Evidence Profile

Recommendation Question 7: Should pain management strategies (including pharmacological and non-pharmacological) during the insertion of a vascular access device be recommended?

Recommendation 7.2: **The guideline panel recommends that health providers offer non-pharmacological and pharmacological pain management strategies during the insertion of a vascular access device to infants and children, tailored to their age and developmental stage.**

Population: All patients who require a vascular access device (peripheral or central)
Intervention: Pharmacological and/or non-pharmacological pain management strategy
Comparison: Standard care/no pharmacological/non-pharmacological pain management strategy
Outcomes: Patient's rating of pain, patient comfort, fear/anxiety (related to poke/needle phobia), and patient satisfaction

Setting: All practice settings where patients with vascular access devices are cared for (e.g., primary care, long-term care, acute care, community care)

Bibliography: 772, 3448, 10270, 3885, 15599, 17, 7759, 3900, 5, 2940, 6953, 3362, 1436, 3556, 257, 424, 1174, 724, 802, 11991, 9004, 3472, 9141, 7671, 101, 8790, 17087, 103, 712, 1562, 1777, 1973, 2114, 2209, 4842, 981, 1816, 3489, 13743, 279, 338, 701, 709, 798, 391, 396, 1541, 539, 362, 660, 417, 418, 437, 460, 471, 2142, 1699, 1734, 1807, 2265, 1658, 1671, 1737, 1894

Quality assessment							Summary of Findings		No. of Participants		Reported Effects/Outcomes	Certainty	Reference
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Country	Intervention	Intervention	Control			
Patient (or observer for infants) rating of pain (assessed with: FLACC, FPS, FPS-R, NRS, Oucher Scale, MBPS, VAS, University of Wisconsin Children's Hospital scale, Neonatal Facial Coding Scale, PIPS, Wong-Baker faces pain rating scale, consolability scale, CAS, NIPS, MOPS, MAISD, DAN Scale, CHIPPS, MFCS, McGill Present Pain Intensity Questionnaire, BOPS, Modified Riley Pain Scale).													
12[a]	Systematic review (of RCTs)	Serious[b]	Not serious[c]	Serious[d]	Not Serious[e]	Not detected	101: Multiple: USA (9 studies), Canada (5 studies), Brazil, Jordan, Australia, India, China, Sweden (2 studies), Turkey, Iran	**Pharmacological Interventions** 101: Any active pharmacological intervention in neonates, infants, or children receiving intramuscular injection either due to vaccination or any other active drug. The following interventions were compared in the various clinical studies: sucrose (24, 25, 50, and 75%), 25% dextrose, glucose (25 and 30%), EMLA, vapocoolant spray, amethocaine, paracetamol, and ibuprofen. Control: placebo	101: n total = 1948 (not specified how many in intervention vs. control groups) pain score (95% CI) analgesia vs. placebo: EMLA: -0.57 (-0.90, -0.25)	101: Not specified	Most reviews found there was a reduction in patient (or observer) rating of pain with the use of pharmacological or non-pharmacological pain management interventions. Additional RCTs supported this finding. 101: Compared to placebo, all interventions were found to reduce pain however topical EMLA cream was observed to be better than 25% dextrose and 50% sucrose. Overall, topical EMLA has the high probability of being the 'best' in the pool as observed by the presence of the corresponding pooled estimate on the top of the Forest plot. There was found to be minimal to noeffect when comparing	⊕⊕◯◯ LOW	101: Sridharan & Sivaramakrishnan (2018)

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							1457: Iran, Sweden 724: Multiple: specific countries not reported	1457: Eutectic mixture of lidocaine (EMLA) is a mixture of lidocaine (25 mg/g) and prilocaine (25 mg/g) in a cream base, which provides dermal anesthesia and/or analgesia. EMLA was given at any dose, location, or length of time before venipuncture. Control groups were placebo or no treatment during venipuncture. **Non-Pharmacological Interventions** 724: Various sweet-tasting solutions were used: 12% sucrose, 24% sucrose, 25% sucrose, 50% sucrose, 75% sucrose, 25% glucose, 30% glucose, 40% lycasin (glucose). The majority of the	24% sucrose: -0.49 (-1.10, 0.11) amethocaine: -0.16 (-0.54, 0.22) vapocoolant spray: -0.13 (-0.88, 0.62) 75% sucrose: -0.10 (-0.52, 0.33) 25% dextrose: -0.04 (-0.19, 0.12) 50% sucrose: 0.00 (-0.47, 0.47) 1457: n=2 studies, 65 participants 724: n=7 studies 24% sucrose, 25% sucrose, 50% sucrose, 75% sucrose,	1457: Not specified 724: not specified	amethocaine and vapocoolant spray to control groups. Among infants and neonates only, 25% sucrose had a positive effect in reducing pain compared to control. 1457: Results were positive, favouring the EMLA intervention group (SMD (95% CI): -0.24 (-0.67 to -0.00). 724: All of the studies except one that used sucrose 12% reported lower pain scores in infants who were given a sweet-tasting solution. Note: meta-analysis was not conducted due to the heterogeneity of interventions		1457: Shahid, Florez & Mbuagbaw (2019) 724: Kassab et al. (2012)

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№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Country	Intervention	Intervention	Control			
								studies used a total volume of 2mLs of sweet solution. Population included: term healthy infants between one month and 12 months of age requiring a needle-related procedure. These procedures included, but were not limited to: subcutaneous or intramuscular injections, venipuncture, and heel lance. Control- placebo (normal saline or water)	25% glucose, 30% glucose, 40% lycasin (glucose) vs. placebo: reduction in pain scores **See study page 11-12**		and outcomes measured.		802: Harrison at al. (2016)
							802: Multiple: Canada, Iran, Turkey, India, Jordan	802: Breastfeeding - All studies involved an intervention group with the mother initiating breastfeeding prior to the procedure and continuing breastfeeding during the procedure. The procedures included, but were not limited to: subcutaneous or intramuscular injection, venipuncture, intravenous line insertion, heel lance, and finger lance. All studies included a comparison group where the infant received no pain treatment. Four studies included other comparator groups: 2mL of 25% dextrose; 1 g EMLA Cream plus 2mL oral distilled water; massage therapy; and topical vapocoolant spray.	802: Breastfeeding vs. control (all pain studies): 5 studies, n=310 infants, SMD -1.7, 95% CI -2.2 to -1.3; P < 0.00001) and moderate between-study heterogeneity (I^2 = 69%)	802: not specified	802: Overall, pain scores were significantly lower amongst infants who were breastfed compared to those that were not. (SMD -1.7, 95% CI -2.2 to -1.3, p<0.00001).		
							3362: Multiple: USA, Brazil, Iran, Canada,	3362: Variety of physical interventions were used: skin-to-skin contact, holding during procedure, holding after procedure, sitting upright, non-nutritive sucking,	3362: Skin-to-skin: 3 studies, n=736 neonates, SMD - 0.65 (95% CI: -	3362: not specified	3362: Skin-to-skin showed a positive effect, holding during vaccine showed a positive effect, holding after showeda positive effect, sitting upright showed minimal to no effect, non-nutritive sucking showed		3362: Taddio et al. (2015)

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							India, China, UK, Netherland, Italy, Australia, Turkey	manual tactile stimulation, tactile stimulation using vibrating device and cold, warming vaccine, breastfeeding. Control: lying supine in crib, infants held transversely after procedure and gently patted on buttocks and returned to crib, or no tactile stimulation, or no application of vibrating device/cold, or no warming of vaccine.	1.05, -0.25). For the recovery procedure phase, the SMD was -0.89 (95% CI: - 1.26, - 0.52). Holding vs. lying supine: 3 studies, SMD -1.25 (95% CI: -2.05, -0.46). Combined Holding Intervention (Including Patting and/or Rocking) After Vaccine: 2 studies, n=417 infants, SMD 0.65 (95% CI: 1.08, 0.22). Sitting upright: 1 study, n=107, SMD 0.07 (95% CI: _-0.31, 0.45) Non-nutritive Sucking (eg, Finger/Thumb, Pacifier): 2 studies, n=186 infants, SMD -1.88 (95% CI: -2.57, -1.18		a positive effect, manual tactile stimulation had minimal to noeffect.		

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							9141: Multiple countries: USA (most), UK, Canada, Australia, Turkey, New Zealand 981: Multiple-specific countries not reported	9141: Various types of vapocoolant spray were used: 1,1,1,3,3,-Pentaflouropropane and 1,1,1,2-tetrafluoroethane, Ethyl chloride, and COLD spray. Control: placebo/ no intervention 981: Various sweet solutions were used (sucrose: 12%, 33%, 25%, 75%, lollypops, sweet gum) in all settings where sweet solutions were administered and evaluated during needle-related procedures. Participants included children aged 1-16 years undergoing needle-related procedures. These procedures included, but were not limited to: venipuncture, heel lance, finger lance, subcutaneous (SC) or intramuscular injection (IM), lumbar	Manual Tactile Stimulation: 6 studies total; for 3 studies (n=893) SMD -0.38 (95% CI: -0.96, 0.21). In the only analysis that included all studies (n=301 infants), the SMD was -0.69 (95% CI: -1.77, 0.39). 9141: SMD (95% CI): −0.29(−0.95, 0.36) n=2 studies, 165 children participants 981: Sucrose vs. control: n=3 studies, 80 children, FLACC scores: SMD -0.26, 95% CI -1.27 to 0.75, P = 0.61, I²=86% Sucrose vs. control (pre-school	9141: not specified 981: not specified	9141: There was a small but imprecise positive effect when comparing vapocoolant vs. no vapocoolant for PVAD insertion (I²=77.7, P heterogeneity= 0.034, p-val 0.383). 981: There was a small but imprecise positive effect between the sucrose and the control groups in composite pain score at time of first needle in the sucrose vs. control groups (based on FLACC data from 3 pooled studies). Two studies enrolling 111 school-aged children reported on the Faces Pain		9141: Zhu et al. (2018 981: Harrison et al. (2015)

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								puncture, and suprapubic bladder aspiration. Control: water or unsweetened gum.	children, CHEOPS): n=1 study, RR for having high pain scores was 0.55 (95% CI 0.45 to 0.67, P < 0.00; RD -0.29, 95% CI -0.37 to 0.20; NNTB 3, 95% CI 3 to 5) favouring the 25% sucrose group. Sweet gum vs. unsweetened gum: n=2 studies, 111 children, WBFPS before procedure: 0.15, 95% CI -0.61 to 0.30, P = 0.51, during procedure: 0.23, 95% CI -0.28 to 0.74, P = 0.38 CAS: before procedure 0.24, 95% CI -0.69 to 1.18, P = 0.83, during procedure: 0.86, 95%CI -0.12 to 1.83, P = 0.09		Scale and Coloured Analogue Scale. These data were pooled for inclusion in meta-analysis. There was a small but imprecise positive effect in children's self report of pain using either pain scale between those who chewed sweet gum versus unsweetened gum before or during the procedure.		

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							772: Multiple countries: Turkey, India, Italy, Canada, USA (most), Iran, Australia, Kuwait, France, Iceland, Greece, Israel, Spain, Vietnam, Sweden, Brazil, Mexico, Netherlands, China, Germany	772: The most common psychological interventions were distraction, combined CBT, and hypnosis. Preparation/information, breathing, suggestion, and memory alteration were also included. Distraction interventions were varied and included watching cartoons or a movie, listening to music or a spoken story, interactive handheld computer or video games, distraction cards, virtual reality, playing with a toy, parent distraction, medical clown, squeezing a rubber ball, or a combination or selection of various distractors such as toys, books, cartoons, games, or music. Control: standard care (varied across studies).	772: distraction: n=32 studies, CBT: n=18 studies, hypnosis: n=8 studies, preparation/information: n=4 studies, suggestion: n=3 studies, memory alteration: n=1 study. Total number of participants: n=5550 Distraction: standardized mean difference (SMD) −0.56, 95% confidence interval (CI) −0.78 to −0.33, Z = 4.83, P < 0.001, I2 = 87%. Combined CBT: SMD−0.27, 95% CI −0.58 to 0.03, Z = 1.74, P = 0.08, I2 = 83% and	772: not specified	772: Distraction techniques were found to have a positive effect on reducing pain. Thirty studies including 2802 participants (intervention group = 1509) revealed a moderate effect of distraction for self-reported pain. Combined CBT was found to have mixed results in reducing patients' pain (self-report, observed, behavioural). Analysis of 14 studies examining combined cognitive-behavioral strategies with 1359 participants (intervention group = 633) revealed a minimal but imprecise positive effect for self-reported pain. Hypnosis was found to have a positive effect on reducing pain. Five studies including 176 participants (intervention group = 97) revealed a large effect of hypnosis for self-reported pain. Preparation/Information was found to have a minimal but imprecise positive effect on reducing pain. Analysis of four studies examining the effects of preparation/ information for self-reported pain included 313 participants (intervention		772: Birnie et al. (2018)

