TABLE I. Literature Review Table – used studies

Children – cancer – pain – CAM

Study	Design	Sample	Intervention(s)	Findings	Findings short**	Quality of evidence	Quality level
Hypnosis							
Katz 1987*	RCT, evaluating **hypnotherapy** versus attention control for pain, anxiety and distress associated with BMAs	Children with acute lymphoblastic leukemia (6-11 years) undergoing repeated BMA who experience significant anxiety, fear, and/or pain during BMA (n=36)	**Hypnotherapy:** Hypnotic induction, active imagery, individually tailored, deep muscle relaxation, and suggestions. Ending with a post-hypnotic suggestion Attention control: Non-directed play sessions designed to control for the amount of time and attention	-An improvement was reported in self-reported pain and distress over baseline with both interventions, with no differences between them. -No significant main effects were found in PBRS scores. -Girls exhibited more distress behavior than boys on three of four dependent measures used. -Results are discussed in terms of potential individual differences in responding to stress and intervention that warrant further research	*Hypnosis vs attention control* = no differences for pain and distress *Post treatment vs baseline* + pain and distress (for hypnosis and control)	RCT, sufficient sample size, randomization process not entirely described, blinding of independent observers, nurses and observers, good inter-rater reliability. No selective reporting, adequate analysis, study completed as planned, no missing data	Moderate
Smith 1996*	RCT, cross-over, repeated measures single group study evaluating **hypnosis** versus distraction for pain, anxiety and distress associated with venipuncture or infusaport access	Children (3–8 years) with hematology and oncology diagnoses undergoing repeated venipuncture or infusaport access (n=27)	**Hypnosis:** favorite place hypnotic induction. Both parents and children were taught the exercises. Attention control/ distraction: activating the pop-up toy, noting interesting aspects of the toy	-Only children with high hypnotizability had reduced child self-reported pain and anxiety, parent-rated pain, and observer anxiety and distress from hypnosis intervention -Children with low hypnotizability in the distraction condition had significantly lower observer-rated anxiety only -Practical: parents and children were both trained in hypnosis exercises. Parents were very positive and exercises were easy to learn and practise.	*Hypnosis vs control* ++ for self-reported pain ++ for parented reported pain ++ for distress All only for children with high hypnotizability	RCT, cross-over design. Observers, trainers and parents were told that both interventions were equally effective, observers were blind to high and low hypnotizability level of children, both self-reported measurements and observer measures. Adherence to the exercises at home was monitored and no significant differences in compliance were observed between the groups. Sufficient sample size, no selective reporting, adequate analysis, study generally completed as planned, some missing data due to death of participants	High
Liossi 2003*	RCT, evaluating **direct hypnosis** and **indirect hypnosis** versus attention control and standard care for pain and distress associated	Children and adolescents (6–16 years) with leukemia or non-Hodgkin lymphoma undergoing repeated LPs (n=80)	**Indirect hypnosis**: Using metaphors, imagination using various senses, develop cues to experience immediate relaxation, and ways to adapt to discomfort. Ending with a post-hypnotic suggestion. Directed by therapist and then self.	-Direct and indirect hypnosis groups were equally effective and reported less pain and anxiety as compared with attention control or standard care groups. -Higher levels of child hypnotizability associated with increased treatment	*Hypnosis vs attention control or standard care* + for pain and distress (indirect and direct hypnotherapy)	RCT, sufficient sample size, independent observers, doctors and behavioral observers were blinded, blinding was measured, observers could only guess which children	High

Study	Design	Sample	Intervention(s)	Findings	Findings short**	Quality of evidence	Quality level
	with LPs		**Direct hypnosis:** "Analgesic" suggestions. Directed by therapist and then self. Attention control: including elements such as development of rapport, non-medical play, and no-medical verbal interactions Equivalent time was spend with the therapist as in hypnotherapy. Standard care: no contact with the therapist, medical care for pain with LP provided by the hospital staff.	benefit. -Treatment benefit lessened with self -hypnosis as compared with therapist-directed	*Indirect vs direct hypnosis* = for pain and distress	were in the direct hypnosis group (intervention 1), they could not distinguish between the other intervention groups and control group, no selective reporting, appropriate analysis, study completed as planned, no missing data.	
Liossi 2006*	RCT evaluating **hypnosis** versus attention control or standard care for pain and distress associated with LPs	Children and adolescents (6–16 years old) with leukemia or non-Hodgkin lymphoma undergoing repeated LPs (n=45)	**Hypnotherapy**: Standard care + "Analgesic" suggestions, ending with a post-hypnotic suggestion. Directed by therapist and then self. Attention control: Standard care + including elements such as development of rapport, non-medical play, and no-medical verbal interactions Equivalent time was spend with the therapist as in hypnotherapy Standard care: EMLA/analgesic cream. Medical care for pain with LP provided by the hospital staff	-Group receiving hypnosis, in addition to local anesthetic (EMLA), reported less pain and anxiety, and less observed behavioral distress as compared with other groups. -Treatment superiority was maintained when switched to self -hypnosis following therapist-directed hypnosis. -Higher levels of child hypnotizability associated with increased treatment benefit	*Hypnosis vs attention control or standard care* ++ for self-reported pain and distress	RCT, sufficient sample size. Independent observers, doctors and behavioral observers were blinded. Blinding was measured, observers could not guess in which groups the children were allocated. Inter-rater reliability was tested and found to be good. No selective reporting, appropriate analysis, study completed as planned, no missing data	High
Liossi 2009*	RCT evaluating **self hypnosis** versus attention control or standard care for pain and distress associated with venipuncture	Children and adolescents (7–16 years) with cancer undergoing venipuncture (n=45)	**Self hypnosis**: Standard care + "Analgesic" suggestions, ending with a post-hypnotic suggestion. Following that, children were taught self-hypnosis. Attention control: Standard care + including elements such as development of rapport and no-medical verbal interactions. Equivalent time was spend with the therapist as in hypnotherapy Standard care: EMLA/analgesic cream. Medical care for pain with LP provided by the hospital staff	-Self-hypnosis + local anesthetic (EMLA) reported less anticipatory and experienced anxiety, pain and observed behavioral distress as compared with other groups. -Parents experienced less anxiety in hypnosis group	*Self-hypnosis vs attention control or standard care* ++ for self-reported pain and distress + anxiety parents	RCT, sufficient sample size. Independent observers, doctors and behavioral observers were blinded, blindness was measured, observers could not guess in which groups the children were allocated. Inter-rater reliability was tested and found to be good No selective reporting, appropriate analysis, study completed as planned, no missing data.	High
Zeltzer 1982	Randomized, not controlled intervention study, evaluating **hypnotherapy**	Children and adolescents (6-17 years) with cancer undergoing BMA or LP (n=33)	**Hypnotherapy:** deep breaths, practice sessions, individual imagery and fantasy. Ending with a post-hypnotic suggestion. Following that, children were taught self-hypnosis.	-Hypnoses and non-hypnotic techniques were associated with an overall reduction in pain for BMA/ LP -Hypnosis was more effective than non-	*Hypnosis vs nonhypnotic techniques* + for self-reported	Randomized study, no control group, sufficient sample size. Not reported if allocation was known by the researcher at forehand	Moderate

