Effectiveness of non-pharmacological interventions to reduce procedural anxiety in children and adolescents undergoing treatment for cancer: a systematic review and meta-analysis.

Running title: Interventions for procedural anxiety in children with cancer

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Abstract

Objective: Children and young people (CYP) with cancer undergo painful and distressing procedures. We aimed to systematically review the effectiveness of non-pharmacological interventions to reduce procedural anxiety in CYP.

Methods: Extensive literature searches sought randomised controlled trials that quantified the effect of any non-pharmacological intervention for procedural anxiety in CYP with cancer aged 0-25. Study selection involved independent title and abstract screening and full text screening by two reviewers. Anxiety, distress, fear and pain outcomes were extracted from included studies. Where similar intervention, comparator and outcomes presented, meta-analysis was performed, producing pooled effect sizes (Cohen's *d*) and 95% confidence intervals (95% CI). All other data were narratively described. Quality and risk of bias appraisal was performed, based on the Cochrane Risk of Bias tool.

Results: Screening of 11,727 records yielded 56 relevant full texts. There were 15 included studies, eight trialling hypnosis, and seven non-hypnosis interventions. There were large, statistically significant reductions in anxiety and pain for hypnosis, particularly compared to treatment as usual (anxiety: *d*=2.30; 95% CI: 1.30 to 3.30, p<0.001; pain: *d*=2.16; 95% CI: 1.41 to 2.92, p<0.001). Evidence from non-hypnosis interventions was equivocal, with some promising individual studies. There was high risk of bias across included studies limiting confidence in some positive effects.

Conclusions: Evidence suggests promise for hypnosis interventions to reduce procedural anxiety in CYP undergoing cancer treatment. These results largely emerge from one research group, therefore wider research is required. Promising evidence for individual non-hypnosis interventions must be evaluated through rigorously conducted randomised controlled trials.

Keywords (up to 10): cancer, oncology, procedure, anxiety, distress, pain, hypnosis, distraction, psychotherapeutic, systematic review, meta-analysis, child and adolescent

Background

Childhood and adolescence is a challenging time to receive a cancer diagnosis [1]. Young people who develop a malignancy are likely to undergo numerous painful procedures during diagnosis and treatment. Such procedures may induce internal feelings of anxiety and worry, which manifest in displays of emotional or physical distress. Distress for young patients and their families is high during cancer treatment and may persist after treatment ends, disrupting family dynamics[2]. Often young patients consider treatment procedures, rather than the condition itself, as the most difficult part of having cancer, with procedural anxiety considered the most negative burden on quality of life in one sample of CYP with cancer [3]. Indeed, up to half of young children with cancer experience clinically significant emotional distress throughout acute treatment [2]. Patients may require many invasive distressing needle procedures as part of intravenous (IV) therapy, such as lumbar puncture (LP), bone marrow aspiration (BMA), IV catheter insertion, IV port access and venepuncture [4].

Anxiety may not decrease with repeated procedures, and in some cases may increase, particularly where pain is not well managed [5]. Young patients may not yet have developed effective coping mechanisms, and may not fully appreciate the significance of their disease [6]. Childhood and adolescence is a transitional time often associated with unique psychosocial and behavioural challenges that independently challenge emotional resilience [7]. Additionally, family coping mechanisms are placed under great strain following diagnosis of childhood cancer, with this potentially exacerbated in proportion to the child's level of pain [8].

Anxiety can be defined as an internal emotion characterised by feelings of tension, worry and activation of the autonomic nervous system [9]. Distress on the other hand is often considered a more vague concept, sometimes understood as functional impairment related to specific stressors [10], or used as an umbrella term for the various responses to such stressors [11] in this case a cancer procedure. The quantification of distress however usually relies on observation of physical manifestations of anxiety, fear or worry. As such distress related to cancer treatment may be transient, dissipating after the procedure, while anxiety, fear and worry may persist. Despite anxiety and distress being defined differently, much literature uses the terms synonymously alongside fear to describe procedural anxiety [2, 12, 13]. Because anxiety, fear and distress are different but closely linked, we consider all three outcomes as important. In this review, we will refer to procedural anxiety as the broad concept to encompass anxiety, fear and distress, but will be driven by the language of the included studies when referring to specific reported outcomes such as those quantifying anxiety, distress and fear.

There is no published guidance about how to reduce procedural anxiety associated with cancer treatment for children. Although guidelines exist for pain management for children with cancer, pain is but one component contributing to procedural anxiety [12]. A variety of approaches to treat procedural anxiety have been trialled, which can be broadly split into pharmacological and non-pharmacological. The former ranges from general and local anaesthesia, to analgesic medication including paracetamol, Non-steroidal anti-inflammatory

drugs, opioids, midazolam and aromatherapy[14-18]. Commonly studied non-pharmacological approaches include cognitive behavioural interventions [19], hypnosis [20] and distraction techniques [21]. Side effects of medications can add to the disease burden of already highly medicated cancer patients. Effectively developing non-pharmacological strategies to manage distress may develop self-efficacy and promote coping and resilience.