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									SMD −0.65, 95% CI −2.36 to 1.06, Z = 0.74, P = 0.46, I2 = 94%. Hypnosis: SMD −1.40, 95% CI −2.32 to −0.48, Z = 2.97, P = 0.003, I2 = 85% and SMD −0.38, 95% CI −1.57 to 0.81, Z = 0.62, P = 0.53, I2 = 83%. Preparation/Information: SMD −0.18, 95% CI −0.60 to 0.23, Z = 0.86, P = 0.39, I2 = 68%. Breathing: SMD −1.04, 95% CI −1.86 to −0.22, Z = 2.48, P = 0.01, I2 = 90% Suggestion: SMD −0.13, 95% CI −0.40 to 0.15, Z = 0.90, P = 0.37, I2 = 0%	group = 155). Breathing was found to have a positive effect on reducing pain. Four studies including 298 participants (intervention group = 149) revealed a large effect of breathing interventions for self-reported pain. Suggestion was found to have a minimal but imprecise positive effect on reducing pain.		
							3448:	3448: Three separate clinical	3448: n=10	3448: not	3448: There were mixed		3448:

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							Multiple countries: USA (5 studies), India (2 studies), Canada, Turkey, Iran 907: Authors from Japan; countries of included studies not given	questions related to variants of the psychological strategy of distraction (directed video; directed toy; non-directed toy) were pursued. 907: Children 0-18 years old who underwent needle-related procedures (NRPs) for any condition (specific settings not given) were included. Vibratory devices during NRPs - devices included Buzzy, Vibration Anesthesia Device, Norco Mini Vibrator, and Hitachi Magic Wand with Wonder Wand. The comparators used in the studies were the nonuse of vibratory devices, placement of the devices without turning them on topical anesthesia and vapocoolant.	studies, total participants: n=1816 Directed Toy Distraction (n=81): SMD -0.47 [95% CI, -0.91 to -0.02]) Non-directed Toy Distraction (n=290): SMD -0.93 [95% CI, -1.86 to 0.00] 907: **Venipuncture (n=7 studies):** self-rated pain outcome: SMD: –0.73; 95% CI: –1.35 to –0.11; I2: 93% Observer rated pain: SMD:–0.52; 95% CI: –1.12 to 0.08; I2: 92% **IM Injection (n=2 studies,**	specified 907: Control group results not specified.	results for the video distraction methods - positive direction of effect for preprocedure and acute+recovery, minimal to no difference for other phases. Directed Toy Distraction: Positive impact of directed toy distraction on infant distress during preprocedure + acute+recovery. Nondirected Toy Distraction: Across the different analyses on the 3 distress outcomes, overall quality of the studies meta-analyzed ranged from very low to low and results were mixed but demonstrated a minimal positive direction of effect. 907: Results from the review demonstrated a positive effect favouring the intervention group (vibration) for decreasing self or observer rated pain during all examined NRPs.		Riddell et al. (2015) 907: Ueki, Yamagami & Makimoto (2019)

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							1502: Multiple-France, Turkey, Iran, Japan 2142: Multiple-Canada, Iran, USA, India	1502: Maternal milk odor during needle procedure - The amount of liquid that gave off odors ranged from one drop to 10 mL, and the odors were given via odor diffuser sterile sponge, clean cotton filter paper, cotton pad or Ookie doll. Comparator was no scent or a scentless diffuser. 2142: All studies examined ice or vapocoolant spray. The comparator groups were usual care/no intervention. **Additional RCTs identified:** **Mixed (Pharmacological and Non-**	**204 participants)** Pain: SMD: –0.78; 95% CI: –2.45 to 0.89 **Heel Lance (n=2 studies, 76 participants)** Observer-rated pain:SMD: –0.89; 95% CI: –1.37 to –0.42; I2: 0% 1502: n=4 studies, 249 (not specified how many per group) 2142: n=2 studies examined ice n=6 studies examined vapocoolant *Note: no raw data of scores was provided.	1502: not specified 2142: not specified	1502: During blood sampling: The pain scores were statistically significantly lower in the maternal milk odor group than in the scentless group (SMD -0.81; 95% CI, -1.18 to -0.44). 2142: Studies showed no difference in pain between groups using ice and control groups. 4 out of 6 studies showed improvement in pain scores using vapocoolant compared with control groups.		1502: Zhang et al. (2018) 2142: Hall et al. (2020)

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							17: Turkey	**Pharmacological Interventions)** 17: The children were randomized into 5 groups: Jet lidokaine (n=39), Buzzy, bubble-blowing, aromatherapy, and the control group. This method (jet lidocaine) employs a compressed carbon dioxide-driven device that delivers 0.2 ml of buffered 1% lidocaine transdermally. None of the children in control group received any other intervention before, during and aftervenipuncture. Only the routine procedure was conducted.	17: Jet lidokaine group: n=39 Jet lidokaine Oucher pain scores before: 3.20 ± 3.51 2.00(0.00–10.00), during: 4.71 ± 4.41 3.00(0.00–10.00), after: 2.82 ± 3.42 1.00(0.00–10.00) Buzzy group: n=39 Oucher pain scores: before: 2.41 ± 3.35 1.00(0.00–10.00), during: 3.51 ± 3.49∗ 2.00(0.00–10.00), after: 1.43 ± 2.47∗ 0.00(0.00–0.00) Bubble blowing group: n=39 Oucher pain scores: Before 2.15 ± 2.73 1.00(0.00–	17: Control group n=39 Oucher scores before: 2.64 ± 2.38 2.00(0.00–8.00), during: 5.87 ± 2.87 6.00(1.00–10.00), after: 2.84 ± 2.60 2.00 (0.00–10.00)	17: There was found to be the biggest reduction in pain levels of control and intervention groups during and after phlebotomy in the Buzzy group, and that children in this group had less pain ($p < 0.05$). There was found to be a minimal but still positive effect between the jet lidocaine vs. other intervention groups and the control group. There was also found to be minimal to no effect of Oucher pain scores when bubble-blowing and aromatherapy were compared to the other interventions and control group before, during, and after phlebotomy procedure ($p > 0.05$).		17: Alemdar and Aktas (2019)

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									10.00), During 4.53 ± 3.25 4.00(0.00–10.00), After 1.66 ± 2.36 1.00(0.00–9.00) Aromatherapy group n=39 Oucher pain scores: Before 2.94 ± 3.05 1.00(0.00–10.00), During 5.46 ± 2.75 5.00(1.00–10.00), After 2.89 ± 2.77 2.00 (0.00–10.00)				
							1816: Iran	1816: Children allocated to EMLA, acupressure, or control groups. about 2 g of EMLA cream was applied to the skin at the venipuncture site (about 5 cm2), and the site was dressed. After 45 minutes, the dressing was removed, the site was cleaned using alcohol, and then venipuncture was performed. Children in the control group only received routine prevenipuncture care.	1816: n=40 EMLA: 2.75±1.4 (Mean±SD). Acupressure: 2.65±1.4 (Mean±SD), n=40	1816: 7.75±1.6, n=40	1816: Pairwise comparisons indicated that venipuncture pain in the local anesthesia group and the acupressure group was significantly lower than that in the control group (mean difference of 5 lower in EMLA group compared to control, 5.1 lower in acupressure compared to control, $p < 0.0001$). There was no difference between the local anesthesia and the acupressure groups (mean difference of 0.1 lower in EMLA group compared to acupressure, $p > 0.692$).		1816: Pour, Ameri, Kazemi & Jahani (2017)

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							10270: Canada 3489: Italy 7671: Indonesia	10270: Infants randomized to 4 groups prior to receiving vaccinations - Group 1: A parent-directed video education about infant soothing, Group 2: video combined with sucrose, Group 3: video combined with sucrose and topically applied lidocaine, Control: Group 4: placebos given for all 3 interventions. **Pharmacological Interventions** 3489: Patients were given either 0.5 mg/kg (max 5 mg) oral melatonin (Melamil®) 30min. before blood drawing. The patients received drugs via oral route by a blinded nurse. Control: placebo (5% glucose solution) **Non-Pharmacological Interventions** 7671: The intervention group in the study consisted of young children who received intervention positioning by parental holding and	10270: Mean Needle Scores: Group 1: n=89 6.7 (± 0.8) Group 2:n=88 6.7 (± 0.8) Group 3: n=87, 6.3 (± 0.8) Observed effect size (standardized mean difference [SMD]): 0.5 3489: n=30 FLACC: 2.5±1.6 FPS and NRS: 1.2 ±0.8	10270: n=88, 6.7 (± 0.8) 3489: n=30 FLACC: 5.2±1.4 FPS and NRS: 2.1±0.8 7671: n=18, Median pain	10270: Needle scores showed group ($p = 0.003$) and time differences ($p < 0.001$). Scores were lower for the video–sucrose–lidocaine group compared with the control (mean difference of 0.4, $p < 0.001$), video (mean difference of 0, $p = 0.003$), and video–sucrose (mean difference of 0, $p = 0.005$) groups, respectively. There were no differences between any of the other groups. Together, these results suggest the benefit derived from the lidocaine component of the regimen only. 3489: The melatonin-treated children had significantly lower FPS and NTS pain scores than did the placebo controls (mean difference of 0.9 lower in melatonin group, $p<0.0039$); moreover, pain was significantly reduced in children under 3 years (FLACC mean difference of 2.7 lower in melatonin group, $p<0.0002$). 7671: In this study it was found that holding in an		10270: Taddio et al. (2017) 3489: Marseglia et al. (2015) 7671: Rahyanti, Nurhaeni & Wanda

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								an upright position. Control: routine positioning (lying down supine).	7671: n=16, Median pain score 6.13	score 10	upright position reduced pain compared to the control group (median difference of 3.87 lower in intervention group, p=000). It was also found that age, fear, and cultural background had a significant effect on pain scores experienced by children during the PVAD insertion procedure ($p < \alpha$; $\alpha = 0.05$).		(2017)
							5: Turkey	5: Children were randomized to 3 groups: external cold and vibration (Buzzy), blowing soap bubbles, or the control group. Buzzy: The researcher placed the Buzzy Bee on the arm of each child in this group. It was placed on the arm, which the nurse preferred for the phlebotomy procedure. Blowing bubbles: The researcher told the children included in this group that they could blow soap bubbles during the phlebotomy. Control: No intervention	5: Self-reported pain scores: Buzzy: n=42, 3.12 ± 0.38, Min: 0, Max: 8 Bubbles: n=43, 2.15 ± 0.35, Min: 0, Max: 9 KW=49.891 P= 0.000	5: n=44, 7.37 ± 0.38, Min: 3, Max: 10	5: This study determined that the pain score on the Wong-Baker Faces Pain Rating Scale was lower in the groups of external cold and vibration and blowing soap bubbles than the pain score of the control group (mean difference of 4.25 lower pain score in Buzzy group, 5.22 lower in bubbles group compared to control). Wong-Baker Faces pain scores assessed by parents, the nurse, and the researcher showed that there was minimal to no difference between the external cold and vibration group and the blowing soap bubbles group (P>.05).		5: Binay et al. (2019)
							1174: Italy	1174: Animated cartoons group: the venipuncture was performed two minutes after the start of the cartoon.	1174: Difference in pains score from before to after	1174: n=39, +1.59	1174: Overall, children's perception of pain, as expressed according to WBFP, increased more in the control group from before to		1174: Bergomi, Scudeller, Pintaldi & Molin (2018)

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								Buzzy device: the wings of the device were removed from the freezer and briefly warmed up in order to avoid causing the child discomfort. Animated cartoons+Buzzy device: both interventions were used. Control: no intervention	venipuncture (WBFP from child): Cartoon group: n=37, +0.43 (p= 0.02) Buzzy: n=36, +0.61 (p= 0.06) Cartoon+Buzzy: n=38, + 0.82 (p=0.13)		after venipuncture compared to the intervention groups. The pain score increased 0.77 to 1.16 points more without any intervention offered compared to the intervention groups. Thus, all interventions demonstrated a positive direction of effect.		
							1436: Australia	1436: Exercise task: Participants performed exercises using elastic resistance bands. Three upper body exercises were performed sequentially. 3 doses of HPV vaccine given at 3 separate times; at each dose the participants repeated the same exercise or control procedure, remaining in the allocated group throughout. Control group: proceeded through the vaccination clinic according to usual care.	1436: n=60 FACES pain scores: Females: (3.64; 95% CI, 2.98–4.30 Males: 2.64; 95% CI, 2.16–3.12	1436: n=56 Females: 4.58; 95% CI, 3.96–5.19 Males: 2.34; 95% CI, 1.60–3.07	1436: Reported pain during the injection (FACES) was less for female students in the intervention group compared to the control group (mean difference of 1 point). There was no difference between male students pain score in the intervention and control groups.		1436: Lee, Bouy, Skinner & Edwards (2018)
							1551: USA	1551: Buzzy Device: the device was held directly over the site of injection for 30 s, moved 3 to 5 cm proximal to the site immediately prior to injection, and held in place during the entirety of the needle stick. Parents stayed in the room with all	1551: n=26 Mean pain difference: −2.39 (95% CI −0.48 to −4.24, t =	1551: n=25	1551: In comparing the post-procedure pain ratings given by children, those in the Buzzy group reported lower pain than those in the control group (difference in mean pain scores 2.39 lower in Buzzy group compared to		1551: Redfern, Chen & Sibrel (2017)

