) or cognitive processes (e.g. cognitive biases), cognitive restructuring, and coping skills training often with problem solving. One intervention [29] also included a behavioural component of graded exposure to traumatic memories. Relaxation and/or exercise featured in three of the interventions [29,30,48–50,53] alongside psychological input and formed a major component in two interventions [30,50,53] which incorporated considerably less psychological input compared to others. The interventions using components other than CBT-based were less problem- and more emotion-focused (active approach) aiming at fostering emotional processing via expressive means. Overall, five interventions involved a substantial psychotherapy component [29,46–49,54] with the remainder being less specialist (e.g. psychoeducation with relaxation, task instructions, etc.).

All nine interventions were delivered individually and for seven this was face to face during admission. One [48,49] also had some remote input and the remaining two were delivered via telephone several months following HSCT [29,51]. Interventions also involved varying degrees of guided and self-directed work with five incorporating both [29,30,48–51,53] and only two consisting primarily of self-directed work [52,53]. Self-directed components included relaxation, cognitive or coping skills practice, and expressive writing and were supplemented by printed material and/or verbal instruction. Four interventions involving substantial psychotherapy input [29,46–49,54] were delivered by healthcare professionals or specifically trained researchers. Less specialist interventions were facilitated by site staff or researchers. Generally, interventions with substantial psychotherapy input were delivered over four and up to fifteen sessions while delivery was more frequent for others, often over several weeks, and mostly self-directed. Session length began at approximately 20 min and rarely exceeded an hour.

Methodological features

Most studies were RCTs comparing the intervention to a control group with only two using a quasi-experimental design (non-equivalent controls). All studies examined longitudinal change with all but one [46] including a baseline measurement prior to administering the intervention. Otherwise, methodology varied in sample size, type of control, outcomes, follow-ups, data analysis, and confounder control.

Sample sizes per group ranged between those appropriate for pilot with approximately ten participants [46,52,54] to a large RCT with an excess of 300 participants while the remainder [29,30,47–51] were modest with 21 to 91 participants. Seven studies recruited consecutively prior to HSCT, two [46,52] did not report sufficient information, one [29] screened participants for high distress (primarily trauma), and another [51] for at least mild survivorship difficulties (including distress). In seven studies control groups were treatment as usual (TAU), in one [29] patients received no care, and in another [53] half of controls also engaged in regular exercise. In a further two studies [47,51] comparison groups received input in addition to TAU including components of the intervention, attentional control, or a delayed intervention.

Regarding measurements and outcomes, seven of the nine interventions were evaluated near their completion. Follow-ups (between three and twelve months) were

DOI: 10.1002/pon

Table I. Summary of studies examining the efficacy of psychological interventions to alleviate distress in HSCT

