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

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PSYCHOLOGICAL INTERVENTIONS FOR DISTRESS IN ADULTS UNDERGOING HAEMATOPOIETIC STEM CELL TRANSPLANTATION: A SYSTEMATIC REVIEW WITH META-ANALYSIS

Short title:
Systematic review of psychological interventions for distress in HSCT

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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 11741 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.

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 judgment 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 due to lack of control for maturation and concurrent effects [37] 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, 33, 34]: 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, 35, 36], 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 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 [43]) 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 [34, 44, 45, 46]. 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 [47] guidelines with 0.2 considered small, 0.5 medium, and 0.8 large. Heterogeneity was examined visually and statistically

(Chi^2 test [44]). 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 [44]. Publication bias, primarily due to underreported studies with null effects [34], was assessed via visual inspection of the funnel plot. Review Manager (Version 5.3) software [48] was employed with *alpha* level of significance set at 0.05 (0.10 for heterogeneity tests [34]).

Results

Included studies

Eleven studies met the inclusion criteria (**Error! Reference source not found.**). Of these, ten were published in peer-reviewed journals [29, 30, 49-56] and another [57] was an unpublished doctoral thesis. One study was in Spanish [49] 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, 51, 52, 54-57] and four (three interventions) were from European countries [30, 49, 50, 53]. 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, 49] 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 [58] for an overview of such methods) with emphasis on cognitive components and two [50, 54] 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, 51-53, 56] alongside psychological input and formed a major component in two interventions [30, 53, 56] 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, 49-52, 57] 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 [51, 52] also had some remote input and the remaining two were delivered via telephone several months following HSCT [29, 54]. Interventions also involved varying degrees of guided and self-directed work with five incorporating both [29, 30, 51-54, 56] and only two consisting primarily of self-directed work [55, 56]. 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, 49-52, 57] 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 minutes 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 [49] 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 [49, 55, 57] to a large RCT with an excess of 300 participants while the remainder [29, 30, 50-54] were modest with 21 to 91 participants. Seven studies recruited consecutively prior to HSCT, two [49, 55] did not report sufficient information, one [29] screened participants for high distress (primarily trauma), and another [54] 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 [56] half of controls also engaged in regular exercise. In a further two studies [50, 54] 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 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, [55]). All 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, 49, 56] reported pairwise comparisons only and one [54] 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 [49, 55] of which one [49] also failed to measure baseline scores for controls. With the exception of three studies [51, 52, 56], sufficient information regarding adherence was also provided (attendance, logbooks, etc.). Only one study [55] 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 [54] 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 [59] 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 & incomplete analysis/Type II error). High risk of bias in the remaining studies included poor evidence of control for individual differences [29, 49, 57] or no baseline control [49, 50].

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 posttraumatic symptomatology. Of these, five were evaluated in the longer-term (three to twelve months) showing enduring benefits. One of these [52] had not been effective during transplantation suggesting a possible delayed effect or lack of power though this discrepancy may be due to questionable baseline outcome control at follow up. In addition, three interventions appeared effective in HSCT patients that were more distressed due to close proximity to the time of transplantation [50] or relevant screening [29, 54]. However, the result reported as significant in one of these [54] 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 [57] 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, & 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 [57], interventions with more intensive psychotherapy components and substantial interventionist input [29, 49, 50, 52, 55] 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 [55].

It was notable that the five interventions with substantial psychological input were among six [29, 49, 50, 52, 54, 55] of the seven studies reporting intervention benefits whose results exhibited considerable threats to internal validity. These were due to 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 [54] 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, 53] were averaged as they referred to the same project. All data were published except for one study [56] for which data were obtained via the authors. Two studies were not included following no response to the data request [55] or due to untraceable contact details [49]. Available data from the more distressed subgroup were included for one study [54] 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 due to the study by Allocca [57] with I^2 decreasing to 0% when this study was removed. This outlying effect may have been due to 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 due to 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 due to the presence of Allocca's study [57]. 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, 60-66] 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 [57]. 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 [60, 62]. However, efficacy was generally lower than those reported in similar research in other illnesses such as diabetes [63] and coronary heart disease [65]. Possible floor effects may have contributed to attenuated efficacy, as studies did not generally limit recruitment to patients with higher distress (though the two studies that screened for distress did not appear more efficacious). Lack of screening has been consistently observed in cancer literature more generally [67-69] though it is also relatively common in other illnesses [e.g., 63, 64-66]. 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 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, 49, 51]), coping skills (e.g., [51, 57]), or emotional acceptance and processing (e.g., [50]). Relaxation, on the other hand, may reflect avoidance coping potentially contributing to smaller effects when used as a primary component (e.g., [56]).

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 [55], 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 due to 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 though 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.

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Table 1. Summary of studies examining the efficacy of psychological interventions to alleviate distress in HSCT

Sources & design	Disease, transplant, & follow up	n_i/n_c	Intervention	Comparison	Relevant outcomes	
					Target	Key findi
Interventions timed to target distress during HSCT only						
Allocca 1998 [57] Quasi-experiment	Breast cancer	10/10	<u>Components:</u> Problem and cognitive biases identification, cognitive techniques (restructuring, problem-solving, etc.), review and future planning <u>Delivery:</u> Individual (face to face) by CBT-trained nurse specialist <u>Timing & intensity:</u> Start within 48 hrs post-transplant 5x, approx. 35 mins, over 5-10 days.	TAU	Anxiety & Depression (HADS) Psychological well-being (QOLS)	Significa and psycl significar Non-sign interventi
Jarden, Baadsgaard 2009 [30]; **Jarden, Nelausen 2009** [53] RCT	79% haem. malignancy Allogeneic <u>Follow up:</u> 6 months	21/21	<u>Components & delivery:</u> CBT-based psychoeducation, exercise, & relaxation training Individual exercise (face-to-face) by researcher & self-directed relaxation <u>Timing & intensity:</u> During admission 5x pw psychoeducation & exercise, 2x pw relaxation	TAU	Anxiety & Depression (HADS) Emotional functioning (QLQ-C30) **Affective functioning** (SCT-SAS)	No signif Significa severity i

