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Review Article

Effect of Clown Therapy on Symptoms and Emotions of Children with Neoplastic Disease: A Systematic Review with Meta-Analysis

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Introduction: Clown therapy is a widely used nonpharmacological intervention for the control and management of symptoms and emotions in pediatric settings. There are some studies evaluating the effect of the intervention on children with neoplastic disease, but a systematic review summarizing the overall benefit is lacking.
Objective: To evaluate the effect of clown therapy on the symptoms and emotions of children with neoplastic pathology.
Methods: Studies (randomized or quasi-randomized parallel-group controlled trials) were searched from biomedical databases, web resources, and trial registries. The intervention was compared with standard care; primary outcomes were pain and anxiety, and secondary outcomes were fear, stress, fatigue, depression, distress, and mood. Risk of bias was assessed with RoB 2, and the overall effect size was calculated with variable effects meta-analysis. The summary of results was illustrated in accordance with the GRADE method.
Results: Five quasi-randomized parallel-group trials with a high risk of bias were included (N = 376, mean age: 6.9–10.9 years). Children who received clown therapy manifested a reduction in anxiety (N = 181; SMD = -2.17 [95% CI: -4.20, -0.14], p < 0.05) and fatigue (N = 176; SMD = -2.03 [95% CI: -5.39, 1.32], p > 0.05). The certainty/quality of evidence is very low.
Conclusions: Clown therapy seems more effective than standard care in reducing anxiety and fatigue in children with neoplastic disease. However, more studies are needed to confirm the results, as the very low certainty/quality of evidence currently does not justify routine implementation of the intervention in pediatric oncology.

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Introduction

Neoplasms are the second leading cause of death among children aged 1–14 years in high-income countries [1]. Thanks to advanced treatment options, survival rates have increased significantly in recent decades (5-year survival currently stands at 85% and 86% for children and adolescents, respectively [2]), but they are often associated with the implementation of complicated, intensive, and prolonged treatment protocols that are a distressing experience for a child [3].

They involve several hospitalizations and/or days of outpatient care over a period of time that varies, but generally exceeds one year [4]; during this time, the child is exposed to invasive procedures that cause him physical and emotional suffering [5]. In addition to this, a diagnosis of malignancy results in a reconfiguration of the child's life and that of their family, since it represents a gateway to the hospital as a place of residence and existence [6]. This new condition is a source of continuous trauma and stress: the child is removed from their family reality to be placed in a restricted, unfamiliar, and threatening environment characterized by fear and pain [7][8].

In addition, because of his or her medical condition, the child often has to give up certain activities and avoid contact with other children; thus, hospitalization is perceived as an assault on the world of play and magic typical of childhood, which can arouse negative feelings such as anger, sadness, and depression [9][10]. The resulting emotional distress, in turn, leads to regression, separation anxiety, apathy, and sleep disturbances [11][12]. When the intensity of distress renders the coping strategies implemented by the child ineffective, the final result is the impairment of the child's quality of life [13][14]. Lastly, the negative symptoms and emotions experienced promote the onset of cognitive dysfunction [15] and may persist into adult life, causing the person to avoid medical treatment [16].

Childhood is a stage of life in which the main occupation, fundamental to a child's physical and mental health, should be made up of play and fun; therefore, because of the above, the promotion of play activities in pediatric oncology is particularly important, and one of the strategies that can minimize the discomfort caused by hospitalization and contribute to the fight against the disease needs to be incorporated as an interface of care [17].

In this perspective, the mission of clown doctors is to advocate for the child's right to play, feel, and imagine himself happy [6][18]. Clown therapy can protect his or her emotional sphere and behavioral processes through improving his or her state of well-being and self-confidence and reducing anxiety and stress levels [19][20]. The intervention helps the child adapt to the hospital environment, can distract him from painful or frightening procedures, and demystify these through "fun pills" [21]. Positive emotional responses from humor and laughter induced by clown doctors are related to increased pain threshold and immunity and reduced stress hormone levels [22][23].