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								children during the entirety of the procedure. Control: Children randomized to the control group were provided no intervention or distraction during injection, however, parents were not restricted from soothing children. Small children were allowed to sit on a parent's lap.	−2.53, p =0.015		control). Mean pain reported between those receiving one injection and those receiving more than one injection without considering group assignment, was not statistically different on Student t-test (p=0.36).		
							3556: Turkey	3556: Buzzy group: experimental group received external cold and vibration stimulation via Buzzy, a plastic bee containing a battery and a vibrating motor. The area for the injection was then cleaned, with Buzzy maintaining vibration in place throughout the procedure. Buzzy was administered about 5 cm above the application area just before the procedure and continued through the end of the procedure. Control: received no intervention (regular vaccination).	3556: n=52 Pain scores (mean ± SD): 1.38 ± 1.92	3556: n=52, 3.42 ± 3.10	3556: The self-reported procedural pain levels showed significant differences between the study groups (P = .001); the experimental group had significantly lower pain levels (P = .001) than the control group (mean difference of 2.04 lower in the Buzzy group).		3556: Şahiner, Inal & Akbay (2015)
							3885: China	3885: Group 1 - Music Therapy (MT) Group: three classical music pieces were played on a loop at least five minutes before heel lance and maintained during blood sampling.	3885: Mean change of neonates' NIPS in four groups over time (mean	3885: n=72, 6.43	3885: There was no difference in pain scores when comparing music therapy alone to the control group. However MT combined with BF vs. the control group had a statistically significant		3885: Zhu et al. (2015)

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							15599: India	Group 2 - Breastfeeding (BF) group: the neonates were breastfed in their mothers' arms, starting five minutes before the procedure and continuing throughout. Group 3 - Breastfeeding+Music Therapy group: neonates were breastfed and classical music was played to them at the same time. Group 4 – no intervention 15599: Infants were randomly allocated in four groups: electronic toy group (1), key toy group (2), simple toy group (3) (i.e "apple dancing toy, doraemon playing drum and rattle") and control group (4). Infants in experimental groups were distracted by toys during immunization procedure. Control: no intervention	difference from control group): Group 1: n=72, 6.06 (-0.33) Group 2: n=72, 3.05 (-3.38) Group 3: n=72, 4.36 (-2.07) 15599: Mean pain scores: Group 1: n=25 (2.60±0.81) Group 2: n=25 (4.80±1.11) Group 3: n=25 (5.44±0.91)	15599: n=25 (7.16± 0.80)	positive effect, and MT+BF vs. MT alone also had a statistically significant positive effect. 15599: Mean pain scores of the electronic toy group were significantly lower than mean pain scores in key toy group (mean difference of 2.2), simple toy group (mean difference of 2.84) and in control group (mean difference of 4.56) respectively.		15599: Dabas (2019)
							7759: Turkey	7759: A manual entitled, ''Medicine is being given from my vein,'' was used to introduce the equipment involved, and a soft toy was used for the child to practice the procedure in advance. The children in the intervention group were asked to read the manual and to implement what they learned on a teddy bear. Control: warning prompt, no other intervention.	7759: n=30, Pain Score During the Process: average=2.97, standard error= 0.33, test scores= Za = 2.453, p= .016	7759: n=30, Pain Score During the Process: average= 5.23, standard error= .20	7759: Procedural pain scores were evaluated for both the intervention and the control groups, and it was determined that both anxiety and pain scores were significantly lower in the intervention group (by a mean difference of 2.26 lower in the intervention group).		7759: Tunc-Tuna and Acikgoz (2015)

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							3900: Italy 257: Turkey 424: USA	3900: Children in the intervention group were accompanied in the procedure room during the venipuncture by a parent, an Animal Assistance Intervention expert, and a dog. They interacted with dog in each of three phases: before, during, and after the blood test. Control group (CG) children were accompanied in the same room during the venipuncture by one parent, without any dogs. Parental presence was considered control group because it is the standard hospital procedure. 257: Group 1 - Cartoon group: Starting before the blood-drawing up to the end of the procedure, the children watched funny animated films. Group 2 - Video game group: Children were allowed to play a game that they could play with 1 hand through the procedure. Group 3 - Parent interaction group: The parents starting before the start of the procedure to try to distract their child's attention away from the venipuncture. Group 4 – Control group: No distraction intervention. 424: VR group: Patients in the VR group received standard of care	3900: n=25, Pain scores intervention group: 4.69 ± 3.82, p= 0.776 257: Children's Self-reported Pain Scores (Mean±SD): Group 1: n=45, 3.02±2.94 Group 2: n=45, 1.42±1.74 Group 3: n=45, 2.89±3.00 424: n=70 Patient reports (mean (SD)) -	3900: n=25, Pain scores control group: 5.08 ±2.93, p= 0.776 257: n=45, 5.11±3.78	3900: There was a minimal reduction in pain in the intervention group compared to control group, though the results were imprecise (mean difference in pain scores -0.38, CI -3.14, 2.37). 257: The pain scores of the video game group were lower than the cartoon group (mean difference -1.6, P=0.003), parent interaction (mean difference -1.47, P= 0.019), and control (mean difference -3.69, P= 0.001) groups, both according to the children's own reports and according to the statements of the parents and observer (P<0.05). Also, the scores of the cartoon group (P= 0.008) and parent interaction groups (P= 0.005) were lower than in the control group (P<0.01). 424: Patients in the VR group experienced significantly less procedural pain (mean		3900: Vagnoli et al. (2015) 257: Inan & Inal (2019) 424: Gold and Mahrer

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								(SOC) and interacted with the VR game a few minutes before, during, and following the blood draw procedure (5min total). Control group: no VR (television present in room to play cartoon at low volume)	Pain VAS: 1.31 (1.59) p=0.001 Pain Color Analogue Scale: 1.58 (2.02) p<0.001 Faces Pain Scale-Revised: 1.40 (.73) p<0.001	424: n=73 Pain VAS: 1.93 (2.22)	difference of 0.62 less in the VR group, as measured by the VAS patient report, and 1.2 less as measured by VAS caregiver report) during the blood draw procedure compared with the standard care.		(2018)
							11991: Iran	11991: Sweet solutions given to neonates undergoing hepatitis B immunization - Oral sucrose: 25%, 2cc, or oral glucose: 25%, 2 cc. Control: no solution.	11991: Mean (SD) NIPS Scores: oral sucrose: n=30, 2.9 (1.44) oral glucose: n=30, 3 (1.66)	11991: n=30, 5.20 (1.03)	11991: no difference was observed between sucrose and glucose (mean difference of 0.1, p=0.78), however there was a positive direction of effect between both sucrose/glucose and control (mean differences of 2.3 and 2.2, p<0.001).		11991: Suhrabi, Taghinejad, Valian, Sayehmiri & Taheri (2014)
							9004: Netherlands	9004: Formula intervention: The intervention consisted of giving the infant formula feeding before, during and after vaccination. During vaccination, infants were seated ina half supine position on the lap of the parent, who held the infants and comforted them in their own way, for example, by talking and cradling. Control: no intervention (nothing in their mouths).	9004: n=24 Mean change in NIPS Score between Time 1 and Time 2: 5.70 (1.85) Mean change in FLACC between time 1 and 2: 8.15	9004: n=24 Mean change in NIPS Score between time 1 and time 2: 1.92 (2.00). Difference in FLACC	9004: According to both FLACC and NIPS pain scores, infant pain decreased more in the intervention group compared to the control group from injection time to 60 seconds after. NIPS scores decreased 3.86 more in the intervention group (ranges from 2.7 to 5.05 more). FLACC scores		9004: Bos-Veneman, Otter & Reijneveld (2018)

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							8790: Iran	Time 1= moment of injection Time 2= 60 seconds after injection 8790: Three different oral feeding conditions were used: feeding from mother's breast, bottle feeding of mother's breast milk, feeding of powdered formula. Control: infants were held in mother's arms and not fed.	(2.56) 8790: Mean (SD) DAN score during (D) and after (A) injection: Breastfeeding – n=25, Face grimaces D: 1.24 (1.16), A: 0.44 (0.51), Limb movement D: 1.36 (0.86), A:0, Vocal responses D: 0.92 (0.996), A: 0.48 (0.585) Bottle fed mother's milk – n=25, Face grimaces D: 2.24 (0.723), A: 1.76 (0.597), Limb movement D: 2.4 (0.577), A: 2.04 (0.538), Vocal responses D: 2.12 (0.832), A: 1.93 (0.64)	FLACC between time 1 and 2 3.72 (2.78) 8790: n=25, Face grimaces D: 3, A: 2.92 (0.276), Limb movement D: 2.84 (0.374), A: 2.72 (0.458), Vocal responses D: 2.72 (0.458), A: 2.56 (0.506)	decreased 4.42 more in the intervention group compared to the control group (ranges from 2.85 to 5.99 more). 8790: The results showed that the mean scores of face grimaces, limb movement, and vocal responses were significantly lower in breastfed infants compared to the control, bottle-fed mother's milk, and powdered formula groups (P < 0.0001).		8790: Bavarsad et al. (2018)

Quality assessment							Summary of Findings		No. of Participants		Reported Effects/Outcomes	Certainty	Reference
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Country	Intervention	Intervention	Control			
							17087: Turkey	17087: Flick Application: The Nurse determined the vaccination area and disinfected it using cotton with 70 % alcohol. The muscle was held with the nurse's left hand, and the vaccination area was flicked with the right hand. The flick was given as follows: the thumb was placed on the nail of middle finger, then the vaccination area was stimulated with a quick tap using upper nail part of middle finger. Control: no intervention	Formula fed – n=25, Face grimaces D: 2.48 (0.714), A: 2.03 (0.789), Limb movement D: 2.64 (0.489), A: 2.12 (0.781), Vocal responses D: 2.32 (0.69), A: 2.16 (0.746) 17087: n=35 NIPS score averages: Before: 0.23 ± 1.05, During: 3.01 ± 2.09, After: 1.04 ± 1.99 F:23.485, p < 0.001	17087: n=35 NIPS score averages: Before: 0.52 ± 1.46, During: 5.43 ± 2.47, After: 4.39 ± 2.24, F:39.227, p < 0.001	17087: There was a positive direction of effect - the NIPS pain score of the intervention group was 2.42 points lower in the intervention during vaccination and 3.35 points lower after vaccination.		17087: Ciftci, Ozdemir & Aydin (2016)
							103: Egypt	103: Infants divided into two groups: Sucrose Group - Administered 2 mL 25% sucrose 1min before vaccine injection by using a needleless syringe. Breastfeeding group – mother initiated breastfeeding 1 min before injection and continued breastfeeding throughout the procedure (before, during, and after the injection). Control group: placebo (sterile	103: FLACC scores: Sucrose group – n=40, During injection: 5.4 ± 1.1, After: 3.2 ± 1.6 Breastfeeding group – n=40, During	103: n=40, During injection: 9.7 ± 0.7, After: 8.9 ± 1.1	103: Mean pain scores of the sucrose and breastfeeding groups were 4.3 and 5.4 points lower when compared with control group during injection (p<.001), whereas the mean pain scores in breastfeeding group were significantly lower when compared with sucrose group (mean difference of 1.1 during injection and 0.6 after		103: Gad et al. (2019)

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								water)	injection: 4.3 ± 1.2, After: 2.6 ± 1.4		injection, p=0.002).		
							712: Iran	712: Neonates in the experimental group were breastfed during two minutes before, during, and after hepatitis B vaccination. At the end of the second minute of breastfeeding, while the infants were still sucking, an experienced nurse performed the immunization injections. For the controls the same procedure was applied while they were held in mothers' arms but not fed.	712: n=65 DAN Score: Facial expressions: 1.39, SD=0.65, Limb movements: 0.83, SD=0.51, vocal expression: 1.31, SD=0.68 Total DAN Score: 3.52 (1.37)	712: n=65 DAN Score Facial expressions 2.58, SD=0.72, limb movements: 1.92, SD=0.69, vocal expression: 2.28, SD=0.57 Total DAN Score: 6.78 (1.69)	712: There was reduction in pain expressed by facial expressions, limb movements and vocal expressions of neonates between the control and experimental groups (favouring the intervention groups - mean differences of 1.19, 1.41, and 0.97, p<0.001). In addition the difference of the DAN total score between two groups was significant (mean difference of 3.26 lower, p<0.001).		712: Modarres, Jazayeri, Rahnama & Montazeri (2013)
							1562: Canada	1562: 2mls of 88% sucrose solution Syrup BP was given two minutes prior to venipuncture. A pacifier was given to the infant only at parental request, and this co-intervention was recorded. Control: placebo (sterile water)	1562: n=41 Mean difference in FLACC Pain scores: 2.84 ± 0.64, p=0.98 NIPS Scores: 2.32 ± 0.47, p=0.6	1562: n=41 Mean difference in FLACC Pain scores: 2.71 ± 0.62 NIPS scores: 1.63 ± 0.49	1562: FLACC pain scores were 0.13 points higher in the sucrose group, and NIPS scores were 0.69 points higher in the sucrose group compared to control (minimal to no difference in effect).		1562: Gouin, Gaucher, Lebel & Desjardins (2018)