Interventions timed to target distress following HSCT only						
DuHamel 2010 [29] RCT	71% haem. malignancy Mixed <u>Follow up:</u> 3-12 months	47/34	<u>Components:</u> CBT for trauma – Education, self-monitoring & cognitive restructuring, graded exposure, communication skills training, relaxation training <u>Delivery:</u> Individual (telephone) by trained postdoctoral fellows & self-directed practice <u>Timing & intensity:</u> 10-16 wks post-HSCT 10x, approx. 1 hour	Assessed only	Trauma (PCL-C) **Distress** (BSI) **Trauma Diagnosis** (CAPS)	Total and improved Faster im Diagnosi at end of Retained Possible
Frick 2006 [50] RCT	92% haem. malignancy Autologous	88/91	<u>Components & delivery:</u> Daydream imagery for emotional processing Individual (face-to-face) by researcher (trained psychotherapist) <u>Timing & intensity:</u> 1-6 months postdischarge 15x, 15-30 mins	Delayed timing (6-12 months postdischarge)	**Emotional functioning** (QLQ-C30)	Significa interventi increased Possible group
Rini 2014 [54] RCT	87% haem. malignancy Mixed	69/ 59-69	<u>Components & delivery:</u> Expressive helping (expressive writing to help prospective patients) Instructions only (telephone) by study	1. Expressive writing only 2. Writing to help	**Distress** (BSI)	Lower in compared writing in survivors

			interviewer, otherwise self-directed Timing & intensity: 9 months to 3 years post-HSCT 4x weekly, 20 mins	peers only 3. Neutral writing		Incomple error. Ex to have lo control fo published
	Follow up: 3 months					
Trask 2003 [55] RCT	n/k	26 in total	Components & delivery: Workbook psychoeducation – coping, problem-solving, CBT principles Instructions only (face to face) by author, otherwise self-directed Timing & intensity: Discharge onwards, self-directed	TAU	Distress (BSI) **Anxiety** (STAI) Coping (WOC)	No signif postdisch 45% of in utilised w Anxiety w who did 2 compared Unclear i on adhere
Interventions timed to target distress during & following HSCT						
de Linares 2007 [49] Quasi-experiment	Haem. malignancy Follow up: 100 days	10/6	Components: Informational, practical coping skills, stress management (psychoeducation & cognitive restructuring), communication with family Delivery: Individual (face to face) Timing & intensity: 4x since and during admission	TAU	**Anxiety & Depression** (HADS)	Fewer cli depressio transplan No baseli
Gaston-Johansson	Breast cancer	52/58	Components: Coping – psychoeducation, cognitive	TAU	Anxiety (STAI)	No signif

2000; **2013** [51, 52]	Autologous		restructuring education & coping, coping skills training, relaxation with guided imagery training		Depression (BDI)	
RCT	Follow up: 1 year	38/35	Delivery: Individual (1st session face-to-face then computer/telephone) by social worker, nurse, researchers, & self-directed practice Timing & intensity: 2 wks prior to then during admission & top-up 3 months later 5x (3x during admission) 1st 1.5 hours, then 20 mins		**Psychological functioning** (QOLI-CV)	Higher in Possible outcome
Jacobsen 2014 [56]	89% haem. malignancy	356/ 355	Components & delivery: Stress management with relaxation, imagery, and coping elements (50% also engaged in exercise) Individual (face-to-face) by trained site personnel & self-directed Timing & intensity: Since admission, ongoing 3x instruction (introduction & reinforcement 30 & 60 days post-HSCT) otherwise self-directed.	TAU (50% also engaged in exercise)	Psychological functioning (SF-36)	No signif months p
RCT	Mixed					Intervent

Note. Sources are listed by name of first author with studies and outcomes supporting intervention benefits in bold letter mentioned where available. n_i/n_c=intervention and comparison group sample sizes respectively; RCT=randomised clinica HSCT=haematopoietic stem cell transplantation; haem=haematological; CBT=Cognitive-Behavioural Therapy; #x = nur 2x=2 sessions); pw=per week; TAU=treatment as usual; HADS=Hospital Anxiety and Depression Scale; QLQ-C30= Th Organization for Research and Treatment of Cancer Quality of Life Questionnaire; SCT-SAS= Stem Cell Transplantatio

Scale; wks=weeks; PCL-C=Posttraumatic Stress Disorder Checklist-Civilian Version; BSI=Brief Symptom Inventory (g
CAPS=Clinician-Administered Posttraumatic Stress Disorder Scale for Diagnostic and Statistical Manual for Mental Dis
mins=minutes; n/k=not known; QOLS=Quality of Life in Bone Marrow Transplant Survivors, City of Hope National Me
Questionnaire; WOC=Ways of Coping; STAI=State-Trait Anxiety Inventory; BDI=Beck Depression Inventory; QOLI-C
Index-Cancer Version; SF-36=Medical Outcomes Short-Form 36 (version 2.0).