Sources and design	Disease, transplant, and follow-up	n_i/n_c	Intervention	Comparison	Relevant outcomes: Target	Relevant outcomes: Key findings/ comments
Interventions timed to target distress during HSCT only						
Allocca 1998 [54]	Breast cancer	10/10	Components: Problem and cognitive biases identification, cognitive techniques (restructuring, problem-solving, etc.), review and future planning	TAU	Anxiety and Depression (HADS)	Significant overall improvement in anxiety and psychological well-being but no significant differences between groups
Quasi-experiment			Delivery: Individual (face to face) by CBT-trained nurse specialist		Psychological well-being (QOLS)	Non-significant increase in depression in intervention group
			Timing and intensity: Start within 48 h post-transplant 5×, approx. 35 min, over 5–10 days.			
Jarden, Baadsgaard 2009 [30]; **Jarden, Nelausen 2009** [50]	79% haem. malignancy	21/21	Components and delivery: CBT-based psychoeducation, exercise, and relaxation training	TAU	Anxiety and Depression (HADS)	No significant effects
RCT	Allogeneic		Individual exercise (face-to-face) by researcher and self-directed relaxation		Emotional functioning (QLQ-C30)	
	Follow-up: 6 months		Timing and intensity: During admission 5× pw psychoeducation and exercise, 2× pw relaxation		**Affective functioning** (SCT-SAS)	Significantly lower distress and less severity in intervention group
Interventions timed to target distress following HSCT only						
DuHamel 2010 [29]	71% haem. malignancy	47/34	Components: CBT for trauma—education, self-monitoring and cognitive restructuring, graded exposure, communication skills training, and relaxation training	Assessed only	Trauma (PCL-C)	Total and intrusive thoughts scores improved similarly in both groups
RCT	Mixed					
	Follow-up: 3–12 months				**Distress** (BSI)	Faster improvement for intervention group
					Trauma Diagnosis (CAPS)	Diagnosis less likely for intervention group at end of therapy
			Delivery: Individual (telephone) by trained postdoctoral fellows and self-directed practice			Retained throughout follow-up
			Timing and intensity: 10–16 wks post-HSCT 10×, approx. 1 h			Possible common factors effect
Frick 2006 [47]	92% haem. malignancy	88/91	Components and delivery: Daydream imagery for emotional processing	Delayed timing (6–12 months postdischarge)	**Emotional functioning** (QLQ-C30)	Significantly better improvement for early intervention group; potentially explained by increased disease severity
RCT	Autologous		Individual (face-to-face) by researcher (trained psychotherapist)			Possible floor effects for late intervention group
			Timing and intensity: 1–6 months postdischarge 15×, 15–30 min			
Rini 2014 [51]	87% haem. malignancy Mixed	69/59–69	Components and delivery: Expressive helping (expressive writing to help prospective patients)	1. Expressive writing only	**Distress** (BSI)	Lower in expressive helping group compared to peer helping and neutral writing in participants with high but not low survivorship difficulties.
RCT	Follow-up: 3 months		Instructions only (telephone) by study interviewer, otherwise self-directed	2. Writing to help peers only		
			Timing and intensity: 9 months to 3 years post-HSCT 4× weekly, 20 min	3. Neutral writing		Incomplete analysis and possible Type II error. Expressive helping group appeared to have lower baseline distress also but control for this was questionable while published data indicated null effect.

(Continues)

DOI: 10.1002/pon

Table 1. *(Continued)*

Sources and design	Disease, transplant, and follow-up	n_i/n_c	Intervention	Comparison	Relevant outcomes: Target	Relevant outcomes: Key findings/ comments
Trask 2003 [52]	n/k	26 in total	Components and delivery: Workbook psychoeducation—coping, problem-solving, and CBT principles Instructions only (face to face) by author, otherwise self-directed Timing and intensity: Discharge onwards, self-directed	TAU	Distress (BSI) **Anxiety** (STAI) Coping (WOC)	No significant effects 2 and 6 months postdischarge 45% of intervention participants had not utilised workbook 1 month postdischarge. Anxiety was significantly lower in those who did 2 and 6 months postdischarge compared to those who did not Unclear influence of individual differences on adherence
RCT						
Interventions timed to target distress during and following HSCT						
de Linares 2007 [46]	Haem. malignancy	10/6	Components: Informational, practical coping skills, stress management (psychoeducation and cognitive restructuring), and communication with family	TAU	**Anxiety and Depression** (HADS)	Fewer clinical criteria for anxiety and depression in intervention group on transplant day and 100 days later
Quasi-experiment	Follow-up: 100 days		Delivery: Individual (face to face) Timing and intensity: 4× since and during admission			No baseline measurement for controls
Gaston-Johansson 2000; **2013** [48,49]	Breast cancer Autologous	52/58	Components: Coping—psychoeducation, cognitive restructuring education and coping, coping skills training, and relaxation with guided imagery training	TAU	Anxiety (STAI) Depression (BDI)	No significant effects
RCT	Follow-up: 1 year	38/35	Delivery: Individual (1st session face-to-face then computer/telephone) by social worker, nurse, researchers, and self-directed practice Timing and intensity: 2 wks prior to then during admission and top-up 3 months later 5× (3× during admission) 1st 1.5 h, then 20 min		**Psychological functioning** (QOLI-CV)	Higher in relation to intervention Possible overfitting: limited baseline outcome control
Jacobsen 2014 [53]	89% haem. malignancy	356/355	Components and delivery: Stress management with relaxation, imagery, and coping elements (50% also engaged in exercise)	TAU (50% also engaged in exercise)	Psychological functioning (SF-36)	No significant effects 100 days and 6 months posttransplantation
RCT	Mixed		Individual (face-to-face) by trained site personnel and self-directed Timing and intensity: Since admission, ongoing 3× instruction (introduction and reinforcement 30 and 60 days post-HSCT) otherwise self-directed.			Intervention adherence was unclear