No previous systematic reviews have conclusively reviewed the quality and effectiveness of trials of non-pharmacological interventions for procedural anxiety in CYP. Instead previous reviews have focused on parent-child interventions and populations that include young adults, [2 22 13 7] while an integrative review by Landier & Tse [23] described relevant trials with a range of study designs, but is now out of date. Perhaps of most relevance to the current review, Thrane [12] examined the effectiveness of integrative modalities on pain and anxiety in 1-18 year olds with cancer. However, relevant articles may have been published since 2013, the author only included studies assessing both pain and anxiety, and did not perform a standardised quality or risk of bias appraisal on the included randomised controlled trials (RCTs) [12].

A systematic review of the effectiveness of interventions aiming to reduce procedural anxiety in CYP with cancer is warranted. Knowledge of the effectiveness of available interventions, or areas showing promise, can help to improve the management of procedural anxiety in this population and direct future research in the area. Therefore, the aim of this review was to investigate the effectiveness of interventions targeting procedural anxiety for children and young people with cancer undergoing treatment procedures.

Methods

The methods used to identify and select evidence followed the methodological approach recommended by the University of York's Centre for Reviews and Dissemination [24]. Initial searching was performed as part of a broader systematic review (protocol registered on the PROSPERO database: PROSPERO CRD42017056863), which focused on other conditions as well as cancer and broader mental health related interventions.

Search strategy

The search methods included extensive database searching and supplementary searching techniques, seeking peer-reviewed and non-peer-reviewed sources. A search strategy was developed and tested in the databases to be searched. The strategy used both controlled headings (e.g. MeSH) and free-text searching.

Thirteen electronic databases were searched: MEDLINE including MEDLINE in-process (via OvidSp), EMBASE (via OvidSp), PsycINFO (via OvidSp), Cochrane Database of Systematic Reviews (via the Cochrane Library), CENTRAL (via the Cochrane Library), DARE (via the Cochrane Library), HTA database (via the Cochrane Library), NHS EED (via the Cochrane

Library), CINAHL (via EBSCOhost), British Nursing Index (via ProQuest), HMIC (via OvidSp), Conference Proceedings Citation Index (via Web of Science), Science Citation Index (via Web of Science). No date restrictions were applied. Searches were conducted between 28th January and 4th February 2016 and updated in July 2017. An example search strategy used for the MEDLINE database is available in Online Supplementary Appendix A. All references identified by the searches were exported into EndNote (EndNote X7, Thomson Reuters, New York, USA) prior to de-duplication and screening.

Supplementary searches were also conducted: backward citation searches were conducted by DMa; forward citation chasing searches were conducted by DMa using Web of Science and Google Scholar. To locate grey literature, CINAHL, HMIC and Conference Proceedings Citation Index were searched, as well as the website OpenGrey via http://www.opengrey.eu/.

Inclusion criteria

Studies were included in the current review if they were RCTs that involved children and young people (aged 0-25 years) with cancer. The participants needed to have received a non-pharmacological intervention of any type targeting procedural anxiety. Effectiveness of the intervention had to be measured in terms of impact on at least one measure of the CYP's anxiety or distress. Only English language papers were included.

Study selection

Relevant studies were identified in two stages based on the inclusion criteria. First, two reviewers conducted title/abstract screening independently for each record within Endnote X7 software. Disagreements were resolved through discussion between two reviewers, with referral to a third reviewer as necessary. Full texts of records were then obtained wherever possible and screened for inclusion independently by two reviewers (MN, DMa). Records were excluded if no full text was available. Disagreements were resolved through discussion between the two reviewers, with referral to a third reviewer as necessary (DMo).

Methods of analysis/synthesis

Data extraction. A data extraction form was developed and piloted. Data on article details and aims, participants, intervention, outcome measures, outcome data (n, mean, standard deviation) and risk of bias were extracted into Microsoft Office Excel 2010 by DMa and checked by MN. Where data were missing authors were contacted for information by MN, however no additional information was retrieved as a result.

Quality appraisal. Quality appraisal was conducted during data extraction using criteria adapted from the Cochrane risk of bias tool [25]. We included additional items on intention to treat analysis, baseline outcome similarities, drop outs, response rate, intervention detail, intervention manuals, adherence, follow up measures and psychometric properties of

outcome measures. Quality appraisal disagreements were resolved through discussion. The appraisals were not used to exclude papers.

Categorisation of variables.

Intervention categories. Due to the number of included studies testing hypnosis interventions, the included interventions were categorised as either hypnosis or non-hypnosis.

Outcome categories. Outcomes of interest were those which quantified patient distress, anxiety, fear or pain during a procedure.