PSYCHOLOGICAL INTERVENTIONS FOR DISTRESS IN ADULTS UNDERGOING HAEMATOPOIETIC STEM CELL TRANSPLANTATION: A SYSTEMATIC REVIEW **WITH META-ANALYSIS**

Short title:
Systematic review of psychological interventions for distress in HSCT

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Keywords:
cancer, oncology, stem cell, bone marrow, ~~**psychology,**~~ intervention

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 11741 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.

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 ~~**remains very costly (up to £100,000 per transplant) and**~~ is very intensive [1]. The initial stages often involve ~~**administration of**~~ high doses of chemotherapy sometimes with radiation aiming at severe depletion of bone marrow cells ~~**including cancer cells**~~ and suppression of the immune system in preparation for ~~**engraftment**~~ **stem cell infusion to restore haematological and immune systems** [1]. ~~**This is followed by stem cell infusion to restore haematological and immune systems.**~~ The process can last several weeks involving very high levels of toxicity often in addition to previous chemotherapy, prolonged periods of isolation ~~**due to immunosuppression**~~, 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 ~~**compared to the general population**~~ [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 ~~**associated with the procedure**~~, it is not surprising that patients ~~**undergoing HSCT**~~ experience considerable psychological distress. Patients report a consuming effort to prepare and an ongoing struggle ~~**with loss of agency**~~, describing the procedure as "walk to hell and back" or "really, really hard" [8, p. 404]. Studies in adult HSCT have observed considerable ~~**loss of personal control and**~~ psychological distress, particularly during hospitalisation, with up to a quarter of patients meeting clinical criteria for anxiety and/or depression ~~**during the procedure**~~ [3, 9-13]. Following transplantation, psychological distress improves but can persist with ~~**studies reporting**~~ up to 40% of patients experiencing depression and up to 30% anxiety even one year later [14].

Apart from psychological well-being, ~~**the consequences of**~~ distress **also** appear**s** to affect physical well-being and recovery although research remains limited and correlational. ~~**Nevertheless,**~~ **S**tudies have observed ~~**a range of**~~ 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~~, even in transient forms,~~ 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 ~~to enhance psychological well-being~~ and supporting recovery. Research in the psychological needs of HSCT patients has indicated ~~some~~ 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 ~~of adjusting to health-related difficulties~~ suggesting that illness appraisals and coping can play an important part in ~~the process~~ **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 ~~an extensive body of literature in~~ related clinical areas and particularly cancer [26, 27]. For example, psychological therapies with educational, cognitive-behavioural, **or** coping skills components~~, and so forth,~~ 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**, and so forth**. This is important to not only guide clinical judgment but also identify **future** research needs ~~towards better evidence base~~. 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 ~~inclusion~~ eligibility criteria were applied:**

- The target population included HSCT patients.
- Patients were ~~**adults (**~~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 due to ~~**limited internal validity stemming from**~~ lack of control for **maturation and** concurrent effects [37] including that of undergoing HSCT.
- ~~**Interventions**~~ **Outcomes** explicitly ~~**targeted and assessed**~~ **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, 33, 34]: 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, 35, 36], **.** ~~**Additional related terms**~~ and relevant subject headings via the databases. ~~**Terms for the target population (e.g., stem cell$, bone marrow, etc.), intervention (intervention$, therap$, etc.), and outcomes (e.g., psycho$, distress, etc.) were grouped separately using OR and then combined using AND operators. Terms were added to the script sequentially from general to specific (where applicable) and were excluded for economy when they did not add any further publications. This process resulted in different but equivalent scripts for each database.**~~ **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 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 abstraction**~~

~~**To answer**~~ **Data relating to** the research questions and ~~**aid the evaluation of**~~ study quality ~~**(see below), the following data**~~ were extracted by two of the authors independently~~:~~ **(details of abstracted data are available online in Appendix B).**

1. ~~***Reference:*** **author names, publication year.**~~
2. ~~***Research design:*** **Type (Randomised Controlled Trial [RCT], etc.), conditions, randomisation, allocation, blinding, confounder control.**~~
3. ~~***Sampling:*** **Site, selection, inclusion and exclusion criteria, accrual, attrition, sizes.**~~
4. ~~***Disease information:*** **Disease, transplant type, conditioning, side effects (particularly GVHD), functional impairment, admission days, time since transplant, number of readmissions, and differences between groups.**~~

~~5. *Demographic information:* age, gender, ethnicity, marital status, socio-economic status (income, employment, or education), and differences between groups.~~

~~6. *Intervention:* components, timing, delivery (sessions, duration, and schedule), interventionist role, and adherence.~~

~~7. *Outcome measures:* Names, constructs, timing of administration, standardisation, reliability, and validity. Planned (e.g., as stated in published protocol) versus reported outcomes.~~

~~8. *Analysis:* Tests, intention to treat analysis, confounder control.~~

~~9. *Key findings and data for meta-analysis:* Significant effects, relevant comments, pre and postintervention or difference means and standard deviations per group, and sample sizes. Unpublished data were requested by authors.~~

~~Study quality~~

~~Use~~ **As use** of composite scales with overall study quality ratings has not been empirically supported [38], ~~therefore,~~ a component **study** quality assessment was employed consistent with Cochrane Foundation practice ~~for clinical trial reviews~~ [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 [43]) 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. ~~The assessment examined several sources of bias including:~~**Further details on adjustments to the Cochrane criteria are available online in Appendix B**.

~~• Selection (e.g., group equivalence): random assignment and allocation concealment~~

- Performance (e.g., group differences in treatment other than intervention): blinding of participants and personnel
- Detection (group differences in outcome assessment): blinding of outcome assessors
- Attrition (e.g., groups differences in withdrawal): intention to treat analyses; however, high bias was assigned if attrition exceeded 60% due to potential unreliability of intention-to-treat analysis.
- Reporting (differences between reported and unreported findings): incomplete reporting of outcome data.

