Scientific Research Publishing

Psychology, 2022, 13, 338-352
https://www.scirp.org/journal/psych
ISSN Online: 2152-7199
ISSN Print: 2152-7180

Effectiveness of Complementary Supportive Interventions on Mental Health Issues in Pediatric Oncology Patients. A Systematic Review of Randomized Controlled Trials

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How to cite this paper: Zarou, C., Micha, M., Bacopoulou, F., & Kanaka-Gantenbein, C. (2022). Effectiveness of Complementary Supportive Interventions on Mental Health Issues in Pediatric Oncology Patients. A Systematic Review of Randomized Controlled Trials. *Psychology, 13,* 338-352.
https://doi.org/10.4236/psych.2022.133021

Received: January 18, 2022
Accepted: March 13, 2022
Published: March 16, 2022

Abstract

Supportive interventions may decrease the psychological health issues, such as distress, anxiety and depression, experienced by pediatric oncology patients, and therefore, they could constitute a therapeutic option for this chronic disease. The aim of this systematic review was to sum up the current evidence from randomized control studies that examined the effectiveness of complementary supportive interventions on mental health issues in pediatric oncology patients. The Web of Science, PubMed and Scopus databases were meticulously searched. The initial search retrieved 468 studies, of which only 17 randomized controlled trials met the selection criteria. The primary outcome was symptom severity, in the manifestation of distress, anxiety and depression in children and adolescents under 19 years old with a diagnosis of cancer. Most (14 out of 17) studies reported statistically significant improvements in at least one of the examined psychological outcomes. These findings suggest that these integrative supportive therapies in children diagnosed with cancer can significantly improve and alleviate their main psychological manifestations of anxiety, distress and depression, thus facilitating diseases' treatment, alleviating their psychological burden and asserting their claim to a normal life.

Keywords

Pediatric Oncology, Childhood Cancer, Mental Health Issues, Anxiety, Depression, Distress, Psychological Interventions, Complementary Therapy

1. Introduction

Suffering from cancer can provoke extensive and excessively emotional, physical and social strains, especially for the very vulnerable demographic population of pediatric oncology. Although great progress has been made in cancer survival, this disease remains the leading cause of death in children and its treatments have short-term and long-term consequences for the well-being of children. This accomplishment, along with the several medical breakthroughs in diagnoses, led to many pediatric patients suffering from either psychological consequences or issues of the pathological condition, in addition to the treatment side-effects or complications. "The psychological impact is varying, extending from increased anxiety eventuality, up to concerns over haggard and tired appearance and viewing oneself as distinct from his peers" according to McDougal (1997). Approximately 25% of patients experience severe mental health problems such as critical anxiety disorders, depression and/or PTSD, with over 50% of patients developing severe warning signs of depression (Seitz et al., 2010; Li et al., 2013).

The main scope of this paper was to delineate if various auxiliary and supportive interventions are effective enough on the main psychological issues and whether they can be considered as a main coping intervention in pediatric oncology. The secondary goal was to detect which types of these therapies are most effective in reducing distress, anxiety and depression in children and adolescents patients with cancer. Numerous random clinical experiments were administered with the use of amalgamating supportive therapies for adults and children, to reduce their anxiety or distress. The majority of papers canvass the pervasiveness of auxiliary therapies practice (Bishop et al., 2010; Post-White, 2006), but not the efficiency of a specific type of interventions for the treatment or relief of the main psychological symptoms (such as distress, anxiety, depression). Although several papers addressed the problem of anxiety or pain in the course of painful methods that have been conducted to combat pediatric cancer (Kleiber & Harper, 1999; Landier & Tse, 2010; Richardson, Smith, McCall, & Pilkington, 2006), no recent review has evaluated supportive interventions putting to action, explicitly regarding the anxiety, distress and depression symptoms restricted in pediatric oncology patients. Therefore, this review focused specifically on the effectiveness of various types of auxiliary interventions comparing the results of those on the main psychological issues (distress, anxiety, and depression) in pediatric oncology patients, regardless of the cancer treatment phase.