Study	Design	Sample	Intervention(s)	Findings	Findings short**	Quality of evidence	Quality level
	versus nonhypnotic techniques for pain associated with BMA or LP		Nonhypnotic techniques: nonhypnotic behavioral techniques (combination of deep breathing, distraction, and practice sessions)	hypnotic techniques in reducing self-reported pain for BMA/ LP.	pain *Post treatment vs baseline* + for self-reported pain (both groups)	or how both groups were matched for age and disease. No blinding, no selective reporting, appropriate analysis, study completed as planned, no missing data.	
Kuttner 1988	RCT, evaluating **hypnotherapy** versus distraction and standard care for distress, pain and anxiety associated with BMA	Children (3-10 years) with acute lymphoblastic leukemia or acute myeloblastic leukemia who according to medical staff needed help in managing BMA (n=48)	**Hypnotherapy:** indirect suggestions related to stories and adventures, individually tailored. Also direct hypnotic techniques such as the "pain switch". Parents were included in the sessions. Distraction: including elements as: showing physical objects (toys, puppets, pop-up books), distracting questions, physical activities (blowing a bubble or squeezing parents hands, deep breathing). Parents were included in the sessions. Standard care: current standard medical practice	*At first intervention* **In the older age group (7-10 years):** -Lower observed pain and anxiety, as well for hypnotherapy as for distraction versus standard care. -Distraction is better in reducing observed and self-reported pain then hypnotherapy. **In the younger age group (3-6,5 years):** -Lower observed and self-reported pain, as well for hypnotherapy as for distraction versus standard care. -Hypnotherapy is better in reducing observed and self-reported pain then distraction *At second intervention:* -All groups showed reductions and the control group appeared to be contaminated. -The hypnotic method with its internal focus had an all-or-none effect, whereas distraction appeared to require that coping skills be learned over one session or more. -Distraction seems to be more age appropriate in older children	*Hypnosis or distraction vs standard care:* + for pain in older and younger children *Hypnosis vs distraction:* + for pain in older children with distraction + for pain in younger children with hypnosis	RCT, sufficient sample size. Lack in blinding, independent observers, inter-rater reliability was tested and found to be good, possible bias in the control group, who at the second intervention also showed clinical effects, due to learning effects of staff. No selective reporting, appropriate analysis, 48 started the study, and 30 finished, so drop-out of 18 patients, due to several reasons (death, not returned for BMA, etc.)	Low
Wall 1989	RCT, evaluating **hypnotherapy** versus active cognitive coping strategies for pain and anxiety associated with BMA or LP	Children (6-18 years), hematology and oncology patients undergoing BMA or LP (n=20)	**Hypnotherapy:** Hypnotic induction, progressing from relaxation to visual imagery. Cognitive coping: Choice from 4 activities designed to cause a shift in attention during BMA or LP.	-No differences in pain reduction by treatment strategy. -Both treatment strategies had better scores post treatment in: self-reported pain, observer-reported pain, child self-reported pain relief, McGill Pain Questionnaire scores and MPQ pain rating index. -Neither technique was effective in anxiety reduction. -Hypnotizability scale scores failed to correlate with degree of pain reduction.	*Hypnosis vs cognitive coping:* = no differences between groups. *Post treatment vs baseline (both groups):* ++ for self-reported pain ++for observer-reported pain	RCT, small sample size. Observers, trainers and experimenters were blind to treatment allocation, patients were not informed that hypnotherapy was one of the strategies, similar attention was given to both groups. No description of monitoring compliance of exercises. No selective reporting, appropriate analysis, study completed	High