As blinding of the interventionists is generally not possible for psychological interventions, a decision was made to consider this criterion satisfactorily met where the comparison group was treatment as usual, the interventionist did not have major involvement with participants other than the intervention, and other care staff remained broadly unaware of the allocation.

Two further components were added: confounders and common factors. Because randomisation may not have been successful particularly in smaller studies, the former required either evidence that groups were comparable on confounding variables to demonstrate success or appropriate statistical control. Confounders included demographics (age, gender, ethnicity, marital status, socio-economic status), disease-related characteristics (disease, transplant type, side effects, hospital days, functional impairment, time since transplant, and readmission), and baseline outcomes. Having measured at least 70% of these together with control for differences was considered low risk. These criteria followed relevant reviews, literature on predictors of distress in HSCT, and quality assessment practice [14, 26, 38, 40-42].

Common factors were incorporated because improvement in psychological therapies may reflect the therapeutic relationship, increased contact, common understanding of the problem, or other factors not specific to the intervention [43]. This component examined whether comparison groups involved some attentional equivalent to provide evidence that effects were more likely attributed to the intervention per se than common factors whilst recognising that constructs such as therapeutic relationship, common understanding, and so forth, may only be partially achieved with attentional control.

~~**Quantitative data**~~

For **the** quantitative **synthesis** ~~**To examine the**~~ **regarding** efficacy ~~**of interventions**~~, mean pre and postintervention 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 ~~**Hedges' *g* representing standardised mean differences (as described in [44]) selected to accommodate use of different outcome measures. This contains an adjustment for small samples [45], as expected in the present review.**~~ **fixed effects where heterogeneity was not significant and Hedges' *g* representing standardised mean differences [34, 44, 45, 46]**. Where multiple postintervention data were available, data from the time point closest to the end of the intervention were entered first~~**. Sensitivity**~~ **followed by sensitivity** analysis ~~**was then conducted**~~ using data from the final follow up ~~**instead.**~~

~~**Fixed effects models were used where heterogeneity was not significant otherwise random effects with the DerSimonian and Laird method were employed (as described in [44, 45]). Random effects generally produce wider confidence intervals and are considered more conservative as they adjust for considerable (and unexplained) heterogeneity [34, 44, 46]. However, this can be misleading if greater weight is assigned to smaller studies with higher risk of bias [44, 45] in which case fixed effects were preferred**~~. Effect sizes were interpreted using Cohen's [47] guidelines with 0.2 considered small, 0.5 medium, and 0.8 large. Heterogeneity was examined visually ~~**via the Forest plot**~~ and statistically ~~**using a**~~ (*Chi*^{2} test ~~**(*Q* statistic**~~ [44]). 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 [44]. Publication bias, primarily due to underreported studies with null effects [34], was assessed via visual inspection of the funnel plot. Review Manager (Version 5.3) software [48] was employed with *alpha* level of significance set at 0.05 ~~**except for the *Q* statistic where an *alpha* level of 0.10 was adopted due to loss of power with smaller sample sizes and few studies**~~ **(0.10 for heterogeneity tests** [34]**).**

Results

Included studies

Eleven studies met the inclusion criteria (**Error! Reference source not found.**). ~~**The relatively large number of initial abstracts appeared due to the generic nature of search terms (e.g., distress also encompassing physical symptom distress, intervention often referring to HSCT itself). Of the included studies, ten were already**~~ **Of these, ten were** published in peer-reviewed journals [29, 30, 49-56] and another [57] was an unpublished doctoral thesis. ~~**Of these, one**~~ **One** study was in Spanish [49] 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, 51, 52, 54-57] and four (three interventions) were from European countries [30, 49, 50, 53]. 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, 49] were aimed solely at psychological distress ~~**targeting either posttraumatic symptomatology or more generally anxiety and depression.**~~. 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 ~~of nine~~ interventions incorporated Cognitive Behaviour Therapy (CBT) methods (see [58] for an overview of such methods) with emphasis on cognitive components and two [50, 54] 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, 51-53, 56] alongside psychological input and formed a major component in two interventions [30, 53, 56] 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, 49-52, 57] with the remainder being less specialist (e.g., psychoeducation with relaxation, task instructions, etc.).

All **nine** interventions were delivered individually and for seven ~~out of nine~~ this was face to face during admission. One [51, 52] also had some remote input and the remaining two were delivered via telephone several months following HSCT [29, 54]. Interventions also involved varying degrees of guided and self-directed work with five ~~out of nine~~ incorporating both [29, 30, 51-54, 56] and only two consisting primarily of self-directed work [55, 56]. 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, 49-52, 57] 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 ~~and,~~ often over several weeks ~~though this was ,~~ **and** mostly self-directed. Session length began at approximately 20 minutes 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 [49] 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 [49, 55, 57] to a large RCT with an excess of 300 participants while the remainder [29, 30, 50-54] were modest with 21 to 91 participants. Seven ~~of eleven~~ studies recruited consecutively prior to HSCT, two [49, 55] did not report sufficient information, one [29] screened participants for high distress (primarily trauma), and another [54] for at least mild survivorship difficulties (including distress). In seven ~~of eleven~~ studies control groups were treatment as usual (TAU), in one [29] patients received no care, and in another [56] half of controls also engaged in regular exercise. In a further two studies [50, 54] 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 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 ~~also~~ assessed process change (coping, [55]). All measures were standardised with acceptable validity and reliability ~~as discussed in all studies~~ 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 ~~for the design~~ except for four studies of which three [30, 49, 56] reported pairwise comparisons only and one [54] ~~which reported~~ **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 [49, 55] ~~which did not examine such confounding with~~ **of which** one [49] also ~~failing~~ **failed** to measure baseline scores for controls. With the exception of three studies [51, 52, 56], sufficient information regarding adherence was also provided (attendance, logbooks, etc.). Only one study [55] 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 ~~**for each together with a graphic summary**~~. 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 ~~**the study**~~ **their** method. Common factor bias was only addressed by one study [54] ~~**via**~~ **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 [59] observed a therapeutic relationship effect ~~**suggesting a common factors 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 & incomplete analysis/Type II error). High risk of bias in the remaining studies included poor evidence of control for individual differences [29, 49, 57] or no baseline control [49, 50].