2. Methods

The study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Moher et al, 2010).

2.1. Selection Criteria

The standards for including or excluding a study were set according to the PICOS components. With regards to *Population*, studies had to be conducted solely on children or adolescents, from 1 up to 19 years old. Participants were incorporated, at any point during the course of their treatment, from cancer diagnosis to ongoing therapy, to long-term follow-up after treatment, or death. The participants recruited must have received a medical diagnosis or positive diagnostic testing of cancer, of any type. Regarding *Intervention*, only studies using interventions to reduce symptoms including distress, anxiety or depression for children diagnosed with cancer were taken into consideration in this systematic review paper. Interventions included should have involved a psychological intervention of either music therapy, video gaming and technological nature, or of hypnosis and other relaxation techniques. As far as *Outcome* a study should have to examine at least one of the desirable outcomes (distress, anxiety, depression) to be included. All types of anxiety whether it was procedural, state, or treatment-related were included in the outcomes of the review in order to examine the full aspect of the anxiety at every stage of the cancer treatment the patient experiences. Young patients may experience anxiety about medical treatments or methods, hospital admission, clinic appointments, or recrudescence, so full aspect examination of the disorder was required. Various types of distress that were manifested either as somatic or psychological were incorporated in the paper, with a range of tools for measuring it. For depression, mainly the common Childhood Depression Inventory (CDI) and Beck Depression Inventory tools have been used for evaluating the studies included. Lastly, with regards to *Studies,* RCTs with a matched control group were sought. Identified research protocols that did not present satisfactory data were also excluded. Additionally, studies had to be published solely in the English language by journals with a peer-review process.

2.2. Search Strategy

An orderly literature inspection was performed within Pub Med, Web of Science & SCOPUS databases without date constraint. Search filter for English language only was applied and no other filter prior or after the search. The keywords used in each database are stated below in the following combination. (*Childhood cancer OR Paediatric Oncology OR paediatric cancer OR pediatric oncology*) *AND* (*child* OR adolescent* OR teen* OR paediatric*) *AND* (*mental health issues*) *AND* (*anxiety OR depression OR Distress OR stress*) *AND* (*supportive therapy OR palliative care OR music* OR video game OR game* OR virtual*).

Terms were searched for in each title and abstract, and in the keywords of each study, and were adapted accordingly to each electronic database. The researchers separately searched introduction sections and reference lists of papers that were to be included for supplementary studies consistent with to the question of the review.

2.3. Data Extraction and Quality Evaluation

The data were collected independently by two researchers (C.Z. and M.M.). Data gathered from the studies included: 1) participant demographics (e.g. sex, age and participants' number), 2) methodology (e.g., interventions' and follow-up measurements' type and length), and 3) results (e.g., psychological consequences on distress, anxiety and depression). Quality assessment of individual studies was conducted according to the Cochrane Collaboration's tool for assessing risk of bias (Higgins et al., 2011) by two researchers (C.Z. and M.M.).

3. Results

3.1. Study Flow and Included Studies

Initial search yielded 468 papers. The reviewing investigators concluded in 17 randomized control trials. The complete screening process is illustrated in **Figure 1**. **Table 1** presents the information gathered from the studies, making allowance for trial intervention, design and type of study, participants' demographics, type of control group, outcomes measures, timeline of follow-up calculation and main judgements.

A total number of 572 pediatric oncology patients with mean age ranging between 5 to 19 years old participated in the studies. All papers consisted of patients with childhood cancer only and excluded cancer survivors. The individuals who participated in the studies received diverse forms of psychological intercessions. The intercession applied can be categorized to 3 subcategories of interventions: music therapy interventions (n = 5), relaxation and hypnosis interventions (n = 7), technology and video games interventions (n = 5). Results and main findings of the studies indicate that 14 out of 17 studies reviewed in this paper reported statistically significant improvements in at least one of the examined psychological outcomes. Studies were compared and analyzed across their own category and type of intervention.