Note. Sources are listed by name of first author with studies and outcomes supporting intervention benefits in bold lettering. Follow-up period mentioned where available. n_i/n_c = intervention and comparison group sample sizes respectively; RCT = randomised clinical trial; HSCT = haematopoietic stem cell transplantation; haem = haematological; CBT = Cognitive-Behavioural Therapy; #x = number of sessions (e.g. 2× = 2 sessions); pw = per week; TAU = treatment as usual; HADS = Hospital Anxiety and Depression Scale; QLQ-C30 = The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; SCT-SAS = Stem Cell Transplantation Symptom Assessment Scale; wks = weeks; PCL-C = Posttraumatic Stress Disorder Checklist-Civilian Version; BSI = Brief Symptom Inventory (global scale only); CAPS = Clinician-Administered Posttraumatic Stress Disorder Scale for Diagnostic and Statistical Manual for Mental Disorders, 4th edition; min = minutes; n/k = not known; QOLS = Quality of Life in Bone Marrow Transplant Survivors, City of Hope National Medical Centre Questionnaire; WOC = Ways of Coping; STAI = State-Trait Anxiety Inventory; BDI = Beck Depression Inventory; QOLI-CV = Quality of Life Index-Cancer Version; SF-36 = Medical Outcomes Short-Form 36 (version 2.0).

reported for five interventions. Psychological distress was assessed with measures of anxiety, depression, posttraumatic stress, affective functioning, and general distress or psychological well-being. Five of nine interventions included more than one relevant outcome measure. Only one study assessed process change (coping, [52]). All

DOI: 10.1002/pon

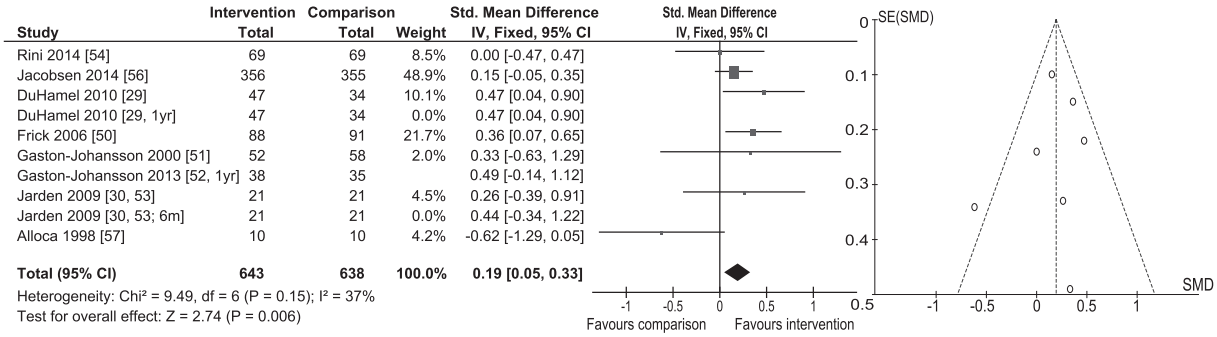


Figure 2. Forest plot of standardised pre/post change comparison between intervention and control groups with funnel plot for the evaluation of publication bias. Studies are listed in increasing risk of bias. Overall, there was a small pooled effect size estimate with non-significant heterogeneity. Follow-up effects were calculated where available but not included in this estimate, as shown above, with sensitivity analysis yielding comparable results. Std. = standardised; IV = inverse variance; CI = confidence intervals; m = months; yr = year

measures were standardised with acceptable validity and reliability and were self-reported with the exception of a clinician-administered trauma scale in one study [29].