Study	Design	Sample	Intervention(s)	Findings	Findings short**	Quality of evidence	Quality level
					+ for child self-report pain relief + for McGill Pain Questionnaire + for MPQ pain rating index = for anxiety	as planned, no missing data.	
Liossi 1999	RCT evaluating **hypnosis** and CBT versus standard care for pain and distress associated with BMA	Children and adolescents (5–15 years old) with leukemia undergoing BMAs (n=30)	**Hypnosis:** visual imagery (favorite place, activity, or television program), relaxation techniques, progressive muscle relaxations and autogenic relaxation. "Analgesic suggestions" as request for numbness, topical, local and glove anesthesia CBT: including relaxation training, breathing exercises and cognitive restructuring Standard care: a standard lidocaine injection, the same as the children in the intervention groups	-Hypnosis and CBT are both more effective for reducing pain and anxiety as compared to standard care. -Hypnosis and CBT are comparable for pain reduction, but less behavioral distress observed in hypnosis group	*Hypnosis vs standard care:* ++ for self-reported pain ++ for observed distress *CBT vs standard care:* ++ for self-reported pain ++ for observed distress *Hypnosis vs CBT:* = no difference for self-reported pain ++ for observed distress	RCT, small sample size, all measures that could be blinded, were blinded. Independent observer and doctor were blinded to allocation of treatment. Involvement of parents and presence of therapists during BMA were the same in all three groups, inter-rater reliability was tested and found to be good, self-reported findings mirrored the observed findings. Selective reporting, appropriate analysis, study completed as planned, no missing data	Moderate
Hawkins 1998	Randomized, not controlled intervention study evaluating **direct hypnotherapy** versus **indirect hypnotherapy** for pain and anxiety associated with LP	Children and adolescents (6-16 years old) with leukemia or non-Hodgkin lymphoma undergoing LPs (n=30)	**Direct hypnotherapy:** direct hypnotic suggestions were all directed towards imagining numbness, topical and local, glove anesthesia and the switchbox. Directed by therapist. **Indirect hypnotherapy**: The setting sun metaphor and the Mexican food metaphor were used for indirect suggestions. Directed by therapist.	-Both groups had significantly reduced self-reported pain and anxiety and observer-reported distress, during LP with hypnosis as compared to baseline -There were no significant differences between types of hypnotic intervention (direct vs indirect) -Higher level of hypnotizability was associated with increased treatment benefit for self-reported pain, anxiety, and observer-rated distress	*Direct vs indirect hypnosis* = no differences in pain, anxiety and distress *Post treatment vs baseline:* + for self-reported pain + for anxiety + for observer-reported distress	Randomized study, no control group, sufficient sample size, independent observer, inter-rater reliability was tested and found to be good, both self-assessment outcomes of children as well as independent observer evaluations mirrored each other with respect to changes in outcome. Lack of blinding, no selective reporting, correct analysis, study completed as planned, no missing data.	Low
Hilgard 1982	Observational study on hypnotherapy induced relief of	Children and adolescents (6-19 years) with cancer,	**Hypnotherapy:** imaginative exercises such as blowing out candles. Indirect suggestions.	-Post-treatment: self-reported pain and observer-rated pain were diminished. -No difference between self-reported and	*Post treatment vs baseline:* + for self-reported	Observational, no control group, sufficient sample size, no blinding, selective	Low

Study	Design	Sample	Intervention(s)	Findings	Findings short**	Quality of evidence	Quality level
	anxiety and pain associated with BMA	chiefly forms of leukemia, undergoing repeated BMAs (n=24)		observed pain for patients under age 10. -For children age 10 and older there was a difference between self-reported and observed pain -There were minor but significant sex differences both in observed pain and in self-reported pain, with the females reporting more pain.	pain ++ for observer-rated pain	reporting, appropriate analysis, study completed as planned, no missing data.	
Kellerman 1983	Prospective observational study on the effects of individualized hypnotherapy on discomfort and anxiety associated with BMAs, LPs and chemotherapeutic injections	Adolescents (mean 14 years) with various types of cancer undergoing BMAs, LPs and chemotherapeutic injections, referred by their oncologists because of procedural distress (n=18)	**Hypnotherapy:** individualized, suggestions for progressive muscular relaxation, slow rhythmic breathing, favorite place hypnotic induction. Posthypnotic suggestions for increased well-being, reduced discomfort, and greater mastery during the procedure were given. Following that, children were taught self-hypnosis.	-Significant reductions in pain, anxiety and multiple measures of distress after hypnosis training. -Pre-intervention data showed no pattern of spontaneous remission or habituation, and, in fact, an increasing anticipatory anxiety was observed before hypnotic treatment. -A non-significant trend toward greater self-esteem was present. The predicted changes in the Locus of Control and General Illness Impact were not found. -Comparisons between hypnosis rejectors and successful users unusually showed higher levels of pretreatment anxiety in the former.	*Post treatment vs baseline:* + for pain before painful procedure, ++ for pain during painful procedure ++ for pain after painful procedure + for anxiety and distress	Observational, no control group, small sample size, heterogonous group, no blinding, authors applied hypnotherapy themselves, selective reporting, appropriate analysis, 2 patients rejected hypnotherapy (religious, feeling uncomfortable), outcome measures are nor well defined.	Low
MIND-BODY (including imagery, meditation, breathing techniques)							
Pourmovahed 2013*	RCT evaluating **regular breathing versus** standard care for pain associated with intrathecal injections	Children and adolescents (6–15 years) with leukemia undergoing a first intrathecal injection (n=100)	**Hey-Hu breathing technique**: the child first takes a deep breath and exhales while whispering 'hey', then inhales deeply again and exhales whispering 'hu' Standard care: current standard medical practice	-Children in the 'Hey-Hu' breathing group reported significantly less pain than control group, particularly among children aged above 10 years. -There was no significant difference between the two sexes. -Nurses could help children learn the method of 'Hey-Hu' breathing and implement it in hospitalized children who undergo painful procedures.	*Hey-Hu breathing vs standard care* + for pain ++ for pain in children >10 years	RCT, sufficient sample size, sampling using random allocation software, some blinding **(s**emi blind, the performer of the procedure was aware of the aim of the study), no selective reporting, appropriate analysis, study completed as planned, some missing data.	Moderate
Pederson 1996	Pretest and posttest with randomized control group design, with an extension in which the control group experienced the intervention following posttest. To evaluate the effect	Children (6-14 years) with acute leukocytic leukemia undergoing LPs (n=8)	Mind-body teaching program: Parent-child program based on distraction, **breathing, relaxing, imagery**, changing perceptions of painful stimuli using videotape, a booklet and distraction materials and a support person during LP Control group: standard care, afterwards the same program as	-No differences between groups for distress and self-reported pain. -The treatment group had: fewer expressions of verbal resistance, fewer instances of muscular rigidity and more instances of parental interventions. -Both groups had post-treatment: fewer requests for emotional support, fewer verbal expressions of fear, fewer	*Mind-body program vs control* = for self-reported pain and distress *Post treatment vs baseline:* + for self-reported	Pre-posttest design with control group, insufficient sample size, no blinding, no selective reporting, appropriate analysis, study not completed as planned (although a sample of 30 had been planned, based on a power analysis, changes	Low