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							1777: Turkey	1777: newborns were swaddled with legs in flexion and abduction without causing any movement restriction while lying in a supine position on the procedure table. After the procedure newborns were immediately comforted by their parents. Control: natural position	1777: n=37 Mean pain score during: 5.43 ±1.19 1, 2, and 3 minutes after: 1.56 ± .82	1777: n=37 Mean pain score during: 6.57 ± .55 1, 2, and 3 minutes after: 3.29 ± 1.47	1777: The mean pain scores of the experimental group during and after the procedure were lower compared with the control group (mean differences of 1.14 during and 1.73 after), and the difference between them was statistically significant ($p < .001$)		1777: Erkut and Yildiz (2017)
							1973: Turkey	1973: Shot Blocker group – the vaccine was administered using Shot Blocker (pressure device) following manufacturer's recommendations. Control: no intervention	1973: n=50 NIPS Scores: Preinjection: 0.62 ± 0.83; 0–2 At the moment: 1.64 ± 0.80; 1–4 Postinjection: 0.74 ± 0.66; 0–3 F = 387.41; P = .000	1973: n=50 NIPS Scores: Preinjection: 0.70 ± 0.81; 0–3 At the moment: 2.96 ± 0.73; 2–4 Postinjection: 1.42 ± 0.76; 0–3 F = 396.47; P = .000	1973: NIPS scores were significantly lower in the ShotBlocker group than in the control group at the time of injection and postinjection, by a mean difference of 1.32 and 0.68 respectively.		1973: Caglar, Buyukyilmaz, Cosansu & Caglayan (2017)
							2114: Turkey	2114: Ten-second manual pressure: 10-second manual pressure was applied on the vaccine injection site prior to vaccination. Rapid injection without aspiration - Then DTaP/IPV/Hib was administered by using rapid injection	2114: Mean NIPS scores: Manual pressure : n=32, before: 0±0, During:	2114: n=32, before: 0 ± 0, during: 5.3 ± 1.9, after: 2.9 ± 2.7	2114: The intervention group had lower mean NIPS pain scores during and after injection compared to the control group (mean difference of 2.1 and 2.0		2114: Göl and Ozsoy (2017)

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								without aspiration technique. 10-second manual pressure combined with rapid injection without aspiration - Next, 10-second manual pressure was applied on the vaccine injection site. Then DTaP/IPV/Hib was administered by using the rapid injection without aspiration technique. Control group- no intervention	2.2 ± 2.3, After: 0.9 ± 1.9 Rapid injection: n=32, before: 0.1 ± 0.4, during: 1.3 ± 2.1, after: 1 ± 2 Combined pressure and rapid injection: n=32, before: 0 ± 0, during: 1 ± 1.6, after: 0.4 ± 1.1		respectively).		
							2209: Turkey	2209: Breastfeeding group: Before the procedure, the breastfeeding position recommended by the World Health Organization for mothers was applied. Vaccination was started after the mothers breastfed their babies for 5 minutes before the procedure. Control: no intervention	2209: n=50 Mean NIPS Scores: before 0.26 ± 1.03, during 6.00 ± 1.31, after 1.86 ± 2.21	2209: n=50, before 0.60 ± 1.16, during 6.64 ± 0.72, after 6.82 ± 0.75	2209: Higher NIPS score indicates more pain; mean NIPS score in the breastfeeding group was significantly lower than in the control group before immunization ($z = 2.63$, $p < 0.05$). Mean NIPS score in the breastfeeding group was significantly lower than in the control group during immunization (mean difference of 0.64, $z = 2.88$, $p < 0.05$). Mean NIPS score in the breastfeeding group was significantly lower than in the control group after immunization (mean difference of 4.96, $z = 8.71$, $p < 0.05$).		2209: Erkul and Efe (2017)
							2940: Iran	2940: Breastfeeding group:	2940: NFCS median scores	2940: n=33, 15sec after	2940: The results demonstrated a positive		2940:

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							3472: China	Neonates were breast-fed within 45 minutes prior to vaccination and were not swaddled. Swaddling group: The swaddled group were swaddled a few minutes before vaccination and a few minutes after, while more than 45 minutes had passed from being breastfed. Breastfeeding + Swaddling group: The infants in the combined group were swaddled a few minutes before vaccination and a few minutes after, and breast-fed within 45 minutes prior to vaccination. Control: The infants in the control group were vaccinated according to the hospital routine without any intervention. 3472: Kangaroo care: 20mins before heel lancing, the infants were held close to their mother's naked chests. The authors assisted infant into a vertical or frog position skin-to-skin. The nurse administered heel lancing after 15mins. Control group: infants were wrapped in a blanket.	(mean): BF: n=33, 15secs after vaccination: 4 (57.48), 2mins after vaccination: 1 (56.05) Swaddling: n=34, 15secs after vaccination: 4 (61.65), 2mins after vaccination: 2 (66.29) Combined: n=31, 15 secs after vaccination: 4 (57.76), 2mins after vaccination: 2 (65.44) 3472: n=20, DAN score: 5.85 ± 0.98, Pain facial expression time(secs) (average): 9.25, p=0.041, crying time (secs) (average): 10.72,	vaccination: 6 (86.74), 2mins after vaccination: 2 (75.18) 3472: n=20, Pain facial expression time (secs) (average): 21.75, crying time (secs) (average): 22.28, No DAN score given.	direction of effect - the mean level of pain in the breastfed and swaddled groups compared to the control group was reduced (p=0.010, p=0.001). 3472: Kangaroo care was shown to have a positive effect in reducing pain compared to the control group (p<0.01). Pain facial expressions were 12.5 seconds shorter on average in the kangaroo care group, and crying time was 11.56 seconds shorter.		Hashemi, Taheri, Ghodsbin, Pishva & Vossoughi (2016) 3472: Liu, Zhao & Li (2015)

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							4842: Australia	4842: Sucrose Group 1 (>4 weeks to 12 weeks corrected age): received 2mls sucrose via syringe onto the anterior portion of the tongue over 30secs 2minutes prior to vaccination. Sucrose Group 2 (>12 weeks to 26 weeks corrected age): same procedure as above Control group 1 (>4 weeks to 12 weeks corrected age): sterile water Control group 2 (>12 weeks to 26 weeks corrected age): same procedure as above.	p=0.033 4842: Pain scores (median) Sucrose group 1: n=21, Baseline 0.0 (2), Skin swab 1.0 (5), Needle insertion 7.0 (5), Blood draw 5.0 (6), Completion of procedure 5.0 (5), 1 min after procedure 1.5 (3), 2 min after procedure 1.0 (2), 3 min after procedure 0.0 (1) Sucrose Group 2: n=21, Baseline 0.0 (2), Skin swab 1.0 (3), Needle insertion 5.0 (6), Blood draw 5.0 (6), At completion of procedure 4.0 (5), 1 min after procedure 1.0	4842: Control group 1: n=20, Baseline 0.0 (3), Skin swab 3.0 (6), Needle insertion 7.5 (5), Blood draw 7.0 (7), Completion of procedure 5.0 (5), 1 min after procedure 3.0 (5), 2 min after procedure 0.0 (4), 3 min after procedure 0.0 (1) Control group 2: n=22, Baseline 1.0 (1), Skin swab 2.5 (6), Needle insertion 7.0 (5), Blood draw 6.0	4842: There was a minimal but positive direction of effect favouring sucrose groups compared to control groups. No confidence intervals were given however; hard to determine the precision of results.		4842: Wilson, Bremmer, Mathews & Pearson (2013)

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									(3), 2 min after procedure 1.0 (2), 3 min after procedure 1.0 (2)	(3), At completion of procedure 3.5 (5), 1 min after procedure 2.0 (5), 2 min after procedure 1.0 (1), 3 min after procedure 0.0 (2)			
							6953: Canada	6953: Syrup BP-88% sucrose: Two minutes before venipuncture, the solution contained in a syringe was administered to the participant by the research assistant (2mls of sucrose solution). Control: sterile water	6953: n=45, FLACC difference at 1 min post intervention(± 1 SD): 1.36 (±0.59), p=0.49 NIPS difference at 1 min post intervention (±1 SD): 0.75 (±0.58), p=0.36	6953: n=43, FLACC difference at 1 min post intervention(±1 SD): 2.07 (±0.77) NIPS difference at 1 min post intervention (±1 SD): 1.73 (±0.62)	6953: The FLACC scores were 0.71 lower in the intervention group, and NIPS scores were 0.98 lower (indicating lower pain experienced with the intervention).		6953: Desjardins et al. (2016)
							338: Vietnam	338: Those in the intervention group performed non-nutritive sucking (NNS) for 120s before the heel prick, during the heel prick, and then for a further 120 s after the heel prick. A medical student held the pacifier and	338:n=22 infants N-PASS score mean (SD): 30s: 4.73	338: n=20 infants N-PASS score mean (SD) 30s: 7.90	338: Results were positive favouring the NNS group at all time points compared to the control group.		338: Vu-Ngoc et al (2020)

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								applied a gentle pressure to keep it in the infant's mouth during the procedure. Newborns in the control group did not receive any form of pain-relief.	(2.78) 60s: 3.64 (3.06) 90s: 2.59 (3.08) 120s: 2.05 (2.94)	(1.52) 60s: 5.55 (2.95) 90s: 5.25 (3.51) 120s: 4.90 (3.99)			
							701: Turkey	701: Acupressure - for two minutes, acupressure was performed. The acupuncture points Kun Lun (UB60) and Taixi (K3) are on the side of the ankle. Each point was applied acupressure for 60 s, and heel lancing was performed right after this procedure. Massage group - Neonates in the massage group were given foot massage for two minutes, and heel lancing was performed right after the massage. Control group received no interventions prior to heel lance.	701: Acupressure (n=46), NIPS pain mean scores during the heel lancing: 4.30 ± 2.25 Massage (n=47), NIPS pain mean scores: 3.95 ± 2.63	701: n=46 NIPS pain mean score: 6.04 ± 1.26	701: The mean difference (SE) and 95% confidence interval (CI) of the mean difference between groups: control-acupressure: 1.73 ± 0.38 and 0.98–2.49; control-massage: 2.08 ± 0.42 and 1.23 –2.93;acupressure-massage: 0.34 ± 0.50 and 0.66–1.35). The NIPS scores of the neonates in the acupressure and massage groups were significantly lower than the control group.		701: Ozkan et al. (2019)
							709: Jordan	709: The pharmacist prepared 2 mL of 50% sucrose solution or sterile water in needleless syringes according to the allocation sequence. All of the solutions were colorless and odorless and differences in viscosity were not apparent. Participants in the intervention group were given a 2ml dose of 50% sucrose solution. Both groups received solutions sublingually over a 30 s period via needleless syringes immediately	709: n=65 Pain score duting immunization: Infants: 6.89 ± 1.05, Children: 7.17 ± 1.21	709: n=67 Pain score duting immunizatio n: Infants: 6.89 ± 0.87, Children: 6.82 ± 1.05	709: Pain scores between the intervention and control groups during immunization were equivalent.		709: Kassab et al. (2020)

Quality assessment							Summary of Findings		No. of Participants		Reported Effects/Outcomes	Certainty	Reference
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Country	Intervention	Intervention	Control			
								before the immunization injections.					
							798: India	798: The intervention was an electric heating pad (40°C) applied at the site of the identified IV access for 10min before PVAD insertion. No heat was applied to the children in the control group.	798: n=42 Note: raw data of pain scores not given; Estimates were obtained from a logistic regression model, and are reported as average marginal effects.	798: n=42	798: A far greater proportion of children in the intervention group experienced less pain as compared to those in the control group. Specifically, those in the intervention group were 45.2 percentage points more likely to experience a discomfort level of "little hurt", as compared to control group children (see table 5).		798: Suchitra & Srinivasan (2019)
							391: Iran	391: In the aromatherapy group, term neonates inhaled 10 drops of lavender essential oil 0.5 % (three drops of lavender essential oil 100% was dissolved in 30 ml glycerin solution, which resulted in lavender essential oil 0.5 %). In the aromatherapy group, familiarization was performed in accordance with the protocol of the previous studies, at 10 pm before the blood sampling. In the second group, neonates received 2 ml of edible glucose 30 %, two minutes before the blood sampling. The third group did not receive any specific intervention and received routine care.	391: aromatherapy: n=40, DAN Score 4.47±1.81 Glucose: n=40, DAN Score 4.80±1.92	391: DAN score 5.97±1.94	391: Results demonstrated a positive effect favouring the lavender or glucose groups over control, with lavender demonstrating the greatest effect.		391: Razaghi et al (2020)
							396: Turkey	396: Before the heel lance procedure, the newborns in the experimental group were subjected to a local dry mildly warm compress for five min using a thermophore. The warmth of the water in the thermophore was kept between 34-	396: n=40, Neonatal Infant Pain Scale Median (min-max) 7(3-10)	396: n=40 Neonatal Infant Pain Scale Median (min-max) 8(2-10)	396: Pain scores were lower in the experimental group compared to the control group.		396: KarabıyıkOğurlu et al. (2020)