The use of clown therapy as a nonpharmacological treatment in the pediatric setting is increasingly popular, as evidenced by various systematic reviews in the literature [24][25][26][27][28][29][30]. However, although some studies focusing on the benefit of clown doctors in pediatric oncology are known [31][32], a systematic review summarizing the effect is lacking. It is considered important to undertake this study because the results obtained may help to fill a significant gap in the knowledge of the effectiveness of clown therapy for children with neoplastic disease; this could prove valuable in optimizing the type and characteristics of nonpharmacological care treatments to be delivered in pediatric oncology.

Objective

This study aims to evaluate the effect of clown therapy on the symptoms and emotions of children with neoplastic disease.

Methods

To achieve the objective, a systematic review with meta-analysis was conducted in accordance with PRISMA guidelines [33]. The review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) (ID: CRD42024524201).

Eligibility Criteria

In compliance with the PICOS framework [34], the inclusion criteria were as follows: [1] participants: subjects with established neoplastic disease, aged 0-18 years, undergoing oncologic treatment (e.g., radio- and/or chemotherapy, bone marrow aspirate, lumbar puncture) in an inpatient or day hospital setting; [2] intervention: clown therapy, performed by one or two clown doctors; [3] control: standard care; [4] outcomes: (a) primary - pain or anxiety, measured by any instrument at the end of the intervention; (b) secondary - fear, stress, fatigue, depression, distress, mood measured by any instrument at the end of the intervention; [5] study design: randomized or quasi-randomized controlled trials with parallel groups, in full text or abstract (but in the latter case only if sample size, mean and standard deviation are available for each group).

Information sources and search strategy

The biomedical databases Cochrane Library, PubMed, EMBASE, CINAHL, PsycINFO, Web of Science, Scopus, SciELO, LILACS, CNKI, J-GLOBAL, J-STAGE were queried. In addition, web resources (Bielefeld Academic Search Engine - BASE, TRIP Medical Database, Google Scholar) and clinical trial registries (ICTRP, ClinicalTrials.gov, EU Clinical Trials Register, ISRCTN) were consulted. For

document searching, the term “clown” followed by the truncation operator “*” and the term “cancer” with its synonyms were used as keywords. The keywords were connected to each other with Boolean operators AND/OR; the search string was adapted to the characteristics peculiar to the queried information source (Table 1). The search was carried out on January 31, 2024. References of eligible studies and reviews relevant to the topic were analyzed to retrieve additional studies of interest. The search was restricted to the pediatric population, but no language or publication date limits were imposed.

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Font	Search strategy
Cochrane Library PubMed EMBASE CINAHL	Clown* AND "Acral Tumor" OR "Acral Tumour" OR Neoplasm OR Neoplasms OR Tumor OR Tumors OR Tumour OR Tumours OR Neoplasia OR Neoplasias OR Cancer OR Cancers OR "Malignant Neoplasm" OR Malignancy OR Malignancies OR "Malignant Neoplasms" OR "Neoplastic Disease" OR "Neoplastic Entity" OR "Neoplastic Mass" OR "Tumoral Entity" OR "Tumoural Entity" OR "Tumoral Mass" OR "Tumoural Mass" OR "Tumorous Entity" OR "Tumourous Entity" OR "Tumorous Mass" OR "Tumourous Mass"
PsycINFO	clown.mp. AND exp Neoplasms/
Web of Science	TOPIC: (Clown*) AND TOPIC: ("Acral Tumor" OR "Acral Tumour" OR Neoplasm OR Neoplasms OR Tumor OR Tumors OR Tumour OR Tumours OR Neoplasia OR Neoplasias OR Cancer OR Cancers OR "Malignant Neoplasm" OR Malignancy OR Malignancies OR "Malignant Neoplasms" OR "Neoplastic Disease" OR "Neoplastic Entity" OR "Neoplastic Mass" OR "Tumoral Entity" OR "Tumoural Entity" OR "Tumoral Mass" OR "Tumoural Mass" OR "Tumorous Entity" OR "Tumourous Entity" OR "Tumorous Mass" OR "Tumourous Mass")
Scopus	TI-AB-KW (Clown*) AND TI-AB-KW ("Acral Tumor" OR "Acral Tumour" OR Neoplasm OR Neoplasms OR Tumor OR Tumors OR Tumour OR Tumours OR Neoplasia OR Neoplasias OR Cancer OR Cancers OR "Malignant Neoplasm" OR Malignancy OR Malignancies OR "Malignant Neoplasms" OR "Neoplastic Disease" OR "Neoplastic Entity" OR "Neoplastic Mass" OR "Tumoral Entity" OR "Tumoural Entity" OR "Tumoral Mass" OR "Tumoural Mass" OR "Tumorous Entity" OR "Tumourous Entity" OR "Tumorous Mass" OR "Tumourous Mass")
sciELO LILACS CNKI, J-GLOBAL J-STAGE	Clown* AND Cancer
BASE TRIP Medical Database	Clown* AND Cancer
Google Scholar	allintitle: clown cancer
ICTRP ClinicalTrials.gov	Clown* AND Cancer
EU Clinical Trials Register ISRCTN	Clown*