The outcome and tools of measurement mentioned in the following table of studies and results are in regard to the desired psychological outcomes (distress, anxiety, and depression) that this review examines. There are also additional outcomes of psychological nature that several studies are reporting, but they are not mentioned in the following table as they are not in the reviewing interest of this paper.

3.2. Qualitative Evaluation of Studies

Figure 2 illustrates the results of the quality evaluation of the involved studies

based on the Cochrane Collaboration's tool for assessing risk of bias (Higgins et al., 2011). The synopsis of the "risk of bias using the Cochrane's ROB 2 tool for every study" is entailed in this review, as shown in Table 2. The five risks of bias areas are individually evaluated, and then rated as a total for a comprehensive risk of bias for every study. From the table of risk of bias, the quality of evidence in every study is evident. Five out of the 17 trials evaluated to be of "Low Risk" thus indicating a higher quality of trials evidence, 7 evaluated to be of "Some

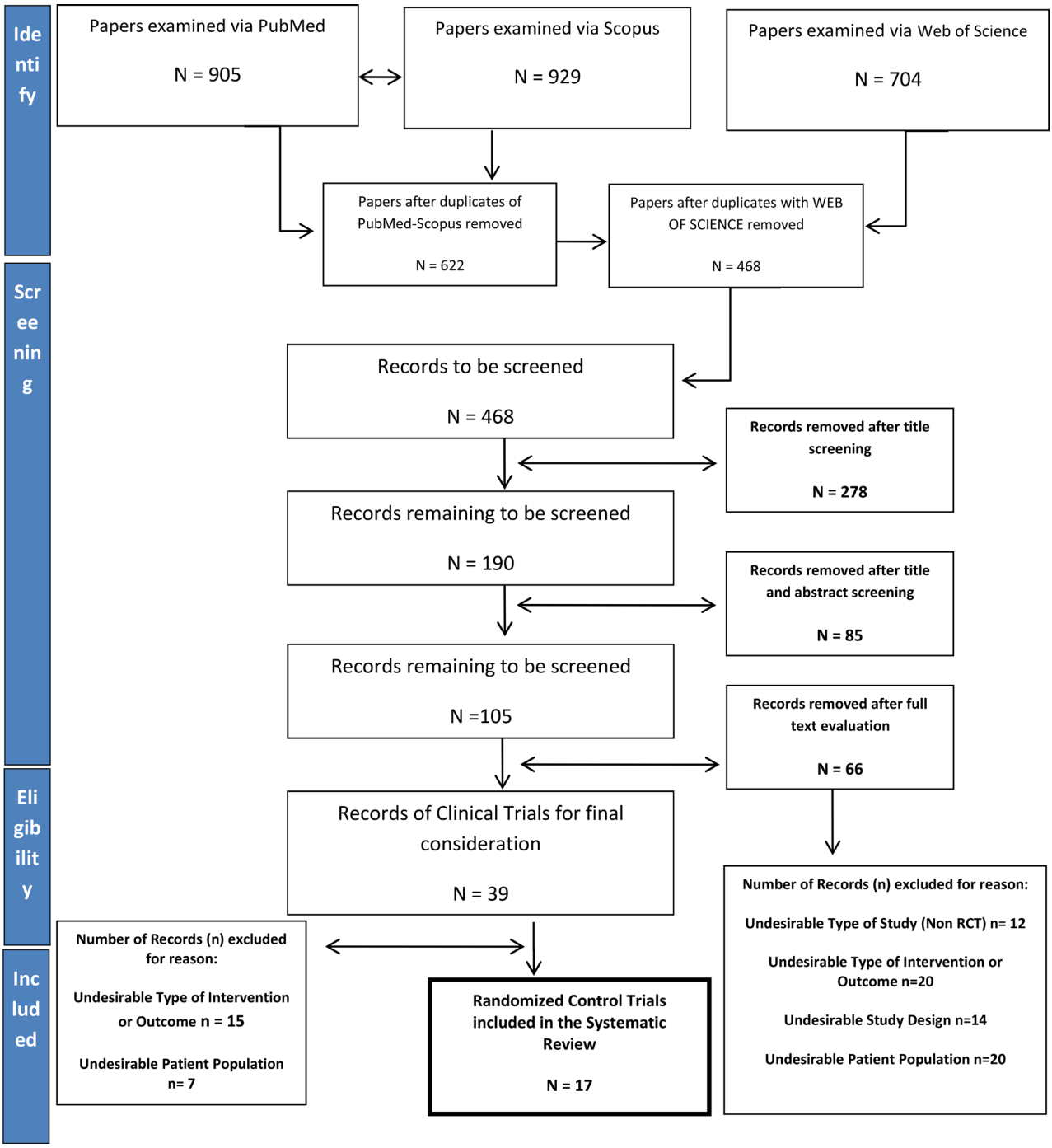

Figure 1. Flow chart and methodology of the selected studies of the review process.

Table 1. Studies characteristics & outcomes.

First Author	Year	Country	Setting	Patients Characteristics	Design OF Study	Control Group	Meausures Timeline (Folow Up)	Reporting Outcomes	Outcomes Measures	Main Findings
Sheri L. Robb	2016	U.S.A.	Inpatient & Outpatient	16 Children 3 - 8 YO and a parent.	RCT in AME (Active Music Engagement) for child and parent Distr.	Low Dose Intervention (Audio-Storybooks Attention Control Condition)	Baseline-Post-30 days Post	Proxy	Distress (Facial Affect Coding)	Behav. Coding---$p = 0.040$---distr. < control group.