Quality assessment							Summary of Findings		No. of Participants		Reported Effects/Outcomes	Certainty	Reference
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Country	Intervention	Intervention	Control			
							1541: Iran	37 ˚C. To prevent the thermophore from contacting the sole of the infant's foot, it was wrapped in a cloth and placed on the sole from which heel lance would be taken. the control group received routine heel lance procedure. No comforting or relaxation interventions were used during the heel lance procedure, and the newborns were immediately comforted after the procedure. 1541: Venipuncture in both groups was carried out by skilled nurses. Failure to locate vessel in the infants resulted in the exclusion from the study. In both the groups, 15 minutes before venipuncture, infants were fed with breast milk or formula. In experimental groups, infants were placed on the mothers' lap for 2 minutes before and after venipuncture and caressed by the mother during this period. In the control group infants were placed on bed 2 minutes before and after venipuncture (according to the usual venipuncture method).	1541: n=60 MBPS Scores: Before venipuncture: Minimum 2 Maximum 7 Mean ± SD 3.53 ± 1.37 During Catheter Insertion Minimum 3 Maximum 10 Mean ± SD 9.28 ± 1.46 After Venipuncture Minimum 3 Maximum 7 Mean ± SD 4.40 ± 1.92	1541: n=60 MBPS Scores: Before venipuncture: Minimum 3 Maximum 10 Mean ± SD 4.20 ± 1.90 During Catheter Insertion Minimum 7 Maximum 10 Mean ± SD 9.85 ± 0.67 After Venipuncture Minimum 3 Maximum 7 Mean ± SD 8.13 ± 2.53	1541: Results demonstrated a positive direction of effect, favouring the hugging/caressing group.		1541: Beiranvand et al. (2020)

Quality assessment							Summary of Findings		No. of Participants		Reported Effects/Outcomes	Certainty	Reference
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Country	Intervention	Intervention	Control			
							539: Turkey	539: The practices made to the acupressure group at 10 min before the venipuncture procedure. Before the start of the acupressure administration, the child was relaxed by rubbing their arm from their fingertips to their elbows. Acupressure was then applied to the acupressure points (Large Intestine Meridian 4th Point [LI 4], Large Intestine Meridian 11th Point [LI 11], and Heart Meridian 7th Point [HT 7]). Acupressure was applied to each spot for approximately 30–40 s. Acupressure was performed for each child for only one session, and the session lasted 10 minutes for each child. Acupressure was performed before the venipuncture procedure, and the venipuncture procedure was immediately performed after the acupressure treatment. No acupressure was given to the control group.	539: n=45 Pain experienced during the Procedure: VAS 19.51 ± 4.98 FPS-R 2.08 ± 0.41	539: n=45 Pain experienced during the Procedure VAS 47.37 ± 9.89 FPS-R 4.84 ± 1.08	539: Results demonstrated a positive direction of effect, favouring the acupressure group.		539: Ozcan and Balci (2019)
							362: Turkey	362: A virtual reality (VR) headset provided an opportunity to watch and listen to VR video and audio. The virtual headsets were introduced to the school-aged children in the intervention groups by the researcher G, and they were told that they could watch applications by wearing the virtual headset during the procedure. The VR applications were chosen by the researchers. During the venipuncture procedure, the families stayed with their children in all groups. The venipuncture procedure was performed by usinga vacuum tube and a 21G needle tip in the left arm of all the children. Blood	362: VR-Rollercoaster n=45 Self-reported wong bakers score 1.2 ± 2.2 (0–10) VR-Ocean Rift n=45 Self-reported wong bakers score 1.0 ± 1.5 (0–6)	362: n=46 Self-reported wong bakers score 4.1 ± 3.5 (0–10)	362: The results demonstrated a positive direction of effect, favouring the VR groups over control. There was little to no difference between the two VR groups in the reduction of pain.		362: Gerceker et al (2019)

Quality assessment							Summary of Findings		No. of Participants		Reported Effects/Outcomes	Certainty	Reference
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Country	Intervention	Intervention	Control			
								was taken from the children in all groups during the first attempt. 660: The virtual reality goggle, was used for distraction in the virtual reality goggle group. The children (aged 4-10) in the virtual reality goggle group were asked if they wanted to wear the virtual reality goggle. Then the children were asked to choose a video to watch during the procedure. At the start of the procedure, the children were distracted via the virtual reality goggle until the procedure was over. Distracting children with a virtual reality goggle was performed by the same researcher. Kaleidoscope group - The children were asked if they wanted to look into the kaleidoscope. At the start of the procedure, the children in the group were given a kaleidoscope to look through until the procedure was over. Distracting children with a kaleidoscope was performed by the same researcher. Control group received no distraction intervention. 417: School-aged children watched cartoon on 7-inch tablet computer device during phlebotomy process, or watched cartoon on VR box device during the phlebotomy process. Nothing was watching by children in the control group.	660: VR group n=46 Mean VAS: 1.97 +/- 1.2 WB-Faces scale: child reported 1.76 +/- 1.4 Kaleidoscope group n=46 Mean VAS: 2.95 +/- 1.9 WB-Faces scale: child reported 2.76 +/- 1.8 417: Cartoon group n=40 WB-FBRS scores: 4.55 ± 3.44 VR group n=40 WB-FBRS	660: n=43 Mean VAS: 6.81 +/- 2.2 Child reported: 6.65 +/- 2.2 417: n=40 WB-FBRS scores: 4.95 ± 3.65	660: The pain scores of the children in the virtual reality goggle group and those of children in the kaleidoscope group during the procedure were significantly different, with the virtual reality goggle group reporting less pain. There was also a difference in pain scores of the children in the kaleidoscope group and those of children in the control group during the procedure, with the kaleidoscope group having less reported pain. There was a difference between pain scores of the children in the virtual reality goggle group and the control group during the procedure, with the virtual reality goggle group having less reported pain. 417: WB-FBRS scores were significantly higher in the control and the tablet groups than in the VR box group during phlebotomy.		660: Ozkan & Polat (2020) 417: Inangil et al (2020)

Quality assessment							Summary of Findings		No. of Participants		Reported Effects/Outcomes	Certainty	Reference
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							418: Turkey	418: Flippits distraction cards feature various pictures and shapes. These pictures and shapes can only be seen when a card is carefully examined. During the distraction process, the child is asked questions pertaining to the cards, such as, "How many ladybugs are there in the picture?" "Can you see the elephant in the picture?" and "How many blue flowers are pictured?". The researcher showed the cards to the children, asking the questions written on the back of each card. Children looked at the cards and answered questions. This distraction procedure started before the phlebotomy procedure and continued until it ended. Kaleidoscope group - The researcher held a kaleidoscope to each child's eye, leisurely turning it and asking about the colors and shapes seen within it. This distraction procedure started before the phlebotomy procedure and continued until it ended. The usual protocols were used for the control group (no distraction).	scores: 1.3 ± 2.15 418: Distraction cards n=30 VAS: 2.32 ± 2.55 Kaleidoscope n=30 VAS: 2.72 ± 3.29	418: n=30 VAS: 6.24 ± 3.93	418: When children's reports of procedural pain were evaluated with VAS, there were significant differences among the control and experimental groups, favouring the distraction card and kaleidoscope groups. When parents' proxy reports were evaluated with VAS, there were also significant differences among the control and experimental groups. There were little to no differences between the distraction card and kaleidoscope groups.		418: Semerci and Kostak (2020)
							437: Turkey	437: Before entering the intervention room, experimental group children (school age children mean age 104) were briefly informed about how to use a virtual reality headset. One minute before the venipuncture procedure, children started to watch	437: n=60 WBFPS Pain mean SD 1.68 ± 1.51 median (min:max) 2 (0:6)	437: n=60 WBFPS Pain mean SD 2.02 ± 1.96 median	437: Results demonstrated a positive direction of effect, favouring the VR group.		437: Aydin and Ozyazıcıoglu (2019)

Quality assessment							Summary of Findings		No. of Participants		Reported Effects/Outcomes	Certainty	Reference
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							460: Turkey	the 3D "Aquarium VR" application via the virtual reality headset. The nurse performed the venipuncture at the patients' antecubital site using a vacutainer. This procedure lasted about 2-3 minutes, during which time the children did not take off the virtual reality headset. No interventional procedure was used for children in the control group. 460: Information Video Group (Group 1).The children in this group watched the information video about PVAD insertion before the procedure. The content of the animated video, which was prepared according to the development level of children aged 6- 12 years, was determined by the researchers. The video was prepared by a computer programmer in accordance with the specified content. The animated video, which was prepared in 3D, was reviewed by 5 experts in the field of pediatric nursing and was finalized in line with their recommendations. The video, which lasts 2 minutes and 44 seconds, explains the features of the equipment used for a PVAD insertion and how the procedure is performed Cartoon Group (Group 2): The children in this group watched a cartoon during the IV insertion procedure. Two popular cartoons that children aged 6-12 years like to watch were selected. When deciding the selection of the cartoons, the opinions and requests of 10 children	VAS Pain mean SD 3.07 ± 2.86 Median (min:max) 2 (0:10) 460: Information group n=159 Child reported mean pain score after insertion: 0.09 (0.48) Cartoon group n=159, 0.30 (0.88)	(min:max) 2 (0:8) VAS Pain mean SD 3.23 ± 3.05 median (min:max) 2 (0:10) 460: n=159 Child reported mean pain score after insertion: 4.14 (1.11)	460: The children who watched the information video before the PVAD insertion procedure and those who watched a cartoon during the procedure had lower pain mean scores as evaluated by the child, parent, and nurse than the children in the control group.		460: Duzkaya et al (2020)

Quality assessment							Summary of Findings		No. of Participants		Reported Effects/Outcomes	Certainty	Reference
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								in the age group of 6-12 years were taken into consideration. The children were asked to select one of the cartoonsbefore the procedure, and they watched their chosen cartoon during the procedure. No distraction was used in the control group.					
							471: China (Hong Kong)	471: In addition to standard care, VR intervention was offered to patients 5 minutes before and during PVAD insertion (children with cancer mean age 10.4). During the intervention, patients experienced a sense of immersion through the device delivering the VR sounds and images. In standard care, phlebotomists explained and performed PVAD insertion. The patients were comforted verbally, but no distraction or analgesic medication was given during the PVAD insertion.	471: n=54 Mean pain levels of patients who received VR intervention increased from 0.74 (1.94) to 1.94 (1.73)	471: n=54 Mean pain levels of the control group increased from 1.11 (1.69) to 4.00 (3.53)	471: Results demonstrated a positive direction of effect, favouring the VR group (estimated mean difference (95% CI): -1.69 (-2.92, -0.45)).		471: Wong et al (2020)
							1699: Turkey	1699: Group 2 received external thermomechanical stimulation using Buzzy. Group 3 received distraction using DistrACTION Cards. Group 4 received both external thermomechanical stimulation and distraction (prior to venipuncture). The control group received no intervention for pain relief.	1699: Pain level during procedure mean±SD Group 2 N= 55 1.38 ± 1.3 Group 3 N=55 2.43 ± 1.3 Group 4 N=52	1699: N=56 Pain level during procedure mean±SD 4.46 ± 2.9	1699: All strategies had lower pain scores compared to the control group. Buzzy and distraction had lowest pain scores, followed by buzzy alone followed by distraction alone.		1699: Inal and Kelleci (2020)

Quality assessment							Summary of Findings		No. of Participants		Reported Effects/Outcomes	Certainty	Reference
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Country	Intervention	Intervention	Control			
									0.53 ± 0.9				
							1734: USA	1734: Intervention groups: Breastfeeding group, oral sucrose group, nonnutritive sucking group, Skin-to-skin contact group (during heel lance). The control did not receive any pain management strategy.	1734: Mean NPASS score (SD) n=45 Breastfeeding 1.88 (2.49) n=42 Oral sucrose 1.01 (1.25) n=51 Nonnutritive sucking 1.84 (2.49) n = 38 Skin-to-skin 3.21 (3.17)	1734: n=50 Mean NPASS score (SD) 5.14 (2.50)	1734: All strategies had lower pain score compared to control group. There was no difference between intervention groups except for oral sucrose compared to skin-to-skin.		1734: Chang, Filoteo and Nasr (2020)
							1807: Turkey	1807: In the intervention group children were given gum to chew during the PVAD insertion. Children who were in the control groups did not receive any pain reduction methods or treatments.	1807: n=37 CAPS mean = 1.27 ± 0.96	1807: n=36 CAPS mean = 1.42 ± 0.91	1807: Pain scores were lower in the gum chewing group than the control group.		1807: Topcu et al. (2020)
							2265: Taiwan	2265: The experimental group used a virtual reality headset during PVAD insertion. In the control group, children were offered verbal comforting only.	2265: n=68 Pain score Mean ± SD: 3.35 ± 2.38	2265: n=68 Pain score Mean ± SD: 4.35 ± 2.95	2265: Pain scores were lower in the group that received virtual reality compared with the control group.		2265: Chen et al. (2019)
							1658: Turkey	1658: Intervention groups included balloon inflation, ball squeezing, or coughing during venipuncture. Children in the control group received no pain management.	1658: Mean ± SD balloon inflation: n=30, 1.87 ± 1.28 n=30 ball squeezing	1658: n=30, Mean ± SD: 4.67 ± 1.21 n=30	1658: Pain scores in all intervention groups were improved compared with the control group. The was no difference in pain scores between balloon inflation, ball squeezing and coughing		1658: Girgin and Gol (2020)