Data analysis and synthesis. Differences between intervention and control groups at post-test were analysed. Where multiple studies shared the same intervention type and similar comparator meta-analysis was considered feasible. Random effects meta-analysis models were fitted to pooled effect sizes (Cohen's *d*) across the studies. For each weighted mean effect size estimate, we calculated 95% confidence intervals. The I^2 statistic was used to quantify heterogeneity with higher values indicating greater heterogeneity [26]. When two or more separate outcomes representing distress and anxiety were reported in a study, the effects were combined into a single summary effect for that study. The standard error for this effect was calculated using the correlation between the measures, obtained from the paper itself or other research [27]. Pooled effect sizes were interpreted as 'small', 'medium' and 'large' effect sizes classified as $d = 0.20$, $d = 0.50$ and $d = 0.80$, respectively. [28] All meta-analyses and associated forest plots were produced using the *metan* command in Stata.

Results

Study selection

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram [29] in Online Supplementary Figure 1 summarises study selection for this review. After the removal of duplicates, a total of 11,727 records were screened at title and abstract stage, identifying 37 articles for full text screening after 11, 669 records did not meet inclusion criteria. Full text screening of these yielded seven studies for inclusion. Additional citation chasing of the seven included articles identified 19 relevant full texts which were screened to yield a further nine includable articles. Therefore, in total 16 articles reporting on 15 studies met our inclusion criteria and were included in the synthesis. Reasons for excluding the 40 studies at full text screening are described in Online Supplementary Figure 1. Inter-rater agreement at full text screening was low at this stage (Cohen's Kappa = 0.37) which is to be expected given the complexity of the area and wide range of terminology and outcome measures presented. However, all disagreements were resolved after discussion between reviewers.

Description of included studies

Study details

The details of included studies are shown in Table 1. Studies were conducted between 1982 and 2010. The majority of studies took place in North America, with nine studies conducted in the USA [21, 30-36]. Five studies took place in Europe, with four by the same research group in Greece [37-40]. One study was conducted in Vietnam [41]. All papers were published in peer reviewed journal articles except one PhD dissertation [42] – although the findings from this thesis were later published [43]. Six of the studies included more than one intervention group.

Sample sizes ranged from 12 to 80 with 585 CYP participants in total. Seventy four parents participated across two studies, engaging in the intervention or reporting outcomes [21, 40]. Overall, 42% of the sample were female (where reported; two studies did not report this [34, 38]), with a mean age of 8.7 years (range one to 24 years old). Inclusion criteria within studies usually specified an age range, ability to understand instructions and no diagnosed mood disorder.

Intervention details

Table 2 details information about interventions trialled across included studies. Nineteen interventions were assessed across the fifteen included studies. We used broad categories of hypnosis (n=9) and non-hypnosis (n=10) to classify intervention groups. Parents were usually present for the intervention. In the study by Dahlquist et al. [21] parents were responsible for prompting the CYP to play with the distracting toy. Interventions varied in duration, while procedures varied from port access to complex and painful procedures such as a bone marrow aspiration. Where reported, hypnosis interventions were all delivered by a trained therapist, however the personnel who delivered non-hypnosis interventions varied from a nurse or clinician [44]; researcher [32, 42]; therapist [31, 37]; or the young person themselves [21, 30, 35, 41]. The 19 intervention arms were compared with treatment as usual (TAU) (n=13); attention control (n=3) or active controls (n=6). In three studies, there were two control groups: attention control and TAU [38-40]. In the study by Hedén et al [41] which compared two active conditions, we were led by the study in determining which was the intervention condition, and which the comparator. Table 2 provides details of active controls where relevant.

Outcomes

There were 33 measures of CYP anxiety, 20 measures of CYP distress and seven of CYP fear. Pain was reported in all studies except Dahlquist et al. [21]. Procedural anxiety was most frequently self-reported using a visual analogue scale (VAS) [30, 32, 36, 37, 40, 44]; the Procedural Behaviour Checklist [37-40], or FACES [45] rating scale [38, 39]. For meta-analysis, multiple measures of procedural anxiety were combined in five studies [30, 37-40, 44] and pain in one study [44].

Quality appraisal and risk of bias

Online supplementary Table 1 provides a summary of the quality and risk of bias appraisal of included papers. All articles scored positively on the description of the intervention, and freedom from selective reporting. Retention rates were greater than 85% in 13 of the 16 articles; however, only four articles included a follow-up assessment beyond post-treatment. The included articles often had high uncertainty or lack of clarity in the reporting of randomisation and allocation concealment, with 15 of 16 papers not reporting clearly in one or both of these domains. Eight papers scored fewer than five positive responses across the 13 domains [21, 30, 32, 33, 36, 42-44]. In particular, the two Kuttner articles [42, 43] only scored positively in three areas. Three papers by Liossi et al. [38-40] were the highest scoring in quality/risk of bias appraisal.