Philippa Barry	2010	Austalia	Inpatient	12 children 6 to 13 YO	RCT on music therapy CD creation for Distr. Reduction.	Gold Standard	Baseline-During-Post.	Self	Distress (Kidcope)	Median Distr. Interv. Grou$p = 1$ (range 0 - 2) Median Distr. Control Grou$p = .5$ (range 0 - 5) Not S. Significant!!
L Uggla	2016	Sweden	Inpatient	24 children 0 - 16 YO	RCT on music therapy, for children undergoing HCST, to reduce Distr.	Gold Standard	Pretreatment-Post.	Proxy	Distress (HR)	Distr. In the Control group Significantly higher $p < .001$ (muscle tension) than in the Interv. Group.
Thanh Nhan Nguyen	2010	Vietnam	Inpatient	40 children 7 - 12 YO years, who undergo LP.	RCT on music medicine for pain and anxiety in children undergoing lumbar punctures.	Gold Standard	Pretreatment-During-Post.	Self	Anxiety (STAI-S)	Anx. Inerv group before LP $p < .001$ (mean = 8.6, SD = 2.78) Anx. Inerv group after LP also S.Significant.
Uggla L.	2017	Sweden	Inpatient & Outpatient	29 children 0-17 YO who underwent HSCT	RCT in music therapy for Anx. during and after HSCT.	Gold Standard & Wait-list.	Baseline-Post-6 monthS Post	Self & Proxy	Anxiety (PedsQL 3C)	PedsQL 3.0 scores increase at hospital discharge for treatment anxiety, worry, cognitive problems and communication $p = .035$. PedsQL 3.0 total scores also increase at six months for both groups.
Deborah H. Ndao	2010	U.S.A.	Inpatient	37 children undergoing stem cell infusion and their parents.	RCT on respiratory administration of bergamot essential oil for Anx.	Placebo	Baseline-Pretreatment-During-Post.	Self	Anxiety (STAI-C)	Negative results on Anx. For Inerv. Group Interv. Group higher Anx. Scores at T3 ($p = .01$) and T4 ($p = .05$). Anx. Also higher in Interv. Group in time-point ($p < .001$). Pain also higher for Interv. Group ($p = 0.003$).