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 posttraumatic symptomatology. Of these, five were evaluated in the longer-term (three to twelve months) ~~with~~ **showing enduring** benefits ~~also present at the longest follow up~~. One of these [52] had not been effective during transplantation suggesting a possible delayed effect or lack of power though this discrepancy may be due to questionable baseline outcome control at follow up. In addition, three interventions appeared effective in HSCT patients that were more distressed due to close proximity to the time of transplantation [50] or relevant screening [29, 54]. However, the result reported as significant in one of these [54] 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 ~~evaluated with~~ **involving** more than one outcome measure resulted in benefits on all of them indicating potentially inflated Type I error. One study [57] 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 ~~suggests that~~ **questions** the reported effect ~~may have indeed been due to chance~~.

Differences in findings did not appear consistently related to many study characteristics. These included general characteristics, some intervention characteristics (use of CBT, & 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 [57], interventions with more intensive psychotherapy components and substantial interventionist input [29, 49, 50, 52, 55] 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 [55].

It was notable that the five interventions with substantial psychological input were among six [29, 49, 50, 52, 54, 55] of the seven studies reporting intervention benefits whose results exhibited considerable threats to internal validity. These were due to 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 [54] 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 ~~**using fixed effects models**~~ was conducted with data from nine of the eleven studies. The effect sizes of two studies [30, 53] were averaged as they referred to the same project. All data were published except for one study [56] for which data were obtained via the authors. Two studies were not included following no response to the data request [55] or due to untraceable contact details [49]. Available data from the more distressed subgroup were included for one study [54] 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%. ~~Sensitivity analysis with the longest follow up data yielded comparable results. All of the contribution to~~ **The sensitivity analysis yielded comparable results**. The heterogeneity appeared due to the study by Allocca [57] with I^2 decreasing to 0% when this study was removed. This outlying effect may have been due to ~~imprecision and poor methodology~~ **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≥0.11, df=1, P≥0.66.**

The loss of two studies due to 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 due to the ~~inclusion~~ **presence** of Allocca's study [57]. 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 ~~that~~ 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 ~~and a small pooled effect size estimate.~~. A range of methodological limitations ~~was~~ **were** also present suggesting a need ~~to interpret evidence with caution~~ **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 ~~addressing appraisals, coping, problem solving, and so forth,~~ 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, 60-66] though there was a notable absence of group delivery ~~in HSCT~~.

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 [57]. ~~In spite of an almost symmetrical funnel plot, this indicated~~ **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 [60, 62]. However, ~~they were~~ **efficacy was** generally lower than those reported in similar research in other illnesses such as diabetes [63] and coronary heart disease [65]. Possible floor effects may have contributed to attenuated efficacy, as studies did not generally limit recruitment to patients with higher distress~~. This~~ **(though the two studies that screened for distress did not appear more efficacious). Lack of screening** has been consistently observed in cancer literature more generally [67-69] though ~~lack of screening at recruitment it~~ is also relatively common in other illnesses [e.g., 63, 64-66]. ~~Such practice and its~~ **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]~~ potentially indicating a need for more tailored interventions~~.

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 to health-related difficulties indicating that more benign appraisals ~~about the situation and its sequelae~~, 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, 49, 51]), ~~problem-solving~~ **coping skills** (e.g., [**51,** 57]~~) and skills training (e.g., [51]) for coping,),~~ or emotional acceptance and processing (e.g., [50]). Relaxation, on the other hand, may reflect avoidance coping ~~with stressors~~ potentially contributing to smaller effects when used as a primary component (e.g., [56]).

These considerations are plausible but it was not possible to establish ~~from the studies in this review whether the interventions operated via the above processes versus other~~ **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 ~~and without within-group control~~. Second, with one exception [55], no study employed a process measure ~~to investigate the mechanism of change~~ 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 ~~per se~~.

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 due to 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 though 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. ~~**Other**~~ **The other** areas of bias ~~**including randomisation, attrition, reporting, and confounder control were**~~ **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~~**, which**~~. **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.