Table 1. Search strategy.

Study selection and data extraction

After the creation of a shared search strategy, the authors (LGR, SCR, VA, and VT) independently queried the information sources by eliminating duplicates and selecting records based on title and abstract or, in doubtful cases, after full-text analysis. The record screening process was managed using a Microsoft Excel version 2016 spreadsheet. Any disagreements were resolved by comparison and discussion. From each included study, the authors independently extracted the following characteristics using a standardized and shared template: first author and year of publication; country and study design; type of procedure (when stated and if appropriate); setting; sample characteristics; inclusion and exclusion criteria; intervention and control characteristics; outcome and its measurement tools; results (summary); and notes, if any.

Risk of bias

The authors independently assessed the risk of bias of the included studies with RoB 2 [35]. Any disagreement was resolved by comparison and discussion.

Data analysis and synthesis

Three authors (LGR, SCR, and VA) independently extracted the data and resolved any differences of opinion through comparison and discussion. The variables of interest were sample size, mean and standard deviation relative to primary (pain, anxiety) and secondary (fear, distress, fatigue, depression, distress, mood) outcomes. Because different measurement instruments were likely to be used for the same outcome, the overall effect size of the intervention was calculated with the standardized mean difference (SMD) and Cohen's d [36]. The effect was considered small, moderate, or large for thresholds of d of 0.2, 0.5, or 0.8, respectively. In case there were at least two studies per outcome, meta-analyses were performed with a random-effects model graphically represented by forest plots. A 95% confidence interval (CI) was considered as the deviation from the point estimate for each individual study and from the overall estimated value for the aggregated studies. The presence of statistical heterogeneity ($p < 0.05$) among studies was highlighted with Cochran's Q-test [37] and quantified with Higgins' I^2 index [38]. Values of $I^2 \leq 30\%$, > 30% but ≤ 60%, > 60% but ≤ 90%, or > 90% were assigned a low, moderate, high, or very high level of heterogeneity, respectively [39]. Statistical processing was performed with ProMeta© version 3.0 software.

Publication bias

Publication bias was assessed by inspecting the funnel plot [40] and applying the trim and fill method [41] in the presence of at least ten studies. An objective assessment of publication bias was performed with Egger's test [42], Begg and Mazumdar's test [43], and the FailSafe N test [44].

Sensitivity analysis

In the presence of one or more studies at high risk of bias, a sensitivity analysis was performed by regenerating the meta-analysis after their exclusion.

Supplementary analyses

Subgroup analyses were planned to assess the effect of clown therapy by gender and age of participants.

Summary of findings

Two authors (LGR and VT) independently performed the overall assessment of certainty/quality of evidence using the GRADE method [45] applied to the meta-

analysis results. Disagreements that emerged were resolved by comparison and discussion.

Results

Selection of studies

The PRISMA flowchart [46] in Figure 1 illustrates the record selection process. A total of 481 records were identified. Net of duplicates and irrelevant records after reading titles and abstracts, 31 studies, for as many records, were analyzed in full text and evaluated for eligibility. 26 were excluded because they did not meet the inclusion criteria, while five were included in the systematic review and quantitative synthesis [31][32][47][48][49]. No other studies of interest were found after consulting the references of studies assessed for eligibility and reviews relevant to the topic.