DOI: 10.4236/psych.2022.133021

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Joyce Wong	2010	U.S.A.	Inpatient & Outpatient	9 chilgren 3 to 18 YO	RCT on stress, pain, and fatigue. Study consisting of 2 arms.	Low Dose Intervention (reading/play activities)	Pretreatment-Post.	Self & Proxy	Distress (Distress Feeling Thermometer)	Distr. In Interv. Group significant lower $p < .001$.
Janice Post-White	2009	U.S.A.	Inpatient	23 children 1 to 18 YO, and 1 parent or guardian.	RCT Cross-over design on providing massage to children with cancer to lower Anx.	Low Dose Intervention (quiet time)	Pretreatment-Post.	Self	Anxiety (STAI-C, STAI)	Anx. in Interv. Group at S4 $p = .04$ --- at S1 $p = .15$ for ages 1 - 13. Anx. in Interv. Group at S4 $p = .058$ --- at S1 no diff. Between groups for ages 14 - 18.
Christina Liossi	2009	Greece	Inpatient	45 children 7 -16 YO who were off active treatment, and had one of their parents present.	RCT on anaesthetic (EMLA) and a combination of EMLA with self- hypnosis in reduction of venepuncture- induced Anx.	a) Gold Standard b) Low Dose Intervention (attention)	Pretreatment-During-Post.	Self & Proxy	Anxiety (VAS) Distress (PBCL)	Anx. and Distr. Lower for Interv. Group during venepunctures $p < .001$.
Christina Liossi	2001	Greece	Inpatient	80 children 6-16 YO	RCT on clinical hypnosis to reduce Anx. and Distr.	a) Gold Standard b) Low Dose Intervention (attention) c) Indirect hypnosis	Baseline-During treatment	Self & Proxy	Anxiety (FACES) Distress (PBCL)	Anx. and Distr. Lower for Interv. Group $p < .001$ for all timepoints. Direct and indirect hypnosis interv. equally effective.
Christina Liossi	1999	Greece	Inpatient	30 children 5 to 15 YO	RCT on clinical hypnosis versus cognitive behavioral (CB) in reducing Distr.	a) Gold Standard b) CBT Intervention	Baseline-During treatment	Self & Proxy	Anxiety (FACES) Distress (PBCL)	Anx. And pain anx. Lower for both Inerv groups compared to control group $p = .005$ (pick at S2) and to their own baseline measurement. Both Interv. Equal effective on pain. Hypnosis group more effective on Distr. - Anx. Than CB group.
Valerie J. Wall	1989	U.S.A.	Inpatient	20 children 5 - 18 YO	RCT on hypnosis or active cognitive strategy for reducing Anx.	Low Dose Intervention (CBT Intervention Condition)	Pretreatment-Post.	Self & Proxy	Anxiety (STAI-C, VAS)	Anx. (patient scores) not significantly changed. Anx. (proxy scores) significantly lower $P = .0036$ & $P = .004$