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Table 1. Summary of studies examining the efficacy of psychological interventions to alleviate distress in HSCT

Sources & design	Disease, transplant, & follow up	n_i/n_c	Intervention	Comparison	Relevant outcomes	
					Target	Key findi
Interventions timed to target distress during HSCT only						
Allocca 1998 [57] Quasi-experiment	Breast cancer	10/10	<u>Components:</u> Problem and cognitive biases identification, cognitive techniques (restructuring, problem-solving, etc.), review and future planning <u>Delivery:</u> Individual (face to face) by CBT-trained nurse specialist <u>Timing & intensity:</u> Start within 48 hrs post-transplant 5x, approx. 35 mins, over 5-10 days.	TAU	Anxiety & Depression (HADS) Psychological well-being (QOLS)	Significa and psyc significa Non-sign interventi
Jarden, Baadsgaard 2009 [30]; **Jarden, Nelausen 2009** [53] RCT	79% haem. malignancy Allogeneic <u>Follow up:</u> 6 months	21/21	<u>Components & delivery:</u> CBT-based psychoeducation, exercise, & relaxation training Individual exercise (face-to-face) by researcher & self-directed relaxation <u>Timing & intensity:</u> During admission 5x pw psychoeducation & exercise, 2x pw relaxation	TAU	Anxiety & Depression (HADS) Emotional functioning (QLQ-C30) **Affective functioning** (SCT-SAS)	No signif Significa severity i

Interventions timed to target distress following HSCT only						
DuHamel 2010 [29] RCT	71% haem. malignancy Mixed Follow up: 3-12 months	47/34	Components: CBT for trauma – Education, self-monitoring & cognitive restructuring, graded exposure, communication skills training, relaxation training Delivery: Individual (telephone) by trained postdoctoral fellows & self-directed practice Timing & intensity: 10-16 wks post-HSCT 10x, approx. 1 hour	Assessed only	Trauma (PCL-C) **Distress** (BSI) **Trauma Diagnosis** (CAPS)	Total and improved Faster im Diagnosi at end of Retained Possible
Frick 2006 [50] RCT	92% haem. malignancy Autologous	88/91	Components & delivery: Daydream imagery for emotional processing Individual (face-to-face) by researcher (trained psychotherapist) Timing & intensity: 1-6 months postdischarge 15x, 15-30 mins	Delayed timing (6-12 months postdischarge)	**Emotional functioning** (QLQ-C30)	Significa interventi increased Possible group
Rini 2014 [54] RCT	87% haem. malignancy Mixed	69/ 59-69	Components & delivery: Expressive helping (expressive writing to help prospective patients) Instructions only (telephone) by study	1. Expressive writing only 2. Writing to help	**Distress** (BSI)	Lower in compared writing in survivors

			interviewer, otherwise self-directed Timing & intensity: 9 months to 3 years post-HSCT 4x weekly, 20 mins	peers only 3. Neutral writing		Incomple error. Ex to have lo control fo published
	Follow up: 3 months					
Trask 2003 [55] RCT	n/k	26 in total	Components & delivery: Workbook psychoeducation – coping, problem-solving, CBT principles Instructions only (face to face) by author, otherwise self-directed Timing & intensity: Discharge onwards, self-directed	TAU	Distress (BSI) **Anxiety** (STAI) Coping (WOC)	No signif postdisch 45% of in utilised w Anxiety who did compared Unclear i on adhere
Interventions timed to target distress during & following HSCT						
de Linares 2007 [49] Quasi-experiment	Haem. malignancy Follow up: 100 days	10/6	Components: Informational, practical coping skills, stress management (psychoeducation & cognitive restructuring), communication with family Delivery: Individual (face to face) Timing & intensity: 4x since and during admission	TAU	**Anxiety & Depression** (HADS)	Fewer cli depressio transplan No baseli
Gaston-Johansson	Breast cancer	52/58	Components: Coping – psychoeducation, cognitive	TAU	Anxiety (STAI)	No signif

2000; **2013** [51, 52]	Autologous		restructuring education & coping, coping skills training, relaxation with guided imagery training		Depression (BDI)	
RCT	Follow up: 1 year	38/35	Delivery: Individual (1st session face-to-face then computer/telephone) by social worker, nurse, researchers, & self-directed practice Timing & intensity: 2 wks prior to then during admission & top-up 3 months later 5x (3x during admission) 1st 1.5 hours, then 20 mins		**Psychological functioning** (QOLI-CV)	Higher in Possible outcome
Jacobsen 2014 [56]	89% haem. malignancy	356/ 355	Components & delivery: Stress management with relaxation, imagery, and coping elements (50% also engaged in exercise) Individual (face-to-face) by trained site personnel & self-directed Timing & intensity: Since admission, ongoing 3x instruction (introduction & reinforcement 30 & 60 days post-HSCT) otherwise self-directed.	TAU (50% also engaged in exercise)	Psychological functioning (SF-36)	No signif months p
RCT	Mixed					Intervent

Note. Sources are listed by name of first author with studies and outcomes supporting intervention benefits in bold letter mentioned where available. n_i/n_c=intervention and comparison group sample sizes respectively; RCT=randomised clinica HSCT=haematopoietic stem cell transplantation; haem=haematological; CBT=Cognitive-Behavioural Therapy; #x = nur 2x=2 sessions); pw=per week; TAU=treatment as usual; HADS=Hospital Anxiety and Depression Scale; QLQ-C30= Th Organization for Research and Treatment of Cancer Quality of Life Questionnaire; SCT-SAS= Stem Cell Transplantatio

Scale; wks=weeks; PCL-C=Posttraumatic Stress Disorder Checklist-Civilian Version; BSI=Brief Symptom Inventory (g
CAPS=Clinician-Administered Posttraumatic Stress Disorder Scale for Diagnostic and Statistical Manual for Mental Dis
mins=minutes; n/k=not known; QOLS=Quality of Life in Bone Marrow Transplant Survivors, City of Hope National Me
Questionnaire; WOC=Ways of Coping; STAI=State-Trait Anxiety Inventory; BDI=Beck Depression Inventory; QOLI-C
Index-Cancer Version; SF-36=Medical Outcomes Short-Form 36 (version 2.0).