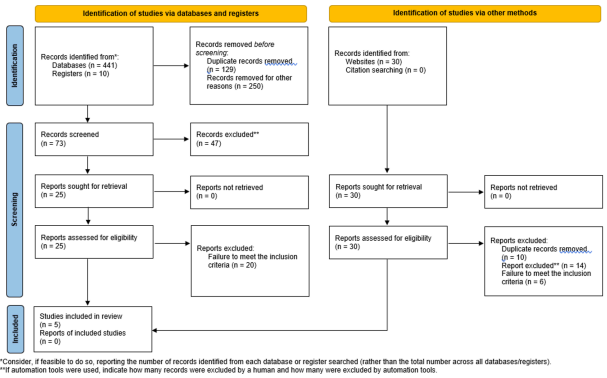

Figure 1. PRISMA flow diagram.

Characteristics of included studies

The studies cover a time span of 10 years, from 2012 [48] to 2022 [32] (Table 2). One study was conducted in Turkey [31], one in Taiwan [32], one in Iran [47], one in Italy [48], and one in Spain [49]. Of one study, only the abstract is available [48]. All studies are quasi-randomized; due to the nature of the intervention, the studies are not blinded. In three studies [32][47][48] clown therapy was offered to children during the inpatient period, while in the other two, the intervention was performed before invasive procedures such as intrathecal chemotherapy [31] and lumbar puncture or bone marrow aspiration [49].

Children were recruited from an outpatient clinic [31] or pediatric oncology units [32][47][48][49]. There were a total of 376 participants, with a mean age ranging from 6.9 years [49] to 10.9 years [32] and a proportion of males ranging from 40.3% [47] to 68.9% [31]; the most frequent inclusion criteria were (a) previous cancer treatment [31][32][47][48]; (b) not suffering from coulrophobia (= fear of clowns) [31][47][49].

The clown therapy intervention was performed by a pair of clown doctors [32] [49] who devoted 5-15 minutes to each child, or by a single clown [31][47], who devoted 3-5 minutes to each child [31] or performed a two-hour performance in the playroom dedicated to all hospitalized children [47]. In all studies, the control group received standard care.

The outcomes of interest in the studies, all referred to the child, were as follows: 1) pain [31], assessed by the Visual Analogue Scale (VAS) [50] and the Faces Pain Rating Scale (FACES) [51]; 2) anxiety [31][47][49], measured by the Visual Analogue Scale (VAS) [50], the Faces Pain Rating Scale (FACES) [51], the Revised Children's Manifest Anxiety Scale (RCMAS) [52] and the modified-Yale Preoperative Anxiety Scale (m-YPAS) [53]; 3) fatigue [47][48], quantified with the Visual Analogue Fatigue Scale (VAFS) [54] and the Pediatric Quality of Life Scale (PedsQL) [55]; 4) fear [49], assessed with a 5-sided scale; and 5) mood [32], measured with the Mood Assessment Scale (MAS) [56]. None of the included studies assessed the effect of the intervention on stress, depression, or distress. Outcomes were measured either at two times (before and after the intervention) [32][47] or at three times (before the procedure, at its end, 20-30 minutes apart) [31][49].

Children in the studies that examined the effect of clown therapy in the presence of an invasive procedure all underwent premedication [31][49]. The original number of subjects was to be equal to 393; however, 17 children (4.3%) were excluded from the studies: 9 due to refusal to participate, 6 due to poor physical condition, and 2 due to not completing the questionnaires.