Study	Design	Sample	Intervention(s)	Findings	Findings short**	Quality of evidence	Quality level
	of the effect of teaching children and their parents about selected **non-pharmacologic techniques** during LPs for pain and distress.		experimental group, though starting a LP later	information-seeking questions and lower level of self-report of pain during LP. -Painful experiences during prior LPs correlated with young age, being female, state anxiety and trait anxiety. -Comments from children and parents indicate that children benefitted from non-pharmacologic techniques.	pain during LP	in the health care delivery system during data collection greatly reduced the number of potential subjects), no missing data	
Phipps 2010	RCT, evaluating the efficacy of **complementary therapies**, including 2 intervention groups (child-targeted or combined with parent-targeted) and 1 standard care group for somatic distress and mood disturbance associated with BMA	Children (6-18 years) with cancer undergoing stem cell BMA (n=178)	Mind-body intervention (child-targeted): based on psychoeducation, **massage and humor** Mind-body intervention (child-targeted combined with parent-targeted): psychoeducation, **massage** and **humor** (for children) and **massage /relaxation** and **guided imagery** (for parents) -Standard care	-Significant changes across time were observed on all patient and parent report outcomes for pain and distress -No significant differences between treatment arms were found on pain and distress. -No significant group differences for days in hospital, time to engraftment, or use of pharmacological interventions	*Mind-body program (child) vs mind-body program (child and parents)vs standard* = for pain and distress, no difference between the 3 groups *Post treatment vs baseline:* + for pain and distress (in all 3 groups)	RCT, sufficient sample size, lack of blinding, no selective reporting, correct analysis, study mostly completed as planned (some missed intervention sessions), no missing data	Moderate
McGrath 1986	Pretest and posttest design, evaluating pain-management program for pain and anxiety associated with cancer treatment	Children (mean age 9 year) undergoing treatment for acute myelogenous or acute lymphoblastic leukemia (n=14)	Pain-management program: individualized, to modify expectations, control, and the relevance of the procedure. Including: **desensitization procedures, guided imagery, hypnotic like suggestions for analgesia**, relaxation training and a teaching plan.	-Children's anxiety and pain were significantly reduced at post, three-month, and six-month follow-ups	*Post treatment vs baseline:* + for pain and anxiety at post, three-month, and six-month follow-ups	Pre-posttest design, no control group, small sample size, lack of blinding, no selective reporting, appropriate analyses, study mostly completed as planned (not discussed why 11 children did not participate in the pain-management program), no missing data	Low
van Aken 1986	Observational, case series pre- and posttest, with control group, evaluating the effects of an intervention program to reduce distress during BMA	Children (mean age 8,6 years) with cancer, undergoing BMAs (n=20)	Mind-body program: including relaxation, **imagination** of a pleasant situation and arousal of the concomitant feelings, watching a model of BMA Standard care: treatment as usual	-The experimental program was effective in reducing distress display. -Effect of the experimental program is significant in the second phase of BMA (the phase of the punction). -There is no significant difference in distress found between pre-procedure and post-procedure scores. -The intensity of distress varied with age and sex of the child, was weaker in older children	*Mind-body program vs standard care* + for distress in the second phase of BMA (the phase of the punction) = for distress in the first phase (pre-procedure) = for distress in the third phase (post-procedure)	Case series with control group, sufficient sample size, no randomization described, or how the choice was made for experimental or control group, no blinding, selective reporting, study mostly completed as planned, no missing data	Low
Broome 1992	Multiple case study design, non-	Children (3-15 years) with acute	Mind-body program: including **imagery**, relaxation techniques and	-Significant difference in pain post-treatment versus baseline	*Post treatment vs baseline:*	Observational, pre-post design, small sample size,	Low