Regarding analyses, multiple regression, analysis of variance, or equivalent non-parametric techniques were conducted as appropriate except for four studies of which three [30,46,53] reported pairwise comparisons only and one [51] reporting an incomplete analysis. Where groups were found not to be equivalent in demographic, disease-related, or baseline information, most studies attempted statistical control except two [46,52] of which one [46] also failed to measure baseline scores for controls. With the exception of three studies [48,49,53], sufficient information regarding adherence was also provided (attendance, logbooks, etc.). Only one study [52] demonstrated poor adherence (45%) but this was factored in the analysis.

Study quality

The quality of the included studies varied considerably. Figure 3 provides a summary of component ratings. Overall, the rating method appeared to differentiate between the types and degrees of bias across studies. Regarding selection bias, most studies were RCTs with low risk, but this was limited by having neglected allocation concealment, which all but one study did not comment on or address.

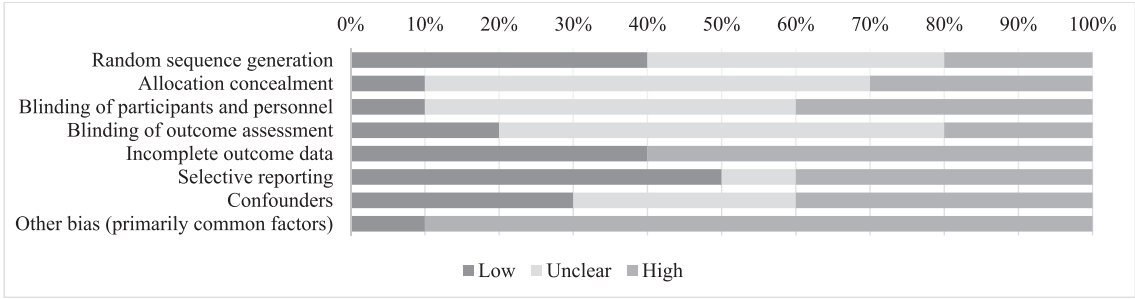
Performance, detection, and common factor bias were also poorly addressed. Regarding the first, four studies exhibited high risk of bias but this was less clear for five studies where the degree of interventionist involvement with TAU was uncertain, some control participants received other types of intervention, the success of participant blinding was uncertain, or there was insufficient information. Detection bias was high in two studies where the investigator was the outcome assessor but had been better addressed in two studies where the assessor was either blind or independent to the study. The remaining studies did not comment on assessor blinding or bias was unclear based on their method. Common factor bias was only addressed by one study [51] including an active form of intervention. This type of bias was particularly problematic for another study [29] where controls received no therapeutic attention and results from the same project published elsewhere [56] observed a therapeutic relationship effect.

Attrition, reporting, and confounder biases were moderately addressed. Intention to treat analyses in approximately half of the studies indicated suitable attrition control, but this was neglected in the remainder. Approximately half of the studies appeared to report outcomes as planned, outcomes were comparable to previous studies by the authors, or distress outcomes were a subset of the intervention targets thereby involving less risk of reporting bias. However, four studies failed to provide data for some of the administered outcome measures discussed in the method or measures used in preceding work, which questioned the validity of reporting. Finally, three of eleven studies demonstrated appropriate confounder control. This was unclear for three studies where controls did not appear statistically valid (overfitting and incomplete analysis/Type II error). High risk of bias in the remaining studies included poor evidence of control for individual differences [29,46,54] or no baseline control [46,47].