(Top of Figure)

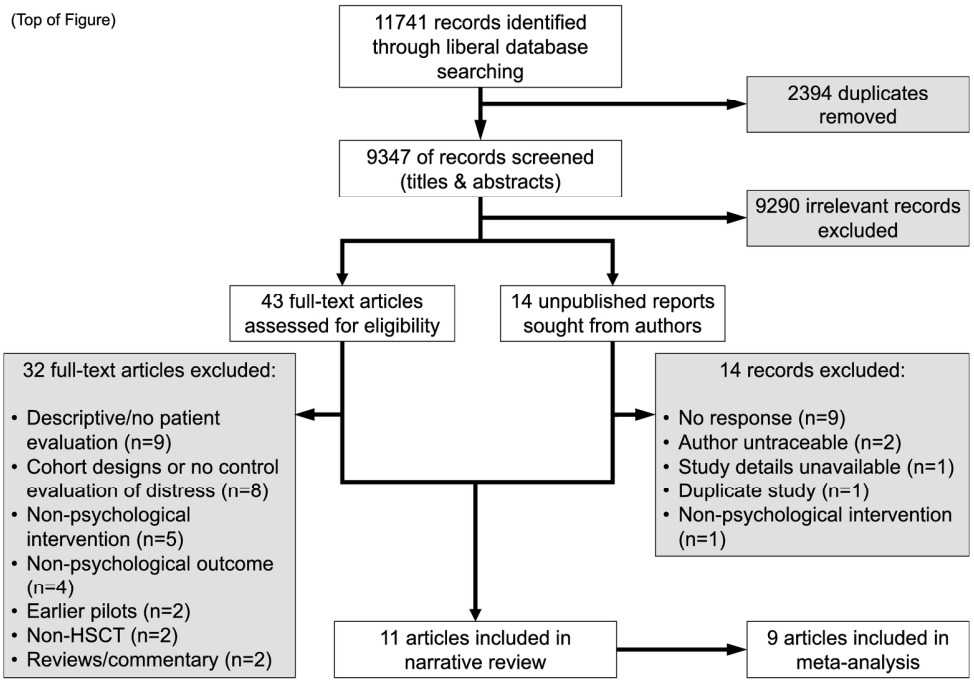

Figure 1. Flowchart of the selection of studies investigating psychological interventions in haematopoietic stem cell transplantation.
186x130mm (300 x 300 DPI)

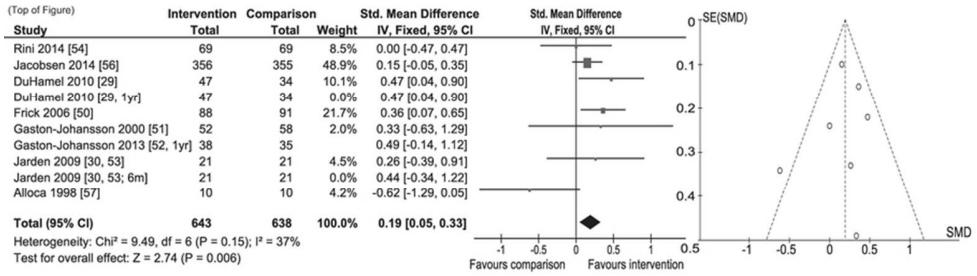

Figure 2. Forest plot of standardised pre/post change comparison between intervention and control groups with funnel plot for the evaluation of publication bias. Studies are listed in increasing risk of bias. Overall, there was a small pooled effect size estimate with non-significant heterogeneity. Follow 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.
76x21mm (300 x 300 DPI)

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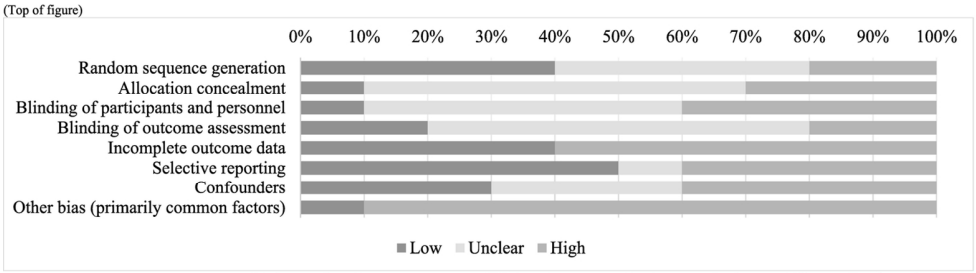

	Rini 2014 [54]	Jacobsen 2014 [56]	DuHamel 2010 [29]	Frick 2006 [50]	Gaston-Johansson 2000 [51]	Gaston-Johansson 2013 [52]	Jarden 2009 [30, 53]	Alloca 1998 [57]	Trask 2003 [55]	de Linares 2007 [49]
Random sequence generation	L	U	L	L	U	U	L	H	U	H
Allocation concealment	L	U	U	U	U	U	H	H	U	H
Blinding: participants & 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.
128x70mm (300 x 300 DPI)

Appendix A

Search strategy

Terms for the target population (e.g., stem cell$, bone marrow, etc.), intervention (intervention$, therap$, etc.), and outcomes (e.g., psycho$, distress, etc.) were grouped separately using OR and then combined using AND operators. Terms were added to the script sequentially from general to specific (where applicable) and were excluded for economy when they did not add any further publications. This process resulted in different but equivalent scripts for each database.