Study	Design	Sample	Intervention(s)	Findings	Findings short**	Quality of evidence	Quality level
	randomized, pre-post observations, evaluating the effects of distraction and **imagery** on anxiety, distress behavior and pain during LPs.	lymphocytic leukemia that previously experienced at least one LP (n=14)	two different **breathing techniques**	-No difference for anxiety and distress scores post-treatment versus baseline -No difference for parent distress and anxiety post-treatment versus baseline	++ for pain = for distress = for anxiety	no control group, no randomization, no blinding, the adherence or compliance to the exercises of the intervention were not monitored, no control for attention given to the child and parents. No selective reporting, study completed as planned, no missing data	
Broome 1998	Repeated measures, one group design evaluating the effects of relaxation, distraction and **imagery** on pain and distress associated with LPs	Children and adolescents (4-18 years) with cancer undergoing repeated LPs (n=19)	Mind-body program: child and parent were taught relaxation, distraction and **imagery**. Information package containing: a videotape of a mime demonstrating the techniques, a booklet for parents explaining how to use the techniques with their child and an age-appropriate audiotape of instructions and music to use to practice relaxation and imagery	-As compared to baseline, children reported decreased pain, but not observed behavioral distress with the intervention. -Frequency of at-home practice was associated with greater treatment benefit; higher perceived effectiveness and frequency of practice parents' comfort and perceived effectiveness of the techniques, were associated with decreased procedural pain -Child temperament was related to experienced pain (between positive mood and pain) -The majority (75%) of parents reported practicing the techniques at least monthly and rated the techniques as effective.	*Post treatment vs baseline:* + for pain over the 5-month period = for observed distress	Repeated measures, no control group, small sample size (although 3 centers were used, the refusal rate of 57% prevented the investigators from obtaining an adequate enough number to reach significance), lack of blinding, design controls for threats to expectancy, history, and testing, as for "spreading" the good news, selective reporting, acceptable analysis, study completed as planned, losses to follow-up with missing data	Low
Ahmed 2014	Retrospective analysis , pre- post analyses to evaluate feasibility and efficacy of **Mantram meditation** for pain and distress associated with cancer treatment	Children undergoing anti-GD2 MoAb 3F8 treatment (as standard care for high-risk neuroblastoma) who received guided meditation (n=34)	**Mantram meditation:** offered to families several days a week by experienced instructors. A single specific Mantram was played on an MP3 player in the background while an experienced meditation teacher taught and led the Mantram. Mudras (hand gestures) and gentle breathing patterns (left nostril breathing, long exhalation, alternate nostril breathing) were interspersed with Mantram to help relieve tension and enhance relaxation and focus.	-No statistically significant changes after first session Mantram; however, after an average of 3 sessions, a small but significant decrease in heart rates was observed -A significant reduction in analgesic doses was observed after the first Mantram session. Patients receiving 2 to 3 Mantram sessions consistently received fewer analgesic rescues, although no further reduction in analgesics was noted.	*Post treatment vs baseline:* = for peak heart rate after first session Mantram) + for peak heart rate after an average of 3 sessions + for reduction in analgesic doses after the first (and more) Mantram session(s)	Retrospective pre-post design, no control group, sufficient sample size, no blinding. No selective reporting, study completed as planned, no missing data (the records from all patients with high-risk neuroblastoma undergoing anti-GD2 MoAb 3F8 therapy during a 10-month period were reviewed)	Low
Massage							
Phipps 2005*	RCT, unbalanced pilot, evaluating **professional massage** and **parent massage** versus	Children (all ages) scheduled to undergo HSCT (n=50)	**Professional massage**: therapeutic massage delivered by licensed massage therapists three times per week for the 4-week period from admission for HSCT through 3 weeks	-No significant differences were observed between the two massage interventions on distress and pain scores. -No significant differences between either	*Professional vs parent massage* = no differences for pain and distress	RCT, insufficient sample size (underpowered, though the sample was representative of the population of patients who	Low

Study	Design	Sample	Intervention(s)	Findings	Findings short**	Quality of evidence	Quality level
	standard care for pain and distress experienced under-going hematopoietic stem cell trans-plantation (HSCT)		post-transplantation. **Parent Massage**: parents were learnt basic massage techniques to use with the child. The routines taught to the parents were essentially the same as those provided in the therapist massage arm. Parents were asked to begin giving their child massage at least three times per week. -Standard care: usual care	massage group and standard care for pain and distress, although there were descriptive trends suggestive of benefit, some of which approached significance. Larger differences emerged on the outcomes of days in hospital and days to engraftment, pointing to the potential cost-benefits of a massage intervention in this setting. -Regarding narcotic usage, there were no significant differences between groups, but descriptively there was a trend for those in the massage arms to use less medication.	between massage groups *Massage vs standard care:* = for pain, distress and narcotic medication use (for professional and parental massage)	underwent transplantation), allocation to treatment arms was not equal but was designed so that participants were twice as likely to enter either intervention arm than the control arm, lack of blinding, no selective reporting, appropriate analysis, not described if study completed as planned, some missing data reported	
Mehling 2012*	RCT, nonblinded pilot, feasibility study, evaluating a **combined massage-acupressure intervention** versus standard care, for decreasing treatment-related symptoms such as nausea, vomiting and pain associated with hematopoietic cell transplant	Children (5-18 years) undergoing hematopoietic cell transplant at an academic medical center (n=23)	**Combined massage-acupressure intervention**: practitioner-provided, combined Swedish and acupressure massage three times a week throughout hospitalization. Parents were trained to provide additional acupressure as needed. -Standard care: Usual care	-There was no statistically significant difference or change in pain between the two groups -Intervention group versus control showed fewer days of mucositis, lower overall symptom burden, feeling less tired and run-down, having fewer moderate/severe symptoms of pain, nausea, and fatigue	*Massage vs control* = for pain	RCT, insufficient sample size (small feasibility study, aim to report standardized effect sizes that allow for sample-size calculations for future studies), no blinding, no selective reporting, appropriate analysis, study completed as planned, no missing data	Low
Celebioglu 2015*	Controlled pretest/posttest quasi-experimental study, investigating the effect of **massage therapy** versus standard care, on pain and anxiety arising from intrathecal therapy or BMA	Children (4-15 years) with primary diagnosis of cancer (n=25)	**Massage therapy**: one massage session from a licensed massage therapist. Massage techniques were a combination of effleurage and petrissage to the shoulders, neck, face, arms, lower back and waist. Standard care: standard treatment offered to patients undergoing IT or BMA.	-No difference between groups for pain or anxiety -It was determined that pain and anxiety levels in the massage group decreased significantly post-treatment versus baseline	*Massage vs control* = for pain and anxiety *Post treatment vs baseline:* + for pain and anxiety (massage group)	Pretest/posttest quasi-experimental study with control group, small sample size, non-probability convenience sampling, children were divided between the groups according to admission date, no blinding, no selective reporting, inappropriate analysis, study completed as planned, no missing data	Low
Post-White 2009	RCT, crossover design in which 4 weekly **massage sessions** alternated with 4 weekly quiet-time control sessions	Children (1-18 years) with cancer, received at least 2 identical cycles of chemotherapy (n=23)	**Massage therapy**: practitioner-provided. Parents' massage: seated chair massage. Children's massage: included back, legs, arms, stomach/chest and face. Strokes used were primarily effleurage, raking ,	-There were no significant differences between massage and quiet time for pain. Mean pain scores were low (<2.0) before and after each massage and control condition.	*Massage vs control* = for pain + for reducing heart rate. + anxiety in children	RCT, sufficient sample size, no blinding. Interview was conducted by 2 researchers who did not collect other data, interviews were transcribed	Low