Key findings

Main results are summarised in Table 1 and overall effect sizes in Figure 2. Seven of the eleven studies (seven of nine interventions) reported some benefits including lower distress, improved emotional functioning, and less post-traumatic symptomatology. Of these, five were evaluated in the longer-term (three to twelve months) showing enduring benefits. One of these [49] had not been effective during transplantation suggesting a possible delayed effect or lack of power although this discrepancy may be because of questionable baseline outcome control at follow-up. In addition, three interventions appeared effective in HSCT patients that were more distressed because of close proximity to the time of transplantation [47] or relevant

DOI: 10.1002/pon



	Rini 2014 [54]	Jacobsen 2014 [56]	DuHamel 2010 [29]	Frick 2006 [50]	Gaston-Johansson 2000 [51]	Gaston-Johansson 2013 [52]	Jarden 2009 [30, 53]	Alloca 1998 [57]	Trask 2003 [55]	de Linares 2007 [49]
Random sequence generation	L	U	L	L	U	U	L	H	U	H
Allocation concealment	L	U	U	U	U	U	H	H	U	H
Blinding: participants & personnel	L	U	H	H	U	U	H	U	U	H
Blinding of outcome assessment	L	U	L	U	U	U	H	H	U	U
Incomplete outcome data	H	L	L	H	H	H	L	L	H	H
Selective reporting	U	L	L	L	H	H	L	L	H	H
Confounders	U	L	H	H	L	U	L	H	U	H
Other bias (primarily common factors)	L	H	H	H	H	H	H	H	H	H

Figure 3. Overall summary and details of component quality ratings for risk of bias for the studies included in the systematic review. Studies are ordered in increasing risk of bias from left to right. L = low risk of bias; U = unclear risk of bias; H = high risk of bias

screening [29,51]. However, the result reported as significant in one of these [51] did not reflect published statistical data which indicated a null effect (cf. Figure 2) with the significant outcome likely reflecting a statistical artefact; therefore, it was treated here as not significant. No study reported economic outcomes.

Notwithstanding some intervention benefits, results appeared mixed both between and within studies. It was notable that none of the five interventions involving more than one outcome measure resulted in benefits on all of them indicating potentially inflated Type I error. One study [54] also reported a (non-significant) effect in favour of the control group. The authors explained this as increased awareness and acceptance of distress in the intervention group but this had not been observed in any other study with a similar therapeutic approach and design and therefore did not appear plausible. This was also the smallest study in the group and demonstrated poor controls in most quality domains. The resulting lack of precision questions the reported effect.

Differences in findings did not appear consistently related to many study characteristics. These included general characteristics, some intervention characteristics (use of CBT, and mode of delivery except for the interventionist), and some methodological features (screening for distress, design, outcome measure, and pairwise versus more appropriate statistical analyses). High risk of selection, detection, attrition, and reporting bias did not appear consistently related to effects either. Notably, the same was observed in relation to timing of the intervention to target distress during HSCT, following HSCT, or both.

Other study characteristics and risks of bias appeared related to results but were generally confounded. With one exception [54], interventions with more intensive psychotherapy components and substantial interventionist input [29,46,47,49,52] appeared to yield larger and more frequently significant effects compared to those where delivery was less psychotherapy-specific and more self-directed (e.g. instructions, workbook, physical methods as main component, etc.). This included both studies with psychological distress as sole target. Poorer adherence particularly in self-directed studies may have contributed to this, as evidenced in one study [52].

It was notable that the five interventions with substantial psychological input were among six [29,46,47,49,51,52] of the seven studies reporting intervention benefits whose results exhibited considerable threats to internal validity. These were because of either poor confounder control (individual differences, baseline outcomes) or possible influence by common factors. Notably, the study demonstrating the largest effect and the only study involving relatively highly distressed patients was also the only one with no care as control [29]. This was in contrast with the only study including at least attentional control [51] which yielded a null average effect (in spite of some screening for higher distress). In addition, all studies with high risk of performance bias reported some significant intervention effects. Overall study quality appeared unrelated to effect size (Figure 2) but studies with lower risk of bias generally appeared to involve larger samples and yield smaller confidence intervals.