Quality assessment							Summary of Findings		No. of Participants		Reported Effects/Outcomes	Certainty	Reference
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									n=30, 1.8 ± 1.1 n=30 coughing n=30, 1.33 ± 1.32 n=30		groups.		
							1671: Turkey	1671: Active distraction group: The rotatable wooden toy is a toy that stimulates children's cognitive, visual, and kinesthetic senses, enabling them to display their own skills. Passive distraction group: The toy wristband used for passive distraction is an audible, colored toy designed by the researcher. It consists of 2 parts: a 7-cm x 37-cm colored plush toy containing a sound device, and an elastic fabric wristband	1671: Active distraction N=72 Passive distraction N=72 Mean pain score WB score passive 3.30 (1.95) active 2.60 (1.54) VAS score passive 1.97 (0.81) active 1.50 (0.65)	1671: N=72 Mean pain score WB score 7.33 (2.41) VAS score 3.79 (1.08)	1671: Distraction techniques had lower pain scores than the control group. The results slightly favour active distraction over passive with lower pain scores in the active group.		1671: Arıkan and Esenay (2020)
							1737: Turkey	1737: Children in the experimental group used a virtual reality headset to watch a rollercoaster video. The only routine practice is parents' presence during the procedure. In the control group, no pain-reducing interventions were applied during the procedure.	1737: n=37 Mean pain score 2.34 ± 3.27	1737: n=37 Mean pain score 5.02 ± 3.35	1737: Pain scores were lower in the virtual reality group compared with the control group.		1737: Semerci et al (2021)
							1894: India	1894: The neonates were to receive one of the following creams one hour prior to venipuncture procedure: •Eutectic mixture of local an aesthetic (EMLA®)	1894: EMLA group: n=66 5% lignocaine group: n=63 Mean NIPS score:	1894: n=61 Mean NIPS score: placebo: 5.7 ± 1.2	1894: Both EMLA and lignocaine groups had lower pain scores than the control group. There was no difference in pain scores		1894: Reddy, Rajan & Aroor (2019)

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								containing 2.5% lidocaine and 2.5% prilocaine •5% lignocaine. Neonates in the control group placebo cream one hour prior to venipuncture.	EMLA: 2.4 ± 1.46 5% lignocaine: 2.5 ± 1.4		between topical anesthetics.		
Outcome: Fear/anxiety (assessed with: CAPS, CFS, PRCD, Spielberger State-Trait Anxiety Inventory for Children, STAIC, OSBD-A, OSBD-R, CASI, FAS, WBFP, CEMS, and NRS)													
3[f]	Systematic Review (of RCTs)	Serious[g]	Serious[h]	Serious[i]	Not Serious	Not detected	3362: Multiple: USA, Brazil, Iran, Canada, India, China, UK, Netherland, Italy, Australia, Turkey 772: Multiple countries:	**Non-Pharmacological Interventions** 3362: Variety of physical interventions were used: skin-to-skin contact, holding during procedure, holding after procedure, sitting upright, non-nutritive sucking, manual tactile stimulation, tactile stimulation using vibrating device and cold, warming vaccine, breastfeeding. Control: lying supine in crib, infants held transversely after procedure and gently patted on buttocks and returned to crib, or no tactile stimulation, or no application of vibrating device/cold, or no warming of vaccine 772: The most common psychological interventions were distraction, combined CBT, and hypnosis. Preparation/information,	3362: Sitting upright: 1 study, n=107, SMD 0.39 (95% CI: 0.77, 0.01) External cold and vibration: 2 studies, n=104, SMD 0.28 (95% CI: 0.11, 0.66) 772: Distraction: n=32 studies, SMD −0.82,	3362: not specified 772: not specified	The systematic reviews found that fear/anxiety levels were reduced with the use of pharmacological or non-pharmacological pain management interventions. The 21 additional RCTs included supported these findings. 3362: Children in the sitting upright group reported lower levels of fear than those lying supine group postintervention (ie, after positioning but before the procedure). The studies that investigated the effect of externally applied vibrating devices with cold showed low quality evidence with no evidence of benefit for reducing fear/anxiety. 772: Distraction: There was a large effect of distraction relative to control groups in meta-analysis of four studies	⊕⊕◯◯ LOW	3362: Taddio et al. (2015) 772: Birnie et al. (2018)

Quality assessment							Summary of Findings		No. of Participants		Reported Effects/Outcomes	Certainty	Reference
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							Turkey, India, Italy, Canada, USA (most), Iran, Australia, Kuwait, France, Iceland, Greece, Israel, Spain, Vietnam, Sweden, Brazil, Mexico, Netherlands, China, Germany 907: Authors from Japan; countries of included studies not given	breathing, suggestion, and memory alteration were also included. Distraction interventions were varied and included watching cartoons or a movie, listening to music or a spoken story, interactive handheld computer or video games, distraction cards, virtual reality, playing with a toy, parent distraction, medical clown, squeezing a rubber ball, or a combination or selection of various distractors such as toys, books, cartoons, games, or music. Control: standard care (varied across studies) 907: Children 0-18 years old who underwent needle-related procedures (NRPs) for any condition (specific settings not given) were included. Vibratory devices during NRPs - devices included Buzzy, Vibration Anesthesia Device, Norco Mini Vibrator, and Hitachi Magic Wand with Wonder Wand. The comparators used in the studies were the nonuse of vibratory devices, placement of the devices without turning them on topical anesthesia and vapocoolant. Anxiety was measured using three observational assessment scales: the Children Fear Scale, Children's	95% CI −1.45 to −0.18, Z = 2.52, P = 0.01, I2 = 89%. CBT: n=18 studies, hypnosis: n=8 studies, SMD −0.26, 95% CI −0.56 to 0.04, Z = 1.69, P = 0.09, I2 = 24% Hypnosis: n=5 studies, SMD −2.53, 95% CI −3.93 to −1.12, Z = 3.53, P < 0.001, I2 = 91% 907:n=4 studies, 314 participants Std. Mean Difference: -1.03 [-1.85, -0.20]	907: n=4 studies, 310 participants	including 426 participants (intervention group = 214) for self-reported distress. Combined CBT: Six studies examining combined cognitive-behavioral strategies for *self-reported* distress with 234 participants (intervention group = 110) also showed a minimal but imprecise positive effect. Hypnosis: Five studies including 176 participants (intervention group = 97) revealed a large effect of hypnosis for *self-reported distress*. 907: The SMD of anxiety was significantly lower in the group with vibratory stimulation than without vibratory stimulation.		907: Ueki, Yamagami & Makimoto (2019)

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							17: Turkey	Anxiety and Pain Scale, and Child Rating of Anxiety Scale. **Additional RCTs Identified:** **Mixed (Pharmacological and Non-Pharmacological Interventions)** 17: The children were randomized into 5 groups: Jet lidokaine (n=39), Buzzy, bubble-blowing, aromatherapy, and the control group. This method (jet lidocaine) employs a compressed carbon dioxide-driven device that delivers 0.2 ml of buffered 1% lidocaine transdermally. Control: no intervention	17: Jet lidokaine group: n=39 Jet lidokaine CFS scores: before: 1.92 ± 0.62 2.00(1.00–3.00) during: 1.46 ± 0.50 3.00(1.00–4.00), after: 1.33 ± 0.48 1.00(1.00–2.00). PRCD scores - before: 1.30 ± 0.46 1.00 (1.00–2.00), during: 1.64 ± 0.48 2.00 (1.00–2.00), after: 1.23 ± 0.42 1.00 (1.00–2.00) Buzzy group:	17: n=39 Control group CFS scores: before:2.20 ± 0.80 2.00(1.00–3.00), during: 2.66 ± 0.90 3.00(2.00–4.00), after: 2.07 ± 0.73 2.00(1.00–3.00) PRCD scores before: 1.51 ± 0.45 2.00 (1.00–2.00), during: 1.92 ± 0.65 2.00 (1.00–3.00), after: 1.23 ± 0.37 1.00	17: The difference between the intervention and control groups in terms of level of fear *during* phlebotomy was significant in favor of the Buzzy group, and the children in the Buzzy group were less frightened *during* phlebotomy ($p < 0.05$). As a result of post-hoc Bonferroni it was found that there was also a difference originating in the bubble-blowing group for fear *before* phlebotomy, and that children in this group were less frightened *before* phlebotomy ($p<0.05$).		17: Alemdar and Aktas (2019)

Quality assessment							Summary of Findings		No. of Participants		Reported Effects/Outcomes	Certainty	Reference
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Country	Intervention	Intervention	Control			
									n=39 CFS Scores: before: 1.82 ± 0.60 2.00(1.00–3.00), during: 1.33 ± 0.47∗ 2.00(1.00–4.00), after: 1.46 ± 0.51 1.00(1.00–2.00) Bubble-blowing group: n=39, before: 1.79 ± 0.52, during: 1.66 ± 0.73, after: 1.66 ± 0.53 Aromatherapy group: n=39, before: 1.82 ± 0.68, during: 1.97 ± 0.77, after: 1.97 ± 0.73	(1.00–2.00)			
							3489: Italy	**Pharmacological Interventions** 3489: Patients were given either 0.5 mg/kg (max 5 mg) oral melatonin (Melamil®) 30min. before blood drawing. The patients received drugs via oral route by a blinded nurse. Control: placebo (5% glucose solution) **Non-Pharmacological**	3489: n=30 CAPS scores: 1.3 ± 1	3489: n=30 CAPS Scores: 2.2 ± 0.9	3489: There were significant differences between melatonin and placebo groups in anxiety and pain scores after blood sampling; patients who received melatonin showed anxiety levels lower than those treated with placebo (mean difference of 0.9 lower in		3489: Marseglia et al. (2015)

Quality assessment							Summary of Findings		No. of Participants		Reported Effects/Outcomes	Certainty	Reference
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Country	Intervention	Intervention	Control			
								Interventions			melatonin group, p<0.0005).		
							1174: Italy	1174: Animated cartoons group: the venipuncture was performed two minutes after the start of the cartoon. Venipuncture was performed using a 21G butterfly needle. Buzzy device: the wings of the device were removed from the freezer and briefly warmed up in order to avoid causing the child discomfort. The device was applied 5cm proximally from the site of venipuncture. Animated cartoons+Buzzy device: both interventions were used. Control: no intervention	1174: CEMS Scores from nurse/mother/father Cartoon group: n=37, −0.73 (0.09), −0.88 (0.49), −0.33 (0.91) Buzzy group: n=38, −0.86 (0.03), −1.75 (0.09), −0.75 (0.32) Cartoon+Buzzy: n=38, −0.89 (0.02), −0.86 (0.51), −1.11 (0.11)	1174: n=39, −0.26, −0.35, −0.2	1174: Children's anxiety and parent's anxiety, as measured by CEMS and NRS, decreased more in the groups with non-pharmacological interventions as compared to the control group.		1174: Bergomi, Scudeller, Pintaldi & Molin (2018)
							1436: Australia	1436: Exercise task: Participants performed exercises using elastic resistance bands. Three upper body exercises were performed sequentially 3 doses of HPV vaccine given at 3 separate times; at each dose the participants repeated the same exercise or control procedure, remaining in the allocated group throughout. Control group: no intervention	1436: n=60 Fearmometer scores (all groups – female vs. male) Females: (4.29; 95% CI, 3.81–4.77) Males: (3.22; 95% CI, 2.71–3.73) CFS Scores:	1436: n=56 Fearmometer scores (control group only): females: (4.57; 95% CI, 3.92–5.23) Males: (2.83; 95% CI, 2.05–3.61	1436: Females reported higher anxiety than males. Post hoc analysis showed a higher anxiety rating in females than in males (p = 0.001) in the Control group. Reported fear (using CFS) during the vaccination showed a significant sex effect (p = 0.002) with females reporting higher fear than males. There were minimal to no group or visit effects.		1436: Lee, Bouy, Skinner & Edwards (2018)