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Study (year)	*Study design Country*	*Procedure*	*Setting*	*Partecipants*	*Inclusion criteria*	*Exclusion criteria*	*Intervention*	*Control*	*Outcome – assessment tolls*	*Results*	*Notes*
Kurudirek (2020)	qRCT Turkey	Intrathecal chemotherapy	Hematology Outpatient Clinic, University Health Research and Application Hospital, Istanbul	N = 74 (SG = 38, CG = 36), mean age 9.3 years, range 7-12 years, males 68.9%	Children diagnosed with acute myeloid leukemia or acute lymphoblastic leukemia diagnosed more than six months ago, subjected to chemotherapy at least three times, with similar analgesic and chemotherapy treatment protocols, in the 7-12 year age group, no fear of clowns, no other chronic pathologies	Children undergoing intravenous chemotherapy	Clown therapy performed for 3-5 minutes for each child, 20 minutes before the placement of the intrathecal line, by a clown doctor (third year student of the Faculty of Fine Arts belonging to the Department of Performing Arts)	Standard care	Child's pain (Visual Analogue Scale - VAS) Child's pain (Faces Pain Rating Scale - FACES) Child's anxiety (Visual Analogue Scale - VAS) Child's anxiety (Faces Pain Rating Scale - FACES) Evaluation in three steps: 1) 20 minutes before the procedure; 2) after clown therapy; 3) 20 minutes after the procedure	After clown therapy: pain reduction ($p < 0.05$) anxiety reduction ($p < 0.05$) After the procedure: pain reduction ($p < 0.05$) anxiety reduction ($p < 0.05$)	N = 4 (2 IG and 2 CG due to refusal to participate) left the study Pain and anxiety were measured 20 minutes before the intervention, as soon as the intervention ended and 20 minutes after the end of the intervention Administered intravenous midazolam to all children (Dormicum; 0.05-0.1 mg/kg) and lidocaine/prilocaine analgesic cream (EMLA) before the procedure
Nikkhah-Beydokhti (2021)	qRCT Iran	-	Pediatric Oncology Unit, University Hospital, Southeastern Iran	N = 77 (SG = 39, CG = 38), mean age 9.6 years, range 7-15 years, males 40.3%	Children who have undergone at least one cycle of chemotherapy, no mental retardation, hearing loss or other chronic diseases, no anti-anxiety drugs or other drugs that can distort the results, no fear of clowns	Children absent for more than one session due to illness	Clown therapy performed for 2 weeks and 2 sessions per week, from 2pm to 4pm in the games room by a suitably trained researcher	Standard care	Child's anxiety (Revised Children's Manifest Anxiety Scale - RCMAS) Child's fatigue (Visual Analog Fatigue Scale - VAFS) Evaluation in two steps: 1) before and 2) after clown therapy	Anxiety reduction ($p > 0.05$) Fatigue reduction ($p > 0.05$)	N = 3 (1 IG due to illness, 2 CG due to refusal to participate) left the study
Petrangeli (2012) *abstract*	qRCT Italy	-	Pediatric oncology unit, Bambin Gesù Hospital, Rome	N = 99 (SG = 54, CG = 45), range 7-18 years	Children undergoing at least one cycle of chemotherapy	-	Clown therapy	Standard care	Child's Fatigue (Pediatric Quality of Life scale - PedsQL)	Fatigue reduction ($p < 0.05$)	-
Quiles (2016)	qRCT Spain	Lumbar puncture, bone marrow aspiration	Pediatric Oncohematology Unit, Virgen of Arrixaca University Clinical Hospital, El Palmar (Murcia)	N = 30 (SG = 15, CG = 15), mean age 6.9 years, range 3-11 years	Children with oncohaematological pathology to be subjected to puncture and/or bone marrow aspiration, no difficulty in understanding the questionnaires, no fear of clowns	Children with neurological problems, children undergoing transplants	Clown therapy performed by a pair of clown doctors for 15 minutes for each child, until complete sedation in preparation for the procedure	Standard care	Child's fear (5-sided scale) Child's anxiety (modified-Yale Preoperative Anxiety Scale - m-YPAS) Evaluation in three steps: 1) before clown therapy; 2) after clown therapy but before the administration of midazolam and ketamine; 3) after the procedure	After clown therapy but before administration of midazolam and ketamine: fear reduction ($p < 0.05$) anxiety reduction ($p < 0.05$) After the procedure: no effect on fear and anxiety	Administered to all children midazolam and ketamine before the procedure