Meta-analysis

A meta-analysis was conducted with data from nine of the eleven studies. The effect sizes of two studies [30,50] were

DOI: 10.1002/pon

averaged as they referred to the same project. All data were published except for one study [53] for which data were obtained via the authors. Two studies were not included following no response to the data request [52] or because of untraceable contact details [46]. Available data from the more distressed subgroup were included for one study [51] as more representative of the patients that might be offered psychological input in practice. Only the attentional control group was considered from the same study, as it did not involve any of the components of the intervention. Results are presented in Figure 2.

There was a small but significant pooled effect size estimate 0.19 [0.05, 0.33] with relatively inconsequential and non-significant heterogeneity, $Chi^2 = 9.49$, $df = 6$, $P = 0.15$, $I^2 = 37\%$. The sensitivity analysis yielded comparable results. The heterogeneity appeared because of the study by Allocca [54] with I^2 decreasing to 0% when this study was removed. This outlying effect may have been because of methodological limitations in this small study. The pooled estimated of the studies that screened for distress appeared larger compared to those that did not but was not significantly different from zero and the paired difference did not reach significance, 0.26 [−0.06, 0.57] versus 0.18 [0.02, 0.33], $Chi^2 \geq 0.11$, $df = 1$, $P \geq 0.66$.

The loss of two studies because of data unavailability may have introduced bias in the meta-analysis. However, both were small with high risk of bias overall; therefore, their exclusion may have resulted in a more accurate and valid pooled estimate. The funnel plot (Figure 2) appeared approximately symmetrical (visual inspection) and even suggested a potential absence of small studies showing a positive intervention effect primarily because of the presence of Allocca's study [54]. However, this was the only unpublished report in the group thereby highlighting a potential risk of publication bias.

Conclusions

The present review examined the efficacy, characteristics, and quality of psychological interventions to alleviate distress in HSCT. An emerging body of literature was identified consisting of RCT (including pilots) and quasi-experimental designs. Eleven studies were identified for nine interventions and the evidence suggested some benefits were maintained up to a year posttransplantation. Results varied and multiplicity of outcome measures indicated lack of clarity but a meta-analysis revealed some yet limited overall benefits. A range of methodological limitations were also present suggesting a need for cautious interpretation.

Interventions were timed to target distress during HSCT and up to nine months postdischarge with diversity in terms of therapeutic modality, components, format, intensity, and delivery. Most interventions incorporated CBT-based components or involved active emotional processing. All were supported by a professional in varying degrees and most involved some self-directed work. These were similar to interventions identified in other relevant clinical populations and more widely in health psychology [26,57–63] though there was a notable absence of group delivery.

Results appeared homogenous overall, and the small number of studies limited conclusions but some patterns emerged. Interventions involving substantial psychological and interventionist input tended to be more efficacious compared to those with less psychological or more self-directed focus. However, this was confounded with methodological limitations and potentially adherence, while the only unpublished study was contradictory [54]. This may indicate possible publication bias although the study's limitations also suggested potential imprecision. Other characteristics did not appear consistently related to efficacy in light of small samples including whether interventions were timed and intended for distress during HSCT, following HSCT, or both.

The small pooled effect size estimate was comparable and often higher than similar contemporary interventions in other cancer populations when assessed with analogous measures of distress [57,59]. However, efficacy was generally lower than those reported in similar research in other illnesses such as diabetes [60] and coronary heart disease [62]. Possible floor effects may have contributed to attenuated efficacy, as studies did not generally limit recruitment to patients with higher distress (although the two studies that screened for distress did not appear more efficacious). Lack of screening has been consistently observed in cancer literature more generally [64–66] although it is also relatively common in other illnesses [e.g. 60–63]. Its effects can prove misguiding when evaluating interventions and limit external validity thus highlighting a need for routine subgroup analyses and better screening where possible. The difference in effect size could also reflect the unique needs and many uncontrollable challenges faced by HSCT and other cancer patients [27].