Analysis of included study findings

Effect of Hypnosis Interventions on procedural anxiety and pain

Eight studies assessed hypnosis techniques for the reduction of procedural anxiety during cancer treatment [33, 34, 36-40, 42] and were compared either with treatment as usual (TAU [37-40, 42]), an attention control [38-40], or other active controls [33, 34, 36]. We identified five variations of hypnosis in the included studies, which were described as follows. *Hypnosis* [33, 34, 37, 39] was characterised by the study authors describing the CYP being induced by the therapist using a variety of relaxation and imagery techniques. *Direct suggestions* [38] included thoughts about 'switching off' pain, or focusing specifically on the patient's body and controlling it. *Indirect suggestions* [38] related to imagining being in a different time or place which holds positive associations. *Imaginative involvement* [36, 42], involved the authors describing a process of the CYP imagining themselves being in a different situation. *Self-hypnosis* [40] placed the emphasis on the child's ability to use hypnosis techniques during the medical procedure.

The forest plot in Figure 1 displays the meta-analysis of hypnosis interventions for procedural anxiety and pain where sample size, mean and standard deviation at post-intervention were reported. Effect sizes (Cohen's *d*) and 95% confidence intervals are included, with a positive effect size representing improvement on the measure. Separate meta-analyses were conducted for the three comparator subgroups: TAU, attention control and active control.

Hypnosis interventions yielded a statistically significant, large pooled effect size indicating a reduction in anxiety when compared with TAU (*d*=2.30; 95% CI: 1.30 to 3.30, p<0.001) and attention controls (*d*=2.06; 95% CI: 1.01 to 3.11, p<0.001). When compared with active controls, hypnosis interventions provided a statistically significant and large pooled effect size indicating a reduction in anxiety (*d*=0.81; 95% CI: 0.02 to 1.60, p=0.049). However, the width of the confidence intervals reflects uncertainty about the true magnitude of this effect. Heterogeneity was large and statistically significant for the TAU and attention control meta-analyses, which suggest differences between the individual studies that warrant further

explanation (TAU I^2=86.8%, p<0.001; attention I^2=88.6%, p<0.001). Heterogeneity was not statistically significant for the active control analysis (I^2=65.8%, p=0.09).

Hypnosis interventions provided a statistically significant and large reduction in pain when compared with TAU (*d*=2.16; 95% CI: 1.41 to 2.92, p<0.001) and attention controls (*d*=2.24; 95% CI: 1.66 to 2.82, p<0.001). When compared with active controls, there was a lack of evidence for the effect of hypnosis over active controls (*d*=0.41; 95% CI: -0.56 to 1.38, p=0.41). Heterogeneity was large and statistically significant for the TAU and active control comparator meta-analyses, reflecting uncertainty (TAU I^2=68.2%, p=0.01; p<0.001; active control I^2=78.4%, p=0.03). For hypnosis compared with attention, heterogeneity was not statistically significant (I^2=43.4%, p=0.15).

The studies by Liossi et al. [37] and Wall et al. [34] were not included in the meta-analysis as raw data were unavailable at post-intervention. Liossi et al. [37] reported favourable effects for both hypnosis and a cognitive behavioural intervention in reducing anxiety and pain, compared to TAU, with hypnosis the more effective of the two interventions. Wall et al. [34] compared hypnosis with an active cognitive strategy intervention for the alleviation of procedural pain and anxiety. The authors reported that both interventions were effective in reducing pain, but neither was able to reduce anxiety.

Effect of Non-Hypnosis Interventions on procedural anxiety and pain

Eleven non-hypnosis intervention arms were identified across nine studies, including arms in Kuttner et al. [42] and Liossi et al. [37], which ran alongside hypnosis interventions. Non-hypnosis interventions were classified as a form of distraction [21, 30, 32, 35, 41, 42, 44], cognitive behaviour therapy (CBT) [37] or music therapy [31]. Distraction interventions were an interactive CD-ROM [30]; heated pillow [44]; listening to music [41]; virtual reality [32]; general distraction such as looking at points in the room [32, 42]; a self-selected device from a variety of games or books [35]; and an interactive device [21]. Comparators included TAU [30, 32, 35, 37, 42, 44], a waitlist group [21] and three active controls: audio books [31], blowing soap bubbles [44] or headphones without music [41].

Only two studies reported data on anxiety outcomes that were suitable for meta-analysis [30, 42] and three reported meta-analysable pain outcome data [30, 35, 42], all compared with a TAU control group. Figure 2 is a forest plot of non-hypnosis interventions for procedural anxiety and pain. When compared with TAU, there was a lack of evidence for the effect of non-hypnosis interventions on either anxiety (*d*=-0.29; 95% CI: -0.81 to 0.23, p=0.28) or pain (*d*=-0.02; 95% CI: -0.54 to 0.49, p=0.93). In both domains negligible increases in symptoms were observed, with wide confidence intervals providing uncertainty about the true effect of the interventions. Heterogeneity was small and not statistically significant for both outcomes (anxiety I^2=0.0%, p=0.6; pain I^2=25.9%, p=0.3), suggesting consistency in the findings.