Study	Design	Sample	Intervention(s)	Findings	Findings short**	Quality of evidence	Quality level
	Evaluating feasibility of providing massage to children with cancer to reduce symptoms in children associated with chemotherapy and anxiety in parents		thumb stroking and petrissage. Guided by the child's feedback and tolerance. Very little conversation and no music was played. Quiet Time (control condition): the child and parent participated together in the quiet-time control condition. A "do not disturb" sign was placed on the door for the same period of time as the massage. Age-appropriate toys were provided and children and parents read, rested, talked quietly, or watched a video.	-Massage was more effective than quiet time at reducing heart rate in children, reducing anxiety in children less than age 14 years and reducing parent -There were no significant changes in blood pressure, cortisol, pain, nausea, or fatigue. -All parents reported liking their massage -Massage in children with cancer is feasible	< 14 years + parent anxiety	verbatim and evaluated by 3 independent researchers. Some selective reporting, appropriate analysis, study not entirely completed as planned (8 male children failed to complete the study because of progressive disease, protocol changes, or their families changed their minds), some missing data	
Healing touch							
Wong 2013*	RCT, evaluating **healing touch** versus attention control on feasibility in pediatric oncology	Children (3-18 years) diagnosed with childhood malignancy, receiving chemo-therapy and/or radiation therapy (n=9)	**Healing touch**: by certificated practitioner, standardized techniques. Attention control: Reading or age-appropriate play activity for the same time as the intervention group	-There were statistically significant differences in pain scores (children and parents) and distress scores (parents) between the healing touch group and the control group. -Among the healing touch group, all scores (pain, distress, and fatigue) decreased significantly after the intervention. Scores among the control group did not show a statistically significant decrease. -The study demonstrates the feasibility of using energy therapy in the pediatric oncology patient population.	*Healing touch vs control* ++ for self-reported pain + for pain reported by parents = for pain reported by staff = for self-reported distress + for distress reported by parents = for distress reported by staff	RCT, insufficient sample size (recruitment rate 60%), the participants in the intervention group received approximately 6.5 times more treatments than the control group, which may bias results. High heterogeneity of groups (age, diagnose and treatment protocols), no blinding. No selective reporting. Inappropriate analysis, study not entirely completed as planned (2 drop-outs, because of prolonged hospitalizations and complicated treatments and 1 participant died while in the study because of disease progression), some missing data	Low
Music therapy							
Nguyen 2010*	RCT, evaluating **music** versus control for pain and distress associated with LPs	Children (7–12 years) with leukemia undergoing LPs (n=40)	**Music group (**earphones with music): Children choose their own music to be played into earphones from an iPod, 10 minutes before the LP procedure started. Control group (earphones without music): same procedure as music group, only without music	-As compared with the control group, children in the music group had significant reduction in self-reported pain (during and after procedure) and anxiety (before and after the procedure) -Significant reductions in heart rate and respiratory (during and after procedure) in music group; blood pressure and oxygen saturation did not differ between groups	*Music vs control* ++ for self-reported pain during and after the lumbar puncture. ++ for heart- and respiratory rates during and after the lumbar puncture.	RCT, sufficient sample size, lack of blinding (all the children were given identical pre-procedural information, randomization was carried out using opaque envelopes, the researcher and the physician did not know to	High