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Study (year)	*Study design Country*	*Procedure*	*Setting*	*Partecipants*	*Inclusion criteria*	*Exclusion criteria*	*Intervention*	*Control*	*Outcome – assessment tolls*	*Results*	*Notes*
Wu (2022)	qRCT Taiwan	-	Pediatric oncology departments of three university hospitals in Taiwan	N = 96 (SG = 48, CG = 48), mean age 10.9 years (range 4-18 years), males 54.2%	Children hospitalized for antineoplastic treatment and who had received antitumor treatment for at least 3 months	Not declared	Clown therapy performed by a pair of professional clown doctors for 5-10 minutes for each child	Standard care	The child's mood (Mood Assessment Scale - MAS) Evaluation in two steps: 1) before and 2) after clown therapy	Mood improvement ($p < 0.05$)	N = 10 were excluded from the study due to failure to complete the questionnaires (N = 2), poor physical condition (N = 5) or for no apparent reason (N = 3)

Table 2 - Characteristics of included studies.

CG = Control Group; qRCT = quasi Randomised Controlled Trial; SG= Sperimental Group.

Risk of bias

For one study [48], risk of bias could not be assessed because only the abstract was available. For the others, the risk of bias is high: in fact, all are at high risk on Domain 4, concerning outcome measurement, because it is likely that their assessment was influenced by knowledge of the intervention received/erogated (Figure 2).

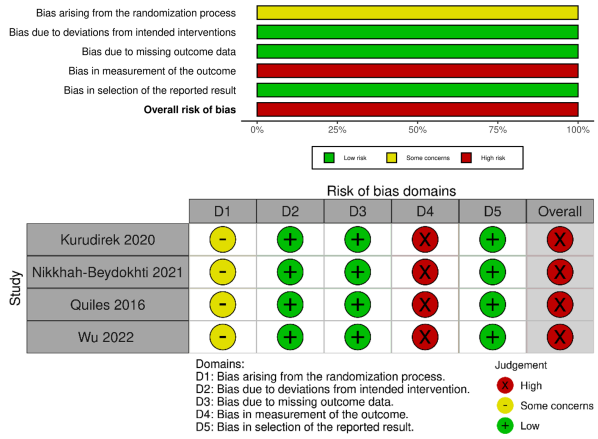

Figure 2. Risk of bias.

Primary outcomes

Pain

One study measured child pain [31], using both the FACES scale and the VAS scale. Analysis of the effect of the intervention on pain compared with standard care included 74 participants. Both just after clown therapy and 20 minutes after the end of the procedure, regardless of the assessment tool, pain decreased more in the experimental group than in the control group; the result obtained was statistically highly significant ($p < 0.001$).

Anxiety

Child anxiety was measured by three studies [31][47][49]. The values considered were those measured just after the end of clown therapy. Since in one of these studies [31] the outcome was calculated using the FACES and VAS instruments, two meta-analyses were generated: the first using values obtained from the FACES scale, the second using values obtained from the VAS scale. The analysis of the effect of clown therapy on anxiety compared with standard care included 191 participants. With the FACES scale, the SMD (95% CI) was -2.17 ([-4.20, -0.14], I^2 = 96.29%) in favor of the intervention statistically significantly (Table 3); with the VAS scale, the SMD (95% CI) was -2.32 ([-4.57, -0.06], I^2 = 96.68%) in favor of the intervention statistically significantly.

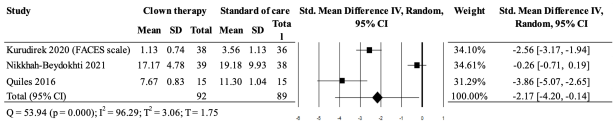

Table 3. Child's anxiety (FACES scale): clown therapy vs standard care.

Secondary outcomes

Fatigue

Child fatigue was measured by two studies [47][48]. Analysis of the effect of clown therapy on fatigue compared with standard care included 176 participants. The SMD (95% CI) was -2.03 ([-5.39, 1.32], I2 = 98.59%) in favor of the intervention in a statistically nonsignificant manner (Table 4).