Of the six studies that were not meta-analysable, it was possible to calculate effect sizes with 95% confidence intervals and p-values for anxiety and pain outcomes reported in Hedén et al. [44] and Nguyen et al. [41]. In the study by Hedén et al. [44], participants were randomised to one of

two distraction techniques. Outcome assessments were compared between distractors, and against baseline data for standard care. A heated pillow was more effective than blowing soap bubbles at reducing distress, according to parent assessments (d=0.91; 95% CI: 0.13 to 1.70, p<0.02), although neither intervention reduced distress or pain compared with standard care according to nurse ratings (p>0.05). Nguyen et al. [41] reported a large effect for listening to music through headphones compared to using headphones without music on reducing both anxiety (d=1.47; 95% CI: 0.76 to 2.17, p<0.001) and pain (d=1.49; 95% CI: 0.78 to 2.19, p<0.001).

It was not possible to extract the data required to calculate effects sizes for the remaining four studies. Burns et al. [31] only obtained data about anxiety for one participant in the control group. Dahlquist et al. [21] did not report raw values, but indicated statistically significantly lower distress in their distraction intervention group, compared to a waitlist group. Gershon et al. [32] did not report raw values other than for pulse, however they indicated that nurse-reported pain was statistically significantly lower in both intervention groups compared with the TAU group, but not for overall observed distress. Liossi et al. [37] only reported median outcome values at post intervention, but indicated that their cognitive behavioural intervention led to statistically significant reductions in pain, anxiety and distress when compared to a control group.

Discussion

The studies included in this systematic review demonstrate a beneficial effect for hypnosis-based interventions for reducing procedural anxiety and pain during treatment for CYP with cancer. While meta-analysis yielded large and statistically significant effects, high statistical heterogeneity was observed for a number of comparisons, reflecting the need for more evidence and further interpretation of findings. The largest effects were seen for studies completed by one research team [37-40]. The other hypnotic interventions provided equivocal results; Kuttner [42] and Katz et al. [33] found no benefit for pain and anxiety, while the results from Olmsted et al. [36] were more closely aligned with the positive findings of the Liossi research group. Without the programme of work led by Liossi and colleagues, the effects of hypnosis would be uncertain and therefore replication of this research in different settings would strengthen the conclusions that can be drawn from this systematic review. Although this caveat must be considered in interpreting these results, these studies were assessed as higher quality than others in the review, meaning there is no suggestion that these results are attributable to methodological bias.

Non-hypnosis interventions provided more equivocal results. We were able to meta-analyse fewer studies, and the meta-analysis suggests no beneficial effect for non-hypnosis distraction on either anxiety or pain outcomes [30] [42] [35]. Single studies contradict this with tentative evidence for a reduction in pain, anxiety or both outcomes for listening to music ([41], pain and anxiety), an interactive device ([21], anxiety) virtual reality or non-virtual reality distraction ([32], pain) and CBT ([37], pain and anxiety). In some cases (e.g. [21, 32]) there were equivocal or unclear results, with absence of raw data impeding synthesis. Given the nature of research in

this area, high-quality studies offering robust evaluations of these interventions are warranted.

The methodological quality of RCTs that evaluate the effectiveness of non-pharmacological interventions for procedural anxiety in children and young people with cancer is generally low. Future trials need to attend to risk of bias in areas such as randomisation and allocation concealment, to ensure that they report this information (as directed by the CONSORT guidelines) and generally improve quality compared to existing research. The inclusion of follow-up assessments to evaluate long-term effectiveness after repeated procedures, whilst assessing fidelity and producing a manual for developed interventions, would also strengthen knowledge in this field. Furthermore, the small number of included studies in each category precluded the analysis of publication bias. [46]

The most relevant previous systematic review examined the effect of interventions on pain and anxiety in CYP with cancer across the entire cancer experience [12]. Thrane [12] found good evidence that complimentary non-pharmacological modalities can reduce distress, particularly during painful procedures. Specifically, virtual reality, different mind–body techniques, music, massage, creative arts therapy and hypnosis were beneficial. The current review goes further, using meta-analysis to pool together findings relating to procedural anxiety and pain for hypnosis and other intervention types. We find promising effects for hypnosis interventions only and call into question the risk of bias, a crucial element that distinguishes this review from others, for the majority of RCTs in this area.