Study	Design	Sample	Intervention(s)	Findings	Findings short**	Quality of evidence	Quality level
				- The findings from the interviews confirmed the quantity results through descriptions of a positive experience by the children, including less pain and fear.	= for blood pressure and O2 saturation	which group the patient belonged), no selective reporting, correct analysis, study completed as planned, no missing data	
Pfaff 1989	Observational pre-posttest design, evaluating the effects of **music** on pain and fear of children undergoing BMAs	Children (7-17 years) diagnosed with leukemia who have a frequency of BMAs every 6 to 8 weeks (n=9)	**Music therapy:** A relaxation master cassette containing five instrumental music selections, from which the child selected their choice of preferred music. A music therapist led the child through the music program until it was time for the BMA. The music began when the child entered the treatment room. Throughout the procedure, the music therapist coached the child on the relaxation exercises when necessary.	-As compared to baseline children in the music group had no change in experienced pain, anticipatory pain or distress	*Post treatment vs baseline:* = for pain and distress	Observational pre-post design, no control group, insufficient sample size, no blinding, no control for attention. Some selective reporting, inappropriate analysis, study not completed as planned (3 out of 9 children did not complete the study, due to moving to another city or did not want to use music), some missing data.	Low
Art therapy							
Madden 2010	RCT, mixed methods pilot study, repeated measures, evaluating **creative arts therapy** versus attention control for quality of life associated with chemotherapy 1.small randomized pilot with the brain tumor patients only. 2.descriptive study observed all eligible hematology/oncology patients who received creative arts therapy	1.Children (2-18 years) receiving chemotherapy for a brain tumor (n=16) 2.Children (3-21 years) receiving chemotherapy for brain tumors and subsequently all patients receiving infusions in the outpatient hematology/oncology clinic (n=32)	**Creative arts therapy:** led by a licensed dance/movement therapist who was experienced in music and art therapies as well. The intervention consisted of 6 sessions, 2 sessions of each modality of creative arts. The sequence of activities replicated developmental expression from body movement, to sound, to graphic representation. Attention control (volunteer's attention): a trained volunteer sitting at the patients' bedside in the infusion room and paying attention to them through reading, talking, or watching TV. No art activities were allowed for the control group during the volunteer's attention.	1. Areas that showed statistically significant improvement were: Parent-report of pain, parent report of nausea 2. As compared to baseline children in the creative arts therapy group showed improved mood, were more excited, happier and less nervous	*Creative arts therapy vs attention control* + for self-reported pain +parent-reported pain / nausea *Post treatment vs baseline:* + improved mood + more excited, more happy, less nervous	RCT, attention control group, small sample size, randomly assigned to treatment or control group, no blinding. Some selective reporting, appropriate analysis, study not completed as planned (2 dropped out: 1 withdrawal, 1patient did not receive chemotherapy), some missing data. If the total number in a group (either creative arts or control was <4 subjects, the group was not analyzed not to bias the results. Therefore, all of the child self-report variables were eliminated.	Low
Aromatherapy							
Ndao 2012	RCT, double-blind, placebo-controlled study, evaluating the effect of the respiratory administration of **bergamot essential**	Children (5-21 years) with malignant and non-malignant disorders undergoing stem cell transplantation (n=37)	**Bergamot essential oil**: an aromatherapy diffuser was turned on and filled or refilled with four drops of bergamot essential oil per hour. Placebo: An aromatherapy diffuser was turned on and filled or refilled with four drops of placebo oil per	-As compared to the placebo group, children in the Bergamot group reported significant more pain before transplantation and the same amount of pain compared to placebo after transplantation -As compared to the placebo group,	*Bergamot essential oil vs placebo* *Before transplantation:* - for self-reported pain	RCT, sufficient sample size, randomization was stratified by age and transplant type to control for the effect of different conditioning regimens, double blinded (the	High

Study	Design	Sample	Intervention(s)	Findings	Findings short**	Quality of evidence	Quality level
	oil on anxiety, nausea, and pain during stem cell infusion.		hour: a non-essential oil-based scented shampoo.	children in the Bergamot group showed no difference for self-reported nausea before transplantation and were more nauseous than the placebo group after transplantation -As compared to the placebo group, children in the Bergamot group showed no difference for anxiety before transplantation and were more anxious than the placebo group after transplantation -Although not significant, the treatment group had a higher rate of adverse events, specifically hypertension, possibly contributing to the marked differences in the experience of anxiety and nausea among the two study groups.	= for self-reported nausea = for anxiety *After transplantation*: = for self-reported pain - for self-reported nausea - for anxiety	research assistant was blinded to treatment arm labelling and wore a mask and nose plugs upon entering the patient room to administer questionnaires and fill the diffuser. At consent, both parent and child were informed that both essential oil and placebo contained a scent, though scent type was not disclosed). No selective reporting, appropriate analysis, study not entirely completed as planned (3 randomized patients did not receive the treatment and were therefore not analyzed), no large losses to follow-up or missing data	

Abbreviations: RCT = randomized controlled trial; LP = lumbar puncture; BMA = bone marrow aspiration; IV = intravenous; CBT = cognitive-behavior therapy; GA = general anesthesia; IM = intramuscular injection
*****: studies used for GRADE assesment
**: + or - → P<0.05
++ → P<0.001
= → no significant difference

Quality of study was evaluated based upon
• type of study (i.e., qualitative, quantitative, and review)
• sampling strategy appropriate for research question
• method of data collection clearly described
• method of data analysis clearly described; analysis appropriate for research question
• sufficient sample size;
• blinding or data collection appropriate to study method
• appropriate analysis;
• reporting comprehensive, clearly described;
• issues with follow-up or missing data clearly described

Used literature

- Ahmed M, Modak S, Sequeira S: Acute pain relief after Mantram meditation in children with neuroblastoma undergoing anti-GD2 monoclonal antibody therapy. *Journal of pediatric hematology/oncology* 2014, 36(2):152-155.
- Broome ME, Lillis PP, McGahee TW, Bates T: The use of distraction and imagery with children during painful procedures. *Oncology nursing forum* 1992, 19(3):499-502.
- Broome ME, Rehwaldt M, Fogg L: Relationships between cognitive behavioral techniques, temperament, observed distress, and pain reports in children and adolescents during lumbar puncture. *Journal of pediatric nursing* 1998, 13(1):48-54.
- Celebioglu A, Gurol A, Yildirim ZK, Buyukavci M: Effects of massage therapy on pain and anxiety arising from intrathecal therapy or bone marrow aspiration in children with cancer. *International journal of nursing practice* 2015; 21: 797–804.
- Hawkins P. J., Liossi C., Ewart B. W., Hatira P., Kosmidis V. H. (1998). Hypnosis in the alleviation of procedure related pain and distress in paediatric oncology patients. *Contemporary Hypnosis*, 15,