Quality assessment							Summary of Findings		No. of Participants		Reported Effects/Outcomes	Certainty	Reference
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Country	Intervention	Intervention	Control			
									Females: (2.50; 95% CI, 2.28–2.73) Males: (1.97; 95% CI, 1.73–2.21)				
							1551: USA	1551: Buzzy Device: the device was held directly over the site of injection for 30 s, moved 3 to 5 cm proximal to the site immediately prior to injection, and held in place during the entirety of the needle stick. Parents stayed in the room with all children during the entirety of the procedure. Control: no intervention (however parents allowed to soothe children)	1551: n=26 Anxiety Mean Scores (WBFS): 5.18	1551: n=25, 4.34	1551: The anxiety ratings by children in both groups were compared by Student t-test; the mean difference in scores was 0.84 higher in Buzzy group, p = 0.43, demonstrating a minimal but negative direction of effect.		1551: Redfern, Chen & Sibrel (2017)
							3556: Turkey	3556: Buzzy group: experimental group received external cold and vibration stimulation via Buzzy, a plastic bee containing a battery and a vibrating motor. Buzzy was administered about 5 cm above the application area just before the procedure and continued through the end of the procedure. Control: no intervention	3556: n=52 Mean CFS Scores: Observer 1: 0.58±0.63 Observer 2: 0.73±0.66	3556: n=52 Mean CFS Scores: Observer 1: 1.96± 1.13 Observer 2: 1.92±1.18	3556: The procedural anxiety levels of children reported by the observers showed a significant difference between the study groups (P=.000). The anxiety levels in the experimental group were 1.38 and 1.19 points lower than in the control group (p=0.001 for both).		3556: Şahiner, Inal & Akbay (2015)
							7759: Turkey	7759: A manual entitled, ''Medicine is being given from my vein,'' was used to introduce the equipment involved, and a soft toy was used for the child to practice the procedure in	7759: n=30 Anxiety Score During the Process: average=	7759: n=30 Anxiety Score During the Process: average=	7759: Patients experienced less anxiety in the intervention group as demonstrated by lower anxiety scores in the intervention group than the control group (mean		7759: Tunc-Tuna and Acikgoz (2015)

Quality assessment							Summary of Findings		No. of Participants		Reported Effects/Outcomes	Certainty	Reference
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Country	Intervention	Intervention	Control			
								advance. Control: verbal prompt only	37.97, standard error= 1.75, t = 7.896 p = 0.0001	54.50, standard error= 1.04,	difference of 16.53 points).		
							3900: Italy	3900: Children in the intervention group were accompanied in the procedure room during the venipuncture by a parent, an Animal Assistance Intervention expert, and a dog. They interacted with dog in each of three phases: before, during, and after the blood test. Control: no intervention (parents were present)	3900: Distress (OSBD-A total): 14.15± 22.24 n=25	3900: 33.15± 22.97 p= .042 mean difference 8.87, CI: (-37.29, -0.70) n=25	3900: The level of total distress was lower in the intervention group than in the control group.		3900: Vagnoli et al. (2015)
							257: Turkey	257: Group 1 - Cartoon group: Starting from 3 minutes before the blood-drawing up to the end of the procedure, the children watched funny animated films. Group 2 - Video game group: Children were allowed to play a game that they could play with 1 hand through the procedure. Group 3 - The parents starting talking 3 minutes before the start of the procedure to try to distract their child's attention away from the venipuncture. Group 4 – Control group: No intervention	257: Anxiety scores: Group 1: n=45, 0.76 ±1.15 Group 2: n=45, 0.27± 0.62 Group 3: n=45, 1.24± 1.45	257: n=45, 2.22± 1.76	257: Anxiety scores in the intervention group were lower in intervention groups 1, 2 and 3 compared to the control group (demonstrated by a mean difference of scores of 1.00, 1.49 and 0.52 respectively). The video game group decreased anxiety the most, followed by the cartoon group and then the parent distraction group.		257: Inan & Inal (2019)
							13743: Turkey	13743: During the intervention, the children were provided training using the Chemo Duck toy and a training	13743: Mean state anxiety scores: 31.50	13743: Mean state anxiety	13743: The state anxiety score of the experimental group was lower than that of		13743: Orhan and

Quality assessment							Summary of Findings		No. of Participants		Reported Effects/Outcomes	Certainty	Reference
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Country	Intervention	Intervention	Control			
								booklet. The Vascular Access Training and Coloring Book prepared by the researcher provides information about the definition, intended use and benefits of peripheral vascular access through caricaturized drawings and gives the children a chance to color them while reading the information. Control: no intervention	± 4.73 n=20	scores: 43.40 ± 5.42 n=20	the control group (mean difference of 11.9). The training provided to the children through therapeutic play before the procedure reduced the state anxiety level of the children caused by venous catheterization.		Yildiz (2017)
							279: Taiwan	279: Group 1 – Storybook reading: involved storybook reading with immersion of the participating child into a character role named Ruirui Bear. Group 2 - Cartoon: A Chinese animated cartoon on YouTube called "Cute Tiger Visited a Physician" was used to distract children. Control Group: No distractions were given. (procedure explained by the nurse)	279: Mean OSBD-R score: Group 1: n=92, 27.4 Group 2: n=92, 28.9	279: 38.5, n=92	279: Children experienced less distress in both intervention groups compared with controls (mean differences of 11.1 and 9.6). The mean OSBD-R score was highest in the control group (38.5) compared with the cartoon-viewing group and the book-reading group. The differences were statistically significant (all with p values <0.05). Although the mean OSBD-R score for the book-reading group was lower compared with the cartoon-viewing group, the mean difference was 1.5, but did not reach statistical significance. The OSBD-R scores varied according to the children's age. The distraction interventions were more effective for children aged 4 to 5 years (F = 4.56, p = 0.004).		279: Kuo, Pan, Creedy & Tsao (2018)

Quality assessment							Summary of Findings		No. of Participants		Reported Effects/Outcomes	Certainty	Reference
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Country	Intervention	Intervention	Control			
							424: USA	424: Virtual Reality (VR) group: Patients in the VR group received standard of care (SOC) and interacted with the VR game a few minutes before, during, and following the blood draw procedure (5min total). Control: no intervention (background cartoons available)	424: Anxiety VAS (mean (SD)): 1.90 (2.22) FAS: 0.28 (0.22) n=72	424: VAS: 2.48 (2.07) FAS: 0.40 (0.24) n=77	424: VR had a positive effect on reducing anxiety compared to the control group, with a VAS mean difference of 0.58 lower in the VR group and FAS mean difference of 0.12 lower in the VR group (indicating less anxiety). Anxiety sensitivity significantly related to higher procedural anxiety (Anxiety VAS, r= -0.20, p<0.05).		424: Gold and Mahrer (2018)
							362: Turkey	362: A virtual reality (VR) headset provided an opportunity to watch and listen to VR video and audio. The virtual headsets were introduced to the school-aged children in the intervention groups by the researcher G, and they were told that they could watch applications by wearing the virtual headset during the procedure. The VR applications were chosen by the researchers. During the venipuncture procedure, the families stayed with their children in all groups. The venipuncture procedure was performed by using a vacuum tube and a 21G needle tip in the left arm of all the children. Blood was taken from the children in all groups during the first attempt.	362: VR-Rollercoaster (n = 45) Fear scores (Self-reported): Before 1.5 ± 1.3 (0–4) After 0.4 ± 1.1 (0–4) Anxiety scores (Self-reported):Before 5.9 ± 3.0 (0–10) After 1.1 ± 2.6 (0–10) VR-Ocean Rift (n = 45)	362: n=46 Fear scores Self-reported Before 1.7 ± 1.4 (0–4) After 2.4 ± 1.6 (0–4) Anxiety scores (Self-reported): Before 6.3 ± 3.2 (0–10) After 6.3 ± 3.6 (0–10)	362: Results demonstrated a positive direction of effect favouring the VR groups over control. There were little to no differences in anxiety/fear between the two VR groups.		362: Gerceker et al (2019)

Quality assessment							Summary of Findings		No. of Participants		Reported Effects/Outcomes	Certainty	Reference
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Country	Intervention	Intervention	Control			
							660: Turkey	660: The virtual reality goggle, was used for distraction in the virtual reality goggle group. The children (aged 4-10) in the virtual reality goggle group were asked if they wanted to wear the virtual reality goggle. Then the children were asked to choose a video to watch during the procedure. At the start of the procedure, the children were distracted via the virtual reality goggle until the procedure was over. Distracting children with a virtual reality goggle was performed by the same researcher. Kaleidoscope group - The children were asked if they wanted to look into the kaleidoscope. At the start of the procedure, the children in the group were given a kaleidoscope to look through until the procedure was over. Distracting children with a kaleidoscope was performed by the same researcher. Control group received no distraction intervention.	Fear Scores (self reported): Before 1.4 ± 1.4 (0–4) After 0.3 ± 0.6 (0–2) Anxiety scores(self-reported): Before 6.1 ± 3.6 (0–10) After 0.5 ± 1.5 (0–8) 660: VR group n=46 Mean CFS (Child reported): 0.43 +/- 0.5 Kaleidoscope group n=46 Mean CFS (Child reported): 0.93 +/- 0.8	660: n=43 Mean CFS: (child reported): 2.79 +/- 1.2	660: Results demonstrated a positive direction of effect favouring VR and kaleidoscope groups over control group, with VR having the greatest effect on reducing fear/anxiety.		660: Ozkan & Polat (2020)

Quality assessment							Summary of Findings		No. of Participants		Reported Effects/Outcomes	Certainty	Reference
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Country	Intervention	Intervention	Control			
							417: Turkey 460: Turkey	417: School-aged children watched cartoon on 7-inch tablet computer device during phlebotomy process, or watched cartoon on VR box device during the phlebotomy process. Nothing was watching by children in the control group. 460: Information Video Group (Group 1).The children in this group watched the information video about PVAD insertion before the procedure. The content of the animated video, which was prepared according to the development level of children aged 6- 12 years, was determined by the researchers. The video was prepared by a computer programmer in accordance with the specified content. The animated video, which was prepared in 3D, was reviewed by 5 experts in the field of pediatric nursing and was finalized in line with their recommendations. The video, which lasts 2 minutes and 44 seconds, explains the features of the equipment used for a PVAD insertion and how the procedure is performed Cartoon Group (Group 2): The children in this group watched a cartoon during the IV insertion procedure. Two popular cartoons that children aged 6-12 years like to watch were selected. When deciding the selection of the cartoons, the	417: Tablet group n=40 CFS scores 2.27 ± 1.56 VR group n=40 CFS scores 0.65 ± 0.92 460: Information group n=159 Child reported mean fear score after insertion: 0.05 (0.36) Before insertion: 1.82 (0.86) Cartoon group n=159 Child reported mean fear score after insertion: 0.32 (0.85) Before insertion: 1.83 (0.85)	417: n=40 CFS scores 2.52 ± 1.33 460: n=159 Child reported mean fear score after insertion: 3.41 (1.00) Before insertion: 1.77 (0.87)	417: Results demonstrated a positive direction of effect favouring the VR group over the tablet and control groups. There were little to no difference in fear scores between the tablet and control groups. 460: The children who watched the information video before the PVAD insertion procedure and those who watched a cartoon during the procedure had lower mean fear scores as evaluated by the child, parent, and nurse than the children in the control group.		417: Inangil et al (2020) 460: Duzkaya et al (2020)

Quality assessment							Summary of Findings		No. of Participants		Reported Effects/Outcomes	Certainty	Reference
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Country	Intervention	Intervention	Control			
								opinions and requests of 10 children in the age group of 6-12 years were taken into consideration. The children were asked to select one of the cartoonsbefore the procedure, and they watched their chosen cartoon during the procedure. No distraction was used in the control group.					
							471: China (Hong Kong)	471: In addition to standard care, VR intervention was offered to patients 5 minutes before and during PVAD insertion (children with cancer mean age 10.4). During the intervention, patients experienced a sense of immersion through the device delivering the VR sounds and images. In standard care, phlebotomists explained and performed PVAD insertion. The patients were comforted verbally, but no distraction or analgesic medication was given during the PVAD insertion.	471: n=54 Mean anxiety score (State Anxiety Scale for Children) of patients who received VR intervention decreased from 20.37 (4.95) to 14.81 (2.93) after the PVAD insertion.	471: n=54 The mean anxiety scores (State Anxiety Scale for Children) of the control group decreased from 19.89 (4.83) to 17.83 (4.69) after the PVAD insertion.	471: Results demonstrated a positive direction of effect favouring the VR group (estimated mean difference (95% CI): -3.50 (-5.07, -1.93)).		471: Wong et al (2020)
							1807: Turkey	1807: In the intervention group children were given gum to chew during the PVAD insertion. Children who were in the control groups did not receive any pain reduction methods or treatments.	1807: n=37 Child reported anxiety score Mean ± SD 1.27 ± 0.96	1807: n=36 Child reported anxiety score Mean ± SD 1.61±1.05	1807: There were minimal differences between anxiety scores in the gum chewing group compared with the control group; slightly favouring gum chewing group.		1807: Topcu et al. (2020)