Continued

Sadaf Sajjad	2014	Pakistan	Inpatient	76 children 10-14 YO	RCT on Psychotherapy video game for reducing Anx. & Depr.	Gold Standard	Pretreatment-2 Months Post.	Self	Anxiety (Beck Anxiety Inventory) Depression (Beck Depression Inventory)	Anx. S.Significantly Reduced for Interv. Group by 29% after the interv. Depr. S.Significantly Reduced for Interv. Group by 22% after the interv.
Stefan Nilsson	2009	Sweden	Inpatient	42 children 5-18 YO	RCT on non-immersive Virtual Reality (VR) during a needle-related procedure for reducing Distr.	Gold Standard	Pretreatment-during-Post.	Self	Distress (FACES, HR)	Self and Proxy Distr. Lower for Intrev. Group. Not S.Significant.
JONATHAN GERSHON	2004	U.S.A.	Inpatient	59 Children 7–19 YO	RCT on a novel technology to reduce anxiety and pain.	a) Gold Standard b) Low Dose Intervention (Non Virtual Reality Intervention)	Pretreatment-During-Post.	Self & Proxy	Anxiety (VAS, HR) Distress(CHEOPS, HR)	Distr. In the Control group Significantly higher $p < .05$ (muscle tension) than both the Interv. Groups. No S.Significance in differences on Anx. For all the groups before the port access procedure.
Minoo Alemi	2015	Iran	Inpatient	11 children, 7–12	RCT on utilizing a humanoid robot for reducing Distr.	Low Dose Intervention (psychotherapy)	Pretreatment-Post.	Self	Anxiety (MASC) Depression (CDI)	Anx. Interv group pre-test 2.23 post-test 1.89. S. Significant $p = .002$ Anx. Control group pre-test 2.36 post-test 2.38. Depr. Interv. Group pre-test 1.35 post-test 1.00. S.Significant $p = .019$ Depr. Control group pre-test 1.31 post-test 1.30.
Lindsay A. Jibb	2018	Canada	Inpatient	40 children 4-9 YO	RCT on a future MEDiPORT trial, in reducing child Distr. during subcutaneous port accesses.	Low Dose Intervention (Robot dancing-singing)	Pretreatment-Post.	Proxy	Distress (BAADS)	Lower Distr. For Control group during procedure. Not S.Significant. No major diff. on pain between groups.

Study	Year	BIAS arising from the randomization process	BIAS due to deviations from intended interventions	BIAS due to missing outcome data	BIAS in measurement of the outcome	BIAS in selection of the reported result	Total Rating of Risk of BIAS
Sheri L. Robb	2016	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Philippa Barry	2010	Low Risk	Low Risk	Low Risk	High Risk	some concerns	High Risk
L Uggla	2016	High Risk	some concerns	Low Risk	High Risk	Low Risk	High Risk
Thanh Nhan Nguyen	2010	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Uggla L.	2017	some concerns	Low Risk	Low Risk	Low Risk	Low Risk	some concerns
Deborah H. Ndao	2010	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Joyce Wong	2010	some concerns	Low Risk	Low Risk	Low Risk	some concerns	some concerns
Janice Post-White	2009	some concerns	some concerns	some concerns	Low Risk	Low Risk	High Risk
Christina Liossi	2009	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Christina Liossi	2001	some concerns	Low Risk	Low Risk	Low Risk	Low Risk	some concerns
Christina Liossi	1999	some concerns	Low Risk	Low Risk	Low Risk	some concerns	some concerns
Valerie J. Wall	1989	Low Risk	Low Risk	some concerns	Low Risk	Low Risk	some concerns
Sadaf Sajjad	2014	some concerns	some concerns	Low Risk	some concerns	High Risk	High Risk
Stefan Nilsson	2009	some concerns	some concerns	some concerns	some concerns	Low Risk	High Risk
JONATHAN GERSHON	2004	some concerns	Low Risk	Low Risk	Low Risk	some concerns	some concerns
Minoo Alemi	2015	some concerns	Low Risk	Low Risk	some concerns	Low Risk	some concerns
Lindsay A. Jibb	2018	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk

LOW RISK
SOME CONCERNS
HIGH RISK

Figure 2. Quality evaluation of studies.

Concerns" and 5 of a "High Risk" of bias. In Figure 2, we can see a graphical representation of the distribution of the studies in every risk of bias area. In Table 2, all the studies are evaluated for every "risk of bias" area and presented in a table form.