Hypnosis is a relatively inexpensive procedure that can be personalised to the individual. Increased self-efficacy may be developed through rehearsal of self-hypnosis techniques, providing an opportunity for mastery and active participation by the CYP in their current and future medical care [47]. There are few adverse effects, medical and nursing staff can be trained in these techniques and the trials included in this review demonstrate acceptability and feasibility in children, young people and parents. Without intervention the impact of repeated exposure to invasive procedures at a time of high levels of parental anxiety, may induce trauma with long lasting effects on mental health and adherence to treatment [48, 49]. Hypnosis appears to show promise as an intervention which may therefore reduce the time taken for invasive procedures, which can be considerable when CYP are distressed and unable to cooperate in their care. However, additional trials of hypnosis techniques are required in order to ascertain the likelihood of these benefits.

Study Limitations

This systematic review is the first to assess the quality and effectiveness of all RCTs of interventions targeting reduced procedural anxiety in CYP undergoing cancer treatment procedures. However the evidence base limits the certainty of any conclusions. Studies frequently suffered from high or unclear risk of bias, while high heterogeneity between research groups assessing hypnosis interventions reduces confidence in pooled estimates.

Furthermore, the four studies by Liossi and colleagues [37-40] were conducted with participants of a mean age around eight years old (despite accepting five to 16 year-olds), indicating a need for studies performed with older and younger groups of CYP. For some interventions, reliance on evidence from single trials which were often poorly reported or conducted, against a range of comparators, highlights the uncertainty of evidence in the area.

The need to assess transient pain and anxiety during procedures necessitates the use of self-report VAS or observational measures completed by clinicians or researchers, which often means that assessors are not blinded. The element of subjectivity in these outcomes reduces reliability, further necessitating larger samples and repeated trials.

The pre-intervention anxiety symptoms of a CYP may determine the effectiveness of any intervention, however this was either not reported or pre-intervention symptoms assessed on scales that do not indicate level of clinical impairment, such as a self-report VAS. Knowledge of baseline distress or anxiety would aid interpretation of results.

Clinical Implications

In order for clinicians to have access to, and confidence in interventions for reducing procedural anxiety, further high quality primary research needs to be undertaken. In particular, existing intervention types such as hypnosis and distraction techniques should be rigorously evaluated with larger samples and wider age ranges to explore the contexts in which effectiveness may hold. Key considerations in addition to trial methodology discussed above are the careful assessment of baseline levels of distress or anxiety, and attention to parental and professional distress and anxiety. The impact of techniques like hypnosis is likely to vary between those who become mildly anxious during a procedure compared to those who meet diagnostic criteria for Post-Traumatic Stress Disorder as a result of repeated procedures [50]. Likewise, the impact of parental distress can be significant, and interventions that focus on the parents of children with anxiety have demonstrated efficacy [51, 52].

The findings of the present review may be transferable to other young people long term medical conditions that requite frequent invasive treatments, for example autoimmune diseases. Interventions that are effective across a range of procedures and physical conditions could be widely implemented and have a significant beneficial impact on care. Further research is first needed to ascertain whether effects are consistent and transferable.

For clinicians seeking to reduce procedural anxiety in children and adolescents undergoing treatment procedures which are distressing and/or painful, there is promising evidence for hypnosis interventions.

Conclusion

Given that children and young people with cancer are often distressed by the various procedures that they need experience, often repeatedly, it is important that any interventions that can reduce procedural anxiety are implemented alongside the typical anaesthetic interventions intended to reduce pain. There is promising evidence that hypnosis

interventions can help children and young people with cancer reduce procedural anxiety. However, research is required to confirm that the very large beneficial effects seen in one set of studies hold in other age groups and clinical settings and are replicable by other research groups. There is anecdotal evidence that CBT [37], virtual reality distraction [32] and music [41] may be effective, but further work here is also needed to build on a relative dearth of high quality evidence.

Conflict of interest statement

We declare no conflict of interest.

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Table 1. Study characteristics

Study	Country	Sample Size	Age M (SD) [range] years	Females (%)	Cancer Type	Treatment Groups
Bisignano (2006)	USA	30	11.4 (NR) [6-18]	50.0	46.5% ALL, 10% sickle cell anaemia, 3.3% lymphoma, 3.3% AML, 3.3% osteosarcoma, 6.7% Hodgkin's disease, 6.7% Glanzmann's thrombasthenia, 3.3% aplastic anaemia, 3.3% chronic myelomonocytic leukaemia	1
Burns (2009)	USA	12	17.5 (3.7) [13-24]	41.7	NR	1
Dahlquist (2005)	USA	29	3.5 (0.8) [2.4-5.2]	24.1	NR	1
Gershon (2004)	USA	59	12.7 (NR) [7-19]	49.0	Various forms of leukaemia, lymphoma, and solid mass tumours.	2
Hedén (2008)	Sweden	28	3.5 (NR) [2.5-7]	39.3	50% leukaemia, 21.4% central nervous system tumour, 28.6% solid tumour	2
Katz (1987)	USA	36	8.25 (1.7) [*6-11*]	33.3	ALL	1
Kuttner (1984)	Canada	48	6.9 (2.0) [3-10]	37.5	Leukaemia	2
Liossi (1999)	Greece	30	8.0 (2.5) [*5-15*]	43.3	Leukaemia	2
Liossi (2003)	Greece	80	8.7 (2.9) [*6-16*]	NR	Leukaemia or non-Hodgkin's lymphoma	2
Liossi (2006)	Greece	45	8.8 (2.9) [*6-16*]	48.9	Leukaemia or non-Hodgkin's lymphoma	1
Liossi (2009)	Greece	45	8.5 (2.2) [*7-16*]	55.6	NR	1