Quality assessment							Summary of Findings		No. of Participants		Reported Effects/Outcomes	Certainty	Reference
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Country	Intervention	Intervention	Control			
							2265: Taiwan 1658: Turkey 1671: Turkey	2265: The experimental group used a virtual reality headset during PVAD insertion. In the control group, children were offered verbal comforting only. 1658: Intervention groups included balloon inflation, ball squeezing, or coughing (during venipuncture). Children in the control group received no pain management. 1671: Active distraction group: The rotatable wooden toy is a toy that stimulates children's cognitive, visual, and kinesthetic senses, enabling them to display their own skills. Passive distraction group: The toy wristband used for passive distraction is an audible, colored toy designed by the researcher. It consists of 2 parts: a 7-cm37-cm colored plush toy containing a sound device, and an elastic fabric wristband. Toys were used during blood sampling procedure.	2265: n=68 Fear score: Mean ± SD: 1.78 ± 1.40 1658: n=30 in each group Fear score Mean ± SD: balloon inflation: 0.83 ± 0.70 ball squeezing: 0.60 ± 0.56 coughing: 0.53 ± 0.63 1671: Mean fear score during sampling passive 2.09 (1.07) n=72 active 1.63 (0.82) n=72	2265: n=68 Fear score: Mean ± SD: 1.32 ± 1.19 1658: n=30 Fear score Mean ± SD: 3.30 ± 0.60 1671: n=72 Mean fear score during sampling 3.91 (1.22)	2265: Fear scores were higher in the control group compared with the VR group. 1658: Fear scores were lower in all intervention groups compares with control. However, there was no difference in fear score between pain management strategies. 1671: Both distraction groups had lower fear score than the control group. Active distraction slightly favoured over passive distraction.		2265: Chen et al. (2019) 1658: Girgin and Gol (2020) 1671: Arıkan and Esenay (2020)
Patient (or parent/guardian) satisfaction (assessed using a 5-point Likert scale, or other satisfaction questionnaire)													
1[j]	Systematic Review (of	Not Serious[k]	Not Serious	Serious[l]	Not Serious	None					The studies in the systematic review demonstrated increased patient (or parent/guardian) satisfaction with the use of non-	⊕⊕⊕◯ MODERATE	

Quality assessment							Summary of Findings		No. of Participants		Reported Effects/Outcomes	Certainty	Reference
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Country	Intervention	Intervention	Control			
	RCTs)						9141: Multiple countries: USA (most), UK, Canada, Australia, Turkey, New Zealand 10270: Canada	**Non-Pharmacological Interventions** 9141: Various types of vapocoolant spray were used: 1,1,1,3,3,-Pentaflouropropane and 1,1,1,2-tetrafluoroethane, Ethyl chloride, and COLD spray. Control: No intervention **Additional RCTs identified:** **Mixed (Pharmacological and Non-Pharmacological Interventions)** 10270: Infants randomized to 4 groups prior to receiving vaccinations - Group 1: A parent-directed video education about infant soothing, Group 2: video combined with sucrose, Group 3: video combined with sucrose and topically applied lidocaine, Control: Group 4: placebos given for all 3 interventions.	9141: n=668 Mean increase in satisfaction scores: 4.62 mm (95% CI 2.23 to 9.57 mm) 10270: Group 1: n=89 Group 2: n=88 Group 3: n=87 2 months Parent satisfaction (Group 3): 3.9 ± 1.1 4 months Parent satisfaction:	9141: Mean increase in satisfaction scores: 4.62 mm (95% CI 2.23 to 9.57 mm) [individual scores not reported] 10270: n=88 2 months Parent satisfaction: 3.7 ± 1.1 4 months Parent satisfaction: 4.2 ± 0.9 6 months Parent	pharmacological pain management interventions, while other additional RCTs demonstrated the pharmacological/non-pharmacological interventions had minimal to no effect on satisfaction. 9141: Vapocoolant spray increased participants' satisfaction compared to placebo spray/no treatment, with a mean difference of 4.62 (ranges from 2.23 to 9.57). *Note: adults and children were combined for this outcome.* 10270: There were minimal to no differences in parent satisfaction scores between groups..		9141: Zhu et al. (2018) 10270: Taddio et al. (2017)

Quality assessment							Summary of Findings		No. of Participants		Reported Effects/Outcomes	Certainty	Reference
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Country	Intervention	Intervention	Control			
							1551: USA	**Non-Pharmacological Interventions** 1551: Buzzy Device: the device was held directly over the site of injection for 30 seconds, moved 3 to 5 cm proximal to the site immediately prior to injection, and held in place during the entirety of the needle stick. Parents stayed in the room with all children during the entirety of the procedure. Control: No intervention (parents allowed to sooth children)	4.5 ± 0.9 6 months Parent satisfaction: 4.7 ± 0.7 12 months parent satisfaction: 4.3 ± 0.0 1551: n=26 Responses N(%): Same: 6 (24) Better: 19 (76) Worse: 0 (0) Definitely yes: 10 (40) Probably: 12 (48) Don't know: 2 (8) Probably not: 1 (4) Definitely not: 0	satisfaction: 4.7 ± 0.6 12 months parent satisfaction: 4.2 ± 1.1 1551: n=2 Responses N(%): Same: 17 (68) Better: 8 (32) Worse: 0 (0) Definitely yes: 8 (32) Probably: 8 (32) Don't know: 7 (28) Probably not: 2 (8) Definitely not: 0	1551: When asked specifically about their child's experience receiving a needle poke, parents whose child received Buzzy did not rate their satisfaction higher than those that did not. In addition, when asked to rate their overall visit experience, there was no difference in satisfaction rating. Parents of Buzzy recipients more frequently rated the visit as better than expected and no parent rated the visit as worse than expected. Parent ratings of satisfaction were more strongly correlated with the parent's rating of their child's pain than any other variable (R=0.58, p<0.001).		1551: Redfern, Chen & Sibrel (2017)

Quality assessment							Summary of Findings		No. of Participants		Reported Effects/Outcomes	Certainty	Reference
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Country	Intervention	Intervention	Control			
							424: USA	424: Virtual Realty (VR) group: Patients in the VR group received standard of care (SOC) and interacted with the VR game a few minutes before, during, and following the blood draw procedure (5min total). Control: no intervention (parents allowed to soothe)	424: n=72	424: n=77	424: In terms of satisfaction with the VR game, patients reported high levels of immersion (M (SD)=22.75 (6.32). Patient, caregiver, and phlebotomist satisfaction scores demonstrated that all three groups recognized the value in VR, reported high levels of satisfaction, would consider using VR again, and would recommend that other patients try VR (results were not statistically analysed).		424: Gold and Mahrer (2018)
Patient comfort (assessed using the Neonates Comfort Behavior Scale)													
1	RCT	Serious[m]	Not serious	Not serious	Very serious[n]	Not detected	396: Turkey	**Non-Pharmacological Interventions** 396:Before the heel lance procedure, the newborns in the experimental group were subjected to a local dry mildly warm compress for five min using a thermophore. The warmth of the water in the thermophore was kept between 34-37 ˚C. To prevent the thermophore from contacting the sole of the infant's foot, it was wrapped in a cloth and placed on the sole from which heel lance would be taken. the control group received routine heel lance procedure. No comforting or relaxation interventions were used during the heel lance procedure, and the newborns were immediately comforted after the procedure.	396: n=40 Neonates Comfort Behavior Scale Median (min-max): 11(13-24)	396: n=40 Neonates Comfort Behavior Scale Median (min-max): 16(14-30)	One RCT examined patient comfort and found that non-pharmacological pain management interventions improved patient comfort.	⊕◯◯◯ VERY LOW	396: KarabıyıkOğurlu et al. (2020)

Quality assessment							Summary of Findings		No. of Participants		Reported Effects/Outcomes	Certainty	Reference
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Country	Intervention	Intervention	Control			

Acronyms & Explanations

SR = systematic review

RCT = randomized controlled trial

FLACC = Face, Legs, Activity, Cry, and Consolability assessment tool

FPS = Faces Pain Scale

FPS-R = Faces Pain Scale-Revised

NRS = Numerical Rating Scale

MBPS = Modified Behavioural Pain Scale

VAS = Visual Analog Scale

PIPS = Premature Infant Pain Scale

EMLA = Eutectic Mixture of Local Anesthetics

SD = standard deviation

CAPS = Children's Anxiety and Pain Scale

CFS = Children's Fear Scale

PRCD = parent perception of child's distress

SMD = standardized mean difference

CAS = Colored Analogue Scale (Pain)

NIPS = Neonatal Infant Pain Scale

MOPS = Modified Objective Pain Scale

MIASD = Measure of Adult and Infant Soothing and Distress

MFCS = Modified Facial Coding System

DAN Scale = Douleur Aiguë du Nouveau-né scale

CHIPPS = Children's and Infant's Postoperative Pain Scale

MFCS = Modified Facial Coding System

BOPS = Behavioral Observational Pain Scale

STAIC = Spielberger State-Trait Anxiety Inventory for Children

OSBD-A = Observation Scale of Behavioral Distress

OSBD-R = Observation Scale of Behavioral Distress Revised

CASI = Childhood Anxiety Sensitivity Index

FAS = Facial Affective Scale

WBFP = Wong-Baker Faces Pain Scale

CEMS = Children's Emotional Manifestation Scale

[a] 12 systematic reviews of RCTs were included. There were 54 additional RCTs included for the outcome of patient (or observer) rating of pain, however the findings supported the results of the SRs and were not GRADED separately.

[b] Of the 12 included systematic reviews, 9 were rated as having 'low risk of bias' and 3 rated as 'unclear risk of bias' using the Risk of Bias in Systematic Reviews (ROBIS) appraisal tool. One SR (101) assessed ROB using the Cochrane ROB tool and found most of the studies had low risk in almost all the domains. Review 724 assessed ROB using the Cochrane ROB tool and found that most included studies had low or unclear ROB. Review 802 assessed ROB using the Cochrane ROB tool and found variation in the ROB of included studies with many rated as high due to lack of blinding and selective reporting. Review 3362 assessed ROB using the Cochrane ROB tool and found that all included studies had a high ROB. Review 9141 assessed ROB using the Jadad score, and both included studies for pediatric populations were rated as high quality. Review 981 assessed ROB using the Cochrane ROB tool, and found variability in ROB among the studies related to lack of blinding and lack of reporting. Review 772 assessed ROB using the Cochrane ROB tool and found variation in the ROB of included studies with many rated as high due to lack of blinding and selective reporting. Review 3448 assessed ROB using the Cochrane ROB tool

and found that all trials had a high ROB. Review 907 assessed ROB using the JBI methodology and noted high risk of bias in some included studies. Review 1502 assessed ROB using the Cochrane ROB tool and noted concerns with some studies regarding blinding and allocation concealment. Review 1457 assessed ROB using the Cochrane ROB tool and noted 6 studies had high ROB due to concerns around allocation concealment. Finally, review 2142 assessed ROB using the Cochrane ROB tool. All studies were noted to be high ROB or unclear. We downgraded by 1 due to some concerns related to ROB among the included studies of the SRs.

[c] There was a variety of different validated pain assessment tools included in the reviews. We downgraded by 0.5.

[d] A variety of needle procedures were included in the review, not just PVAD insertion (e.g., vaccine injection). We downgraded by 0.5.

[e] Number of events was >400 across the 11 systematic reviews. We did not downgrade.

[f] Three systematic reviews were included for this outcome. There were 21 additional RCTs included for the outcome of fear/anxiety, however the findings supported the results of the SRs and were not GRADED separately.

[g] The three included SRs were rated as having 'low risk of bias' using the ROBIS appraisal tool. One SR (3362) assessed ROB using the Cochrane ROB tool and found that all included studies had a high ROB. Review 772 assessed ROB using the Cochrane ROB tool and found variation in the ROB of included studies with many rated as high due to lack of blinding and selective reporting. Review 907 assessed ROB using the JBI methodology and noted high ROB in some of the included studies. We downgraded by 1 due to some concerns of ROB among the included studies of the SRs.

[h] Different validated fear/anxiety scales were used in the studies, and one of the reviews (772) noted high heterogeneity among the included studies (I2=89-96%). We downgraded by 0.5.

[i] Various needle procedures were examined (3362 only examined studies on vaccinations). We downgraded by 0.5.

[j] One systematic review examining 4 studies was included for this outcome. There were 3 additional RCTs included for the outcome of patient (or guardian) satisfaction. Two RCTs found equivalent levels of satisfaction between the intervention and control groups, and one RCT found higher satisfaction in the intervention group compared to the control group. The RCTs were not GRADED separately due to the moderate certainty SR included.

[k] Risk of bias of the included studies in the SR (9141) was assessed using the Jadad score and both included studies for pediatrics were rated as high quality.

[l] Adults and children were grouped together for this outcome. We downgraded by 1.

[m] One RCT included was assessed for ROB using the Cochrane ROB 2.0 tool. The RCT was rated as 'some concerns' due to lack of blinding and lack of information on the randomization process. We downgraded by 1.

[n] There were less than 100 events. We downgraded by 2.