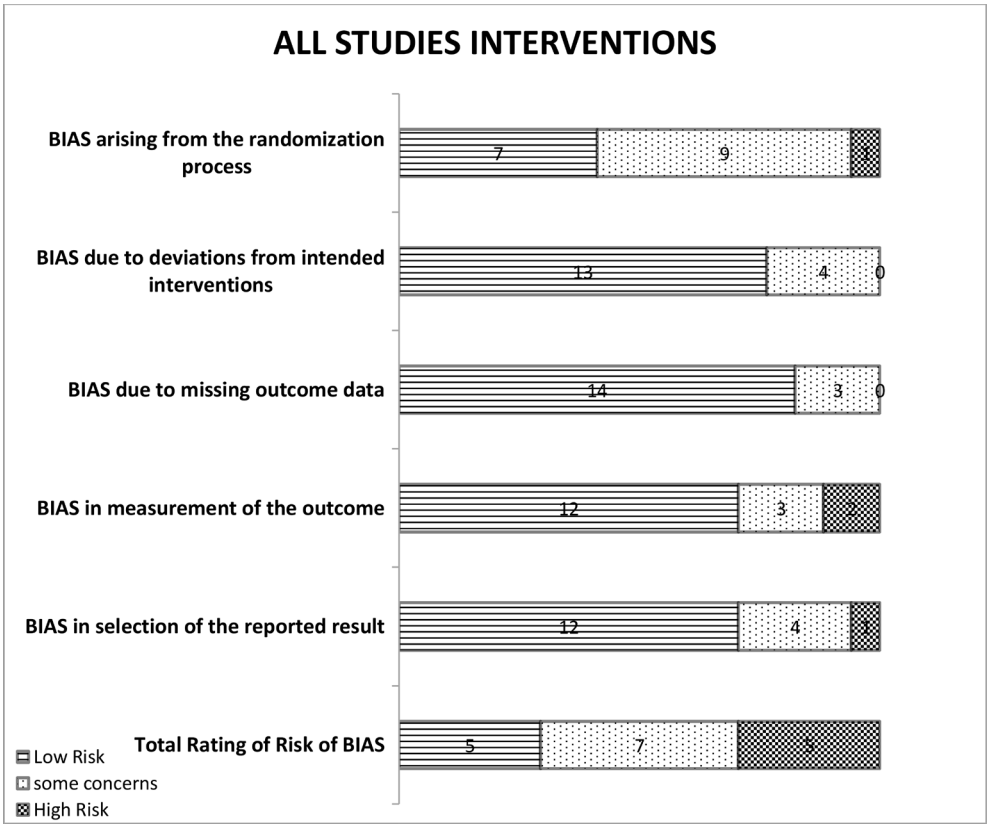
3.3. Results of Supportive Interventions

As mentioned above, studies in this review are sorted by type of similarity of intervention. Although all trials involve supportive psychological interventions, further categorizations by type of intervention were required to clearly appraise the effectiveness of each trial on the main psychological outcomes, not only by any individual intervention, but by type of intervention as well. Thus, we can examine which type of trials are the most efficient.

3.4. Music Therapy Interventions

There are five studies involving music-related interventions examining the effectiveness of music therapy on the main psychological symptoms of distress and anxiety. From these five trials, four are reporting significant positive results, two on distress outcomes (Robb et al., 2017; Uggla et al., 2016) and two on anxiety outcomes (Nguyen et al., 2010; Uggla et al., 2018). There was a study that reported positive results on distress, but it was not considered statistically significant (Barry et al., 2010).

Table 2. Risk of bias.



3.5. Relaxation and Hypnosis Interventions.

There are seven studies involving relaxation and hypnosis-related interventions examining the effectiveness of these interventions on the main psychological symptoms of distress and anxiety. There are 4 trials involving hypnosis and self-hypnosis techniques, two examine massage techniques as their main intervention, and one experiment with an aromatherapy intervention. Of these seven trials, three reported statistically significant positive results, across all measured checkpoints, for both distress and anxiety outcomes (Liossi & Hatira, 1999; Liossi et al., 2003; Liossi et al., 2009), two reported statistically significant results for anxiety outcomes (Wall & Womack, 1989; Post-White et al., 2009) and one reported statistically significant results for distress (Wong et al., 2013). There is also one study with significant negative results for the intervention group (Ndao et al., 2012).