Mechanism of change

Support of the efficacy of interventions involving CBT-based or active emotion processing components is consistent with the HSCT literature highlighting avoidance coping, appraisal of HSCT as threat, or loss of self-efficacy as predictors of distress [17–21]. It is also supported by the wider theoretical literature of adjustment

DOI: 10.1002/pon

to health-related difficulties indicating that more benign appraisals, greater sense of control, and approach versus avoidance coping are considered important predictors of adaptation [24,25]. The interventions aimed to address these in various ways, for example cognitive restructuring and psychoeducation for appraisals (e.g. [29,46,48]), coping skills (e.g. [48,54]), or emotional acceptance and processing (e.g. [47]). Relaxation, on the other hand, may reflect avoidance coping potentially contributing to smaller effects when used as a primary component (e.g. [53]).

These considerations are plausible but it was not possible to establish the change mechanisms. There are three reasons for this. First, the majority of interventions incorporated more than one component but were assessed as a whole. Second, with one exception [52], no study employed a process measure and even that study did not examine the relationship between process and outcome. Third, lack of control for common factors limited the present body of evidence almost in its entirety leaving open the possibility that reductions in distress may have reflected the influence of the therapeutic relationship, increased input, or other factors other than the intervention content.

In light of these considerations, several methodological improvements could enhance intervention studies in the field. These could include process change measurements, experimental within-subjects control, and between-subjects control equivalent in interventionist attention. Multiple components with unclear benefits also pose an ethical issue in a population that is already burdened considerably which may contribute to poor outcomes. In a climate of economic austerity, this may also result in inefficient use of resources particularly for individual interventions. Therefore, it is important to improve intervention efficiency aiming at highest impact with fewest components. Delivery in a group format may also be helpful in reducing both burden and economic impact.

Quality of the evidence

The method of assessing quality appeared to capture the diversity of risk of bias together with some meaningful findings, for example, larger studies demonstrating lower risk of bias. However, lack of statistical analyses because of the small number of studies limited conclusions. In spite of the majority of studies classed as RCTs the quality assessment revealed several areas of weakness relating to allocation concealment, common factors, detection, and performance bias although the latter is inherent in delivering psychological interventions. While there was little variation in common factors ratings, the inclusion of this component was critical in evaluating the body of evidence and conclusions. Largely insufficient information on allocation and blinding highlighted a much neglected area in the literature and a need for better control and explicit reporting. The other areas of bias appeared less problematic but could improve further. Overall, most information was from studies at unclear or high risk of bias which lowers confidence in the evidence.

Limitations

The review employed a comprehensive search strategy using six databases including theses and was supplemented by manual searches to maximise retrieval. However, the process was undertaken by two individuals and involved subjective judgement at different stages, for example, identifying publications, abstracting data, rating study quality, and analysis including visual inspections of distributions of effects and results. It follows that it is possible to have missed studies or data and alternative analyses by different individuals could yield different results.

A major limitation arose from a relative lack of studies. This may not be surprising in light of the many barriers to running such studies such as physical burden, potential difficulties with accessing services, mortality, and so forth, but the small number restricted many analyses to visual inspections. Together with variability in interventions, methods, outcomes, methodological limitations, and risk of bias this made the results difficult to interpret and the conclusions regarding efficacy and study characteristics associated with it tentative. Lack of power also indicated that the pooled effects might not be genuine while there was also a possibility of publication bias in spite of an effort to include unpublished studies. Finally, as studies were of western origin with primarily white participants, it is unclear whether findings would generalise to individuals from different backgrounds.

In conclusion, results suggested a potential albeit small benefit of psychological interventions for distress in HSCT particularly when involving a major psychological component such as CBT or emotional expression together with substantial interventionist input. Further research could examine individual components and process change together with developing interventions that are more efficient. Conclusions remain tentative in light of methodological limitations and threats to internal validity such as lack of control for common factors, high risk of bias, and possible publication bias. Future studies could address methodological limitations and improve reporting in order to increase confidence in the evidence and benefit clinical practice.

Conflict of interest

The authors have declared no conflicts of interest.

DOI: 10.1002/pon

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Supporting information

Additional supporting information may be found in the online version of this article at the publisher's web site.

Appendix A: Search strategy
Appendix B: Data abstraction