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 7.1: The guideline panel *recommends* that health providers *offer* adults non-pharmacological and pharmacological pain management strategies during the insertion of a vascular access device .

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: 2481, 9141, 16001, 50, 1100, 1882, 256, 15646, 405, 7024, 8550, 3281, 3191, 3860, 662, 3360, 1568, 382, 507, 524, 525, 541, 554, 764, 1409, 2142

Quality assessment							Study Details		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's Rating of Pain (assessed with: NRS, VAS, FACES Pain Scale, and the Present Pain Inventory)													
5[a]	SR (of RCTs)	Serious[b]	Not serious[c]	Not serious	Not serious	Not detected[d]	2481: Multiple (countries not specified)	**Pharmacological Interventions** 2481: Studies in the review compared the use of a local anaesthetic prior to peripheral vascular access device (PVAD) insertion with no local anaesthetic (control) prior to PVAD insertion in adults in secondary care receiving routine PVAD insertion (non-emergency). Local anaesthetics used included: Ametop® (S&N Healthcare) Bupivacaine hydrochloride Chloroprocaine EMLA® cream (AstraZeneca) Ethyl Chloride	2481: n=27 studies Results of network meta-analysis: Pooled VAS mean difference (95% CI) from indirect and direct evidence: Lidocaine 2% vs. no treatment: -25.42 (-32.25, -18.57) [lonotocaine, lidocaine +	2481: n=Not specified	Most reviews demonstrated that both pharmacological and non-pharmacological pain management strategies were effective in reducing patient's rating of pain. An additional 20 RCTs were identified. The majority of which demonstrated lower pain ratings following pain management strategies. 2481: When all of the agents are compared with no treatment, the majority are estimated to be more effective at reducing pain than no treatment (positive direction of effect). In particular, 2 % lidocaine is estimated as the most effective. An examination of the forest plot shows that members of the 'caine' family of drugs are estimated to be much more effective than no treatment, as are Ametop®, EMLA® and Rapydan patch.	⊕⊕⊕◯ MODERATE	2481: Bond et al. (2016)

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								liontocaine Lidocaine (ligocaine) Myolaxin ointment (Geno Pharmaceuticals) Tetracaine (amethocaine) **Non-pharmacological and pharmacological Interventions** 1409: Adult patients undergoing arterial blood gas punctures. Topical anesthetics included EMLA given 60mins before procedure, tetracaine (amethocaine) 4% given either 