3.6. Technology/Video Games Interventions

There are five studies involving video gaming and robotics interventions examining the effectiveness of technologically advanced and innovative therapies on the main psychological symptoms of distress, anxiety and depression. Out of these five studies, three are using a video game intervention and two are an innovative robotic psychotherapy experiment. From these five studies, three are reporting significant positive results, two on anxiety and depression outcomes (Sajjad et al., 2014: Alemi et al., 2016) and one on distress outcomes, but not on anxiety, which was also examined (Gershon et al., 2004). One study reported positive results on distress but not statistically significant (Nilsson et al., 2009) and one shows non-significant negative results for its intervention on outcomes of distress (Jibb et al., 2018).

4. Discussion

Investigating the summary of evidence, it's evident that from the systematic research of the literature a collectively considerable amount of research material has been gathered providing clear evidence for the efficacy of innovative supportive methods in dealing with distress, anxiety and depression in young patients suffering from cancer. All three examined types of interventions included many trials with significantly positive results and high-value effect sizes, thus proving the effectiveness of these therapies and validating their use and standardization in future clinical methodology and psychological treatment approach in pediatric oncology.

Twelve out of 17 trials achieved high quality of evidence across all bias areas, a fact that underlines and further promotes the significance of these outcomes.

Regarding the music therapy-related interventions, 3 out of 5 studies are reporting significantly positive results through all measured sessions of the trials, achieving an effect size up to 1.49. However, music interventions on the other hand presented the highest amount of "High Risk of Bias" with two studies in-

dicating an overall rating of "high risk" and another study with "some concerns" concerning their quality of evidence.

In terms of the hypnosis and relaxation-related interventions, 5 out of 7 studies are reporting significantly positive results through all measured sessions and for all examined outcomes, achieving an effect size up to 1.0. On the quality of evidence hypnosis and relaxation related interventions, presented a high amount of "Some Concerns" rating with four of the studies indicating an overall rating of "some concerns" and another one with "High Risk" for their quality of evidence.

Regarding the video games and technology-related interventions, 2 out of 5 studies are reporting significantly positive results through all measured sessions and for all the examined outcomes, achieving an effect size up to 0.7, which, in many cases, is regarded as statistically significant. Technology-related interventions also are the only type that examines the depression outcome with 2 trials reporting significantly positive results. Video games and technology-related interventions also presented a significant amount of lower quality of evidence, with 2 out of 5 studies indicating an overall rating of "high risk" or "some concerns" for their quality of evidence.

Taking into account all the above, we can see that hypnosis and relaxation-related interventions are the most effective as they presented the highest amount of statistically significant results which continued to be significantly positive across all measured sessions. Video games and technology-related interventions presented an overall highest quality of evidence showing 3 out of 5 trials with a "low risk of bias" rating.

5. Limitations

While efforts were carried out to eliminate bias in the best possible way, there is a possibility that the concluding remarks of this paper had inherent limitations and weaknesses. To strengthen the impact of potential significant findings, only reviews applying randomization techniques were taken into consideration. This was the primary concern, as it posed great limitations to the papers produced abroad, prone to conducting open, non-randomized designs.

6. Conclusion

There is solid evidence that auxiliary and supportive interventions, which complement the overall palliative care, may support children receiving cancer remedy in general and especially in uncomfortable and aching procedures. This area of expertise is of essential and fundamental importance to children fighting cancer, as well as to their relatives. This paper proves that a variety of psychological & social interventions and measures are helpful and efficacious and can have a beneficial effect on their mental health and alleviate their psychological burden. Overall, the results demonstrate that children and adolescents' mental health needs when facing cancer are addressable, while complementary supportive psychological interventions are essential in addressing the issue of their psychological

wellbeing and fast rehabilitation, which is of paramount significance for ascertaining quality of life.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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