Population

- **MEDLINE**
  (Hematopoietic Stem Cell Transplantation/ OR Bone Marrow Transplantation/) OR ((Stem cell$ OR bone marrow) AND (transplant$))

- **PsycINFO**
  (Stem cell$ OR bone marrow) AND (transplant$)

- **EMBASE**
  (exp hematopoietic stem cell transplantation/ OR exp bone marrow transplantation/) OR ((Stem cell$ OR bone marrow) AND (transplant$))

- **CINAHL**
  ("Stem cell*" OR "bone marrow") AND ("transplant*")

- **ProQuest**
  AB,TI(((Stem-cell*) OR bone-marrow) AND (transplant*))

- **Google Scholar**
  (("Stem cell" OR "bone marrow") AND (transplant OR transplantation))

Intervention

- **MEDLINE**
  (exp Psychotherapy/ OR exp Counseling/ OR Patient education as topic/) OR (intervention$ OR therap$ OR counsel$ OR self-help group$ OR support group$)

- **PsycINFO**
  (exp Prevention/ OR exp Treatment/ OR exp Counseling/ OR exp Psychotherapy/ OR Support groups/) OR (intervention$ OR therap$ OR counsel$ OR self-help group$ OR support group$)

- **EMBASE**
  (exp "psychological and psychiatric procedures"/ OR exp counselling OR exp self help/ OR exp support group/) OR (intervention$ OR therap$ OR counsel$ OR self-help group$ OR support group$)

- **CINAHL**
  (MH "Clinical Trials+") OR (("intervention*" OR "therap*" OR "counsel*" OR "self-help group*" OR "support group*"))

- **ProQuest**
  AB,TI(intervention* OR therap* OR counsel* OR (self-help-group*) OR (support-group*))

- **Google Scholar**
  (intervention OR therapy OR therapies OR counselling OR (("self-help" OR "self help") AND group) OR (support AND group))

Outcomes

- **MEDLINE**
  (exp emotions/ OR exp affective symptoms/ OR exp affect/ OR adaptation, psychological/ OR interpersonal relations/ OR Exp mental disorders/) OR (psycho$ OR social OR distress OR anxi$ OR depress$ OR stress OR quality of life OR mental health OR psychiatr$ OR mental disorder$)

- **PsycINFO**
  (exp Adjustment/ OR exp Emotions/ OR exp Satisfaction/ OR exp Life experiences/ OR exp Mental Disorders/ OR exp Psychiatric Symptoms/) OR (psycho$ OR social OR Distress OR anxi$ OR depress$ OR stress OR quality of life OR mental health OR psychiatr$ OR mental disorder$)

- **EMBASE**
  (exp emotion/ OR mental disease/) OR (psycho$ OR social OR Distress OR anxi$ OR depress$ OR stress OR mental health OR psychiatr$ OR mental disorder$) [1]

- **CINAHL**
  (MH "Psychological Processes and Principles+") OR ("psycho*" OR "social" OR "distress" OR "anxi*" OR "depress*" OR "stress" OR "quality of life" OR "mental health" OR "psychiatr*" OR "mental disorder*")

- **ProQuest**
  AB,TI(Psycho* OR social OR Distress OR anxi* OR depress* OR stress OR (quality-of- life) OR (mental-health) OR psychiatr* OR (mental-disorder*))

- **Google Scholar**
  ((psychological OR psychology OR psychologic OR psychosocial OR "psycho social" OR "psycho-social") OR social OR distress OR distressed OR anxiety OR anxious OR depression OR depressed OR stress OR stressed OR ("quality of life") OR ("mental health") OR (psychiatry OR psychiatric) OR (mental AND (disorder OR disorders)))

[1] Quality of life added 2127 irrelevant papers mostly in relation to quality of life of HSCT as intervention. Consequently, quality of life terms were excluded from the final EMBASE script to reduce the probability of human error whilst screening the pooled database list of abstracts.

Appendix B

Data abstraction

The following data were extracted:

1. ***Reference:*** author names, publication year.
2. ***Research design:*** Type (Randomised Controlled Trial [RCT], etc.), conditions, randomisation, allocation, blinding, confounder control.
3. ***Sampling:*** Site, selection, inclusion and exclusion criteria, accrual, attrition, sizes.
4. ***Disease information:*** Disease, transplant type, conditioning, side effects (particularly GVHD), functional impairment, admission days, time since transplant, number of readmissions, and differences between groups.
5. ***Demographic information:*** age, gender, ethnicity, marital status, socio-economic status (income, employment, or education), and differences between groups.
6. ***Intervention:*** components, timing, delivery (sessions, duration, and schedule), interventionist role, and adherence.
7. ***Outcome measures:*** Names, constructs, timing of administration, standardisation, reliability, and validity. Planned (e.g., as stated in published protocol) versus reported outcomes.
8. ***Analysis:*** Tests, intention to treat analysis, confounder control.
9. ***Key findings and data for meta-analysis:*** Significant effects, relevant comments, pre and postintervention or difference means and standard deviations per group, and sample sizes. Unpublished data were requested by authors.

Details on adjustments to study quality criteria

As blinding of the interventionists is generally not possible for psychological interventions, a decision was made to consider this criterion satisfactorily met for performance bias where the comparison group was treatment as usual, the interventionist did not have major involvement with participants other than the intervention, and other care staff remained broadly unaware of the allocation. High attrition bias was assigned if attrition exceeded 60% even if intention to treat analysis was used due to potential unreliability.

Confounders included demographics (age, gender, ethnicity, marital status, socio-economic status), disease-related characteristics (disease, transplant type, side effects, hospital days, functional impairment, time since transplant, and readmission), and baseline outcomes. Having measured at least 70% of these together with control for differences was considered low risk. These criteria followed relevant reviews, literature on predictors of distress in HSCT, and quality assessment practice [14, 26, 38, 40-42].