Nguyen (2010)	Vietnam	40	9.1 (1.8) [7-12]	37.5	Leukaemia	1
Olmsted (1982)	USA	33	10.1 (3.2) [6-17]	48.5	84.9% Leukaemia, 9.1% non-Hodgkin's lymphoma, 6.1 neural tumour	1
Wall (1989)	USA	20	NR [*5-13*]	NR	NR	1
Windich-Biermeier (2007)	USA	50	10.5 (3.8) [5-18]	46.0	64% Leukaemia, 12% lymphoma, 18% solid tumour, 6% histiocytosis	1

M=mean; SD=standard deviation; NR=not reported; ALL=Acute Lymphoblastic Leukaemia; AML=Acute Myeloid Leukaemia. *Note, italicised age range reflects inclusion criteria, in lieu of reported range of sample.*

Table 2. Intervention details

Study	Study Intervention Name	Intervention Category	Intervention structure	Medical Procedure	Comparator(s)	Outcome measures
Bisignano (2006)	CD-ROM Intervention*	Distraction	1 x 20 minute session	IV Catheter Insertion	TAU	Anxiety VAS, Children's Fear SR Faces Scale; Children's Pain SR Faces Scale; PBRS; Threat Appraisal Questionnaire; Kidcope
Burns (2009)	Therapeutic Music Video	Music therapy	2 x 60 minute sessions per week for 3 weeks	SCT	Active control: Low-Dose Audio Books	STAIC; Child Health Questionnaire; Short Form Health Survey Medical Outcomes Study; SDS; Jalowiec Coping Scale-Revised; Herth Hope Index; Reed Spiritual Perspective Scale; Nowotny Hope Scale; Reed Self-Transcendence scale; Rosenberg Self-Esteem Scale; Index of Wellbeing; LASA Uniscale
Dahlquist (2005)	Portable Electronic Toy	Distraction	3 LOP sessions	Intramuscular Injections and PA	Wait-List Control	STAI; Anxiety VAS; OSBD
Gershon (2004)	VR distraction*	Distraction	1 x 5 minute practice + LOP session	PA	TAU	VAS Anxiety; VAS Pain; CHEOPS; Heart Rate
Gershon (2004)	Non-VR Distraction*	Distraction	1 x 5 minute practice + LOP session	PA	TAU	

Hedén (2008)	Blowing Soap Bubbles*	Distraction	1 x LOP session	PA	Active control: Heated Pillow	Fear VAS; Distress VAS; Pain VAS
Katz (1987)	Hypnosis	Hypnosis	2 x 30 min training session + 3 x 20 min pre-procedural session, every 1-6 months	BMA	Active control: Play	Nurse Rating of Anxiety (likert); Fear SR Faces Scale; PBRS (revised); Pain SR VAS; Rapport Ratings; Response to Hypnosis
Kuttner (1984)	Active Distraction*	Distraction	1 x 20 min preparation + 2 x LOP sessions, twice per year	BMA and LP, or BMA only	TAU	PBRS-revised; Anxiety Judgement Rating Scale (likert); Pain Judgement Rating Scale (likert); Anxiety SR Faces Scale; Pain SR Faces Scale
Kuttner (1984)	Imaginative Involvement*	Hypnosis	1 x 20 min preparation + 2 x LOP sessions, twice per year	BMA and LP, or BMA only	TAU	
Liossi (1999)	Hypnosis*	Hypnosis	3 x 30 minute sessions	BMA	TAU	Anxiety SR Faces Scale; Pain SR Faces Scale; The Stanford Hypnotic Clinical Scale for Children; PBCL; Pain VAS
Liossi (1999)	Cognitive Behaviour*	CBT	3 x 30 minute sessions	BMA	TAU	
Liossi (2003)	Direct hypnotic suggestions	Hypnosis	3 x 40 minute (self-hypnosis – 45 minute) sessions	LP	Attention, TAU	Wong–Baker FACES Pain Rating Scale; Wong–Baker FACES Anxiety Rating Scale; PBCL; Stanford Hypnotic Clinical Scale for Children
Liossi (2003)	Indirect hypnotic suggestions	Hypnosis	3 x 40 minute (self-hypnosis – 45 minute) sessions	LP	Attention, TAU	
Liossi (2006)	Hypnosis*	Hypnosis	4 x 40 minute (self-hypnosis – 45 minute) sessions	LP	Attention, TAU	Wong–Baker FACES Pain Rating Scale; Wong–Baker FACES Anxiety Rating Scale; PBCL; Stanford