199-207. 10.1002/ch.135

- Hilgard JR, LeBaron S: Relief of anxiety and pain in children and adolescents with cancer: quantitative measures and clinical observations. *The International journal of clinical and experimental hypnosis* 1982, 30(4):417-442.
- Katz ER, Kellerman J, Ellenberg L. Hypnosis in the reduction of acute pain and distress in children with cancer. *Journal of Pediatric Psychology* 1987;12(3):379–94.
- Kellerman J, Zeltzer L, Ellenberg L, Dash J: Adolescents with cancer. Hypnosis for the reduction of the acute pain and anxiety associated with medical procedures. *Journal of adolescent health care : official publication of the Society for Adolescent Medicine* 1983, 4(2):85-90.
- Kuttner L, Bowman M, Teasdale M: Psychological treatment of distress, pain, and anxiety for young children with cancer. *Journal of developmental and behavioral pediatrics : JDBP* 1988, 9(6):374-381.
- Liossi C, Hatira P: Clinical hypnosis versus cognitive behavioral training for pain management with pediatric cancer patients undergoing bone marrow aspirations. *The International journal of clinical and experimental hypnosis* 1999, 47(2):104-116.
- Liossi C, Hatira P: Clinical hypnosis in the alleviation of procedure-related pain in pediatric oncology patients. *The International journal of clinical and experimental hypnosis* 2003, 51(1):4-28.
- Liossi C, White P, Hatira P: Randomized clinical trial of local anesthetic versus a combination of local anesthetic with self-hypnosis in the management of pediatric procedure-related pain. *Health psychology : official journal of the Division of Health Psychology, American Psychological Association* 2006, 25(3):307-315.
- Liossi C, White P, Hatira P: A randomized clinical trial of a brief hypnosis intervention to control venepuncture-related pain of paediatric cancer patients. *Pain* 2009, 142(3):255-263.
- Madden JR, Mowry P, Gao D, Cullen PM, Foreman NK: Creative arts therapy improves quality of life for pediatric brain tumor patients receiving outpatient chemotherapy. *Journal of pediatric oncology nursing : official journal of the Association of Pediatric Oncology Nurses* 2010, 27(3):133-145.
- Mehling WE, Lown EA, Dvorak CC, Cowan MJ, Horn BN, Dunn EA, Acree M, Abrams DI, Hecht FM: Hematopoietic cell transplant and use of massage for improved symptom management: results from a pilot randomized control trial. *Evidence-based complementary and alternative medicine : eCAM* 2012, 2012:450150.
- McGrath PA, DeVeber LL: Helping children cope with painful procedures. *The American journal of nursing* 1986, 86(11):1278-1279.
- Ndao DH, Ladas EJ, Cheng B, Sands SA, Snyder KT, Garvin JH, Jr., Kelly KM: Inhalation aromatherapy in children and adolescents undergoing stem cell infusion: results of a placebo-controlled double-blind trial. *Psycho-oncology* 2012, 21(3):247-254.
- Nguyen TN, Nilsson S, Hellstrom AL, Bengtson A: Music therapy to reduce pain and anxiety in children with cancer undergoing lumbar puncture: a randomized clinical trial. *Journal of pediatric oncology nursing : official journal of the Association of Pediatric Oncology Nurses* 2010, 27(3):146-155.
- Pederson C: Promoting parental use of nonpharmacologic techniques with children during lumbar punctures. *Journal of pediatric oncology nursing : official journal of the Association of Pediatric Oncology Nurses* 1996, 13(1):21-30.
- Pfaff VK, Smith KE, Gowan D The effects of musicassisted refaxation on the distress of pediatric cancer patients undergoing bone marrow aspirations. *Child Health Care* 18:232-236, 1989 34.
- Phipps S., Barrera M., Vannatta K., Xiong X., Doyle J.J., Alderfer M.A.: Complementary therapies for children undergoing stem cell transplantation: Report of a multisite trial. *Cancer* 2010, 116 (16): 3924-3933
- Phipps S., Dunavant M., Gray E., Rai S.N.: Massage therapy in children undergoing hematopoietic stem cell transplantation: Results of a pilot trial 2005, *Journal of Cancer Integrative Medicine*. 3 (2): 62-70
- Post-White J, Fitzgerald M, Savik K, Hooke MC, Hannahan AB, Sencer SF: Massage therapy for children with cancer. *Journal of pediatric oncology nursing : official journal of the Association of Pediatric Oncology Nurses* 2009, 26(1):16-28.
- Pourmovahed Z, Dehghani K, Sherafat A. Effectiveness of regular breathing technique (hey-hu) on reduction of intrathecal injection pain in leukemic children: A randomized clinical trial. *Iran J Pediatr* 2013;23:564–568.
- Smith J. T., Barabasz A., Barabasz M. Comparison of hypnosis and distraction in severely ill children undergoing painful medical procedures. *Journal of Counseling Psychology* 1995; 43, 187-195.
- van Aken MA, Heezen TJ, van Lieshout CF: [Bone marrow biopsy in children with leukemia. Determination and reduction of pain and fear reactions]. *Tijdschrift voor kindergeneeskunde* 1986, 54(4):112-118.
- Wall VJ, Womack W: Hypnotic versus active cognitive strategies for alleviation of procedural distress in pediatric oncology patients. *The American journal of clinical hypnosis* 1989, 31(3):181-191.
- Wong J, Ghiasuddin A, Kimata C, Patelesio B, Siu A: The impact of healing touch on pediatric oncology patients. *Integrative cancer therapies* 2013, 12(1):25-30.
- Zeltzer L, LeBaron S: Hypnosis and nonhypnotic techniques for reduction of pain and anxiety during painful procedures in children and adolescents with cancer. *The Journal of pediatrics* 1982, 101(6):1032-1035.