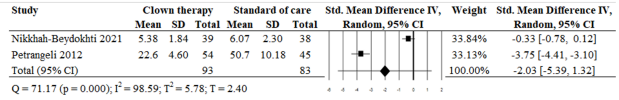

Table 4. Child fatigue: clown therapy vs standard care.

Fear

One study measured the child's fear [49]. Analysis of the effect of the intervention on fear compared with standard care included 30 participants. Just after clown therapy and before sedation in anticipation of the procedure, fear decreased more in the experimental group than in the control group, and the result obtained was statistically significant ($p < 0.05$); however, after the procedure, no statistically significant difference was observed between the two groups.

Mood

One study measured the child's mood [32]. Analysis of the effect of the intervention on mood compared with standard care included 96 participants. After clown therapy, mood tone improved more in the experimental group than in the control group, and the result obtained was statistically highly significant ($p < 0.01$).

Additional analyses

Gender

No study has measured the effect of clown therapy according to the gender of participants.

Age

No study measured the effect of clown therapy as a function of the age group of participants.

Sensitivity analysis

Sensitivity analysis was not performed because all included studies were at high risk of bias.

Publication bias

Since there are fewer than ten studies included, the funnel plot was not created, and therefore neither was the trim and fill method applied for graphical assessment of the risk of bias. However, the objective assessment suggests that the risk of publication bias is possible but unlikely. In fact, (a) Egger's test and Begg's and Mazumdar's test are not statistically significant (p = 0.360 and p = 0.602, respectively); (b) the failsafe N value {m/60/} is beyond the safety limit (5k + 10 = 25).

Summary of findings

Implementation of the GRADE method shows very low certainty/quality of evidence for the effect of clown therapy on anxiety and fatigue in children with neoplastic disease (Table 5).

Summary of findings. Clown therapy for symptoms and emotions of children with neoplastic disease.					
Clown therapy compared to standard care for symptoms and emotions of children with neoplastic disease					
Patient or population: children with neoplastic disease Setting: hospital, clinic Intervention: clown therapy Comparison: standard care					
Outcome	Anticipated absolute effects* (95% CI)		N° of participants (studies)	Certainty/quality of the evidence (GRADE)	Comments**
	Risk with standard care	Risk with clown therapy			
Children anxiety	-	The mean level of anxiety with clown therapy was 2.17 standard deviations lower (4.20 to 0.14 lower).	181 (3 qRCTs)	⊕⊖⊖⊖ Very low[a,b]	This result equates to a large difference in favor of clown therapy.
Children fatigue	-	The mean level of anxiety with clown therapy was 2.03 standard deviations lower (5.39 lower to 1.32 higher).	176 (2 qRCTs)	⊕⊖⊖⊖ Very low[a,b]	There is no evidence of an effect of clown therapy.
Children pain	-	-	74 (1 qRCT)	-	This outcome was assessed in one study only.
Children fear	-	-	30 (1 qRCT)	-	This outcome was assessed in one study only.
Children mood	-	-	96 (1 qRCT)	-	This outcome was assessed in one study only.
*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). **0.2 represents a small difference, 0.5 a moderate difference, 0.8 a large difference, 1.0 a very large difference. CI: confidence interval; qRCT: quasi randomized controlled trial.					
GRADE Working Group grades of evidence High certainty - We are very confident that the true effect lies close to that of the estimate of the effect Moderate certainty - We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different Low certainty - Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect Very low certainty - We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect					
[a] Downgraded once for serious study limitations: trials had some concerns/high risk of bias. [b] Downgraded twice for imprecision: analysis based on < 100 participants per group.					

Table 5 - Summary of findings.