						Hypnotic Clinical Scale for Children
Liossi (2009)	Hypnosis*	Hypnosis	1 x 15 minute session	Venepuncture	Attention, TAU	Pain VAS; Anxiety VAS; PBCL; Anxiety VAS (parental)
Nguyen (2010)	Music	Distraction	1 x 10 minute session + LOP	LP	Active control: Earphones Without Music	6-item STAI; Numeric Rating Scale for pain; Heart Rate; Respiratory Rate; Oxygen Saturation; Blood Pressure
Wall (1989)	Hypnosis	Hypnosis	2 sessions of unknown duration	BMA or LP	Active control: Active Cognitive Strategy Group	Pain VAS; Anxiety VAS; Pain relief; STAI; McGill Pain Questionnaire; Stanford Hypnotic Clinical Scale for Children; Heart Rate; Temperature; Degree of imaginary involvement
Windich-Biermeier (2007)	Self-Selected Distracter*	Distraction	1 x LOP session	PA or Venepuncture	TAU	Glasses Fear Scale; Color Analogue Scale (pain); OSBD; Poke Questionnaire
Olmsted (1982)	Hypnosis	Hypnosis	1-6 x LOP session	BMA or LP	Non-Hypnosis Intervention	Anxiety Scale (5 point); Pain Scale (5 point)

IV=Intravenous; TAU=Treatment as Usual; LOP=Length of Procedure; NR=Not Reported; BMA=Bone Marrow Aspiration; SCT=Stem Cell Transplant; PA=Port Access; LP=Lumbar Puncture; VR=Virtual Reality; CBT=Cognitive Behaviour Therapy; SR=Self-Report; VAS=Visual Analogue Scale; PBRS=Procedural Behavioral Rating Scale; STAI=Spielberger's State-Trait Anxiety Inventory; STAIC=Spielberger's State-Trait Anxiety Inventory for Children; SDS=McCorkle Symptom Distress Scale; OSBD=The Observation Scale of Behavior Distress; CHEOPS=Children's Hospital of Eastern Ontario Pain Scale; *experimental and control groups also received anaesthetic
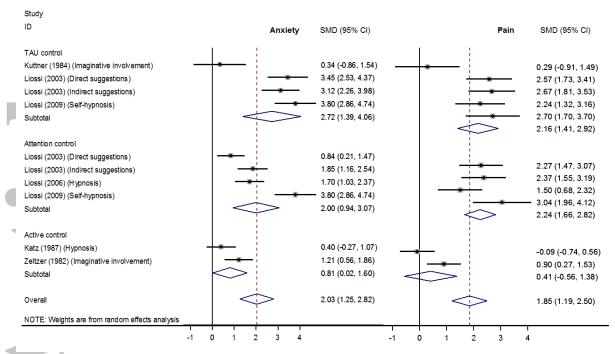
Figure 1. Forest plot showing the results of meta-analysis of the effects of hypnosis on anxiety (left y axis) and pain (right y axis) during cancer procedures at post-intervention. Outcomes are grouped by comparator. SMD=Standardised Mean Difference (Cohen's *d*); CI=Confidence Interval; TAU=Treatment As Usual. A positive effect represents reduced anxiety or pain.
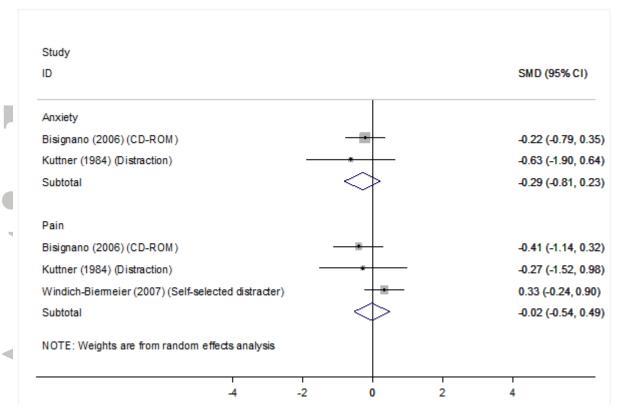
Figure 2. Forest plot showing the results of meta-analysis of the effects of non-hypnosis interventions on anxiety and pain during cancer procedures at post-intervention. SMD=Standardised Mean Difference (Cohen's *d*); CI=Confidence Interval. A positive effect represents improvement on the measure.