Discussion

Main results

This study aimed to evaluate the effect of clown therapy on the symptoms and emotions of children with neoplastic disease. The included studies evaluated the benefit of the intervention on pain, anxiety, fatigue, fear, and mood. According to the results that emerged, the intervention seems to reduce children's anxiety: the effect size (SMD = 2.17; $p < 0.05$) corresponds to an NNT (Number-Needed-to-Treat) of 1.143 [57]. This value indicates that 7 out of every 8 children treated with clown therapy experience a reduction in anxiety. The level of certainty/quality of evidence is very low, so there is very little confidence about the effect estimate: the actual effect is likely to be substantially different. Clown therapy is promising for decreasing child fatigue (SMD = 2.03; $p > 0.05$); again, the level of certainty/quality of evidence is very low. The intervention is also effective in reducing pain and fear and improving mood; however, each of these outcomes is present in only one study, and although the results are statistically significant, more research is needed to reinforce the observed positive trend.

Comparison with other reviews

Our findings are consistent with those reported by previous systematic reviews that focused on the effect of the intervention on anxiety in children who are hospitalized [24][28][29] or who are to undergo potentially algogenic procedures such as venipuncture or peripheral vein cannulation [26][27]. The results of the review that evaluated the benefit of the intervention on fatigue [28] also agree with ours.

Studies show that the intervention not only appears to be effective but also cost-effective [58]. Unfortunately, in the included studies, clown doctors were only available at certain times and on certain days of the week.

Implications for practice

In children with neoplastic disease, clown therapy appears effective for anxiety control and shows a positive trend for fatigue management. The results should be considered provisional in light of the few studies available, their high risk of bias, small sample size, and lack of blinding. The effects on pain, fear, and mood are also promising, but the outcomes measured are derived from individual studies.

Statistical heterogeneity is very high, but this is not surprising, as the sources of clinical heterogeneity are multiple: (a) the mean age of participants is 6.9-10.9 years (school-age children), but the age range is much wider (3-18 years) and includes preschool- or school-age children, preadolescents, and adolescents. This may have resulted in different efficacy of the intervention depending on the child's level of neurocognitive development; (b) the temperament and sense of humor of each participant are different, and for the same performance of the clown doctors, varied and contrasting reactions may have been triggered; (c) the health and illness conditions of the participants (e.g., type and stage of neoplasm), beyond the inclusion criteria applied, may be very heterogeneous, hence different sensitivity and predisposition toward the intervention.

Other sources of heterogeneity include the following: (a) the different cultural patterns of the countries (Italy, Spain, Turkey, Iran, Taiwan) where the studies were conducted may have influenced the child, the practitioners, and the evaluator in terms of perception, measurement, management, and approach to symptoms and emotions; (b) clown therapy was delivered to a child or a group of children by one or two clown doctors (the different role models may not have worked indifferently for any child) with heterogeneous levels of training, experience, professionalism, skills, and abilities; (c) standard care was not described; (d) it was not specified whether or not the intervention took place in the presence of the parents (and therefore it is not possible to know, if so, what their role was during clown therapy); (e) the outcome measurement instruments have different intrinsic characteristics (e.g., duration and/or mode of compilation and administration, sensitivity and specificity).

Implications for research

Further studies with larger sample sizes are needed, preferably multicenter studies, with better methodological quality and low risk of bias, to be more confident about the effectiveness of clown therapy for children with neoplastic disease. A greater number of studies and participants could allow the effect of the intervention to be stratified according to the gender and age of the child and his sociocultural characteristics. It would also be desirable for future studies to clarify the role assumed by parents to highlight the net benefit of the intervention.

Due to the intrinsic nature of the latter, the authors of the included studies were unable to guarantee double blinding of participants and healthcare professionals; however, as demonstrated by a previous study [59], it would be possible to blind the evaluator.

Limits

The small number of participants, the low methodological quality, the high risk of bias, and the considerable statistical and clinical heterogeneity of the included studies represent limitations which, taken together, suggest adopting great caution regarding the reliability of the results obtained and their external validity.

Conclusions

Clown therapy seems to have a positive effect on the symptoms and emotions of children with cancer, foremost on anxiety and fatigue but also on pain, fear, and mood. That said, given that the certainty/quality of the evidence is very low, pending further research, the results should be considered with great caution because it is not possible to make a definitive judgment on the benefit of the intervention.

Statements and Declarations

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Potential competing interests

The authors declare that they have no known competing interests that could influence the work reported in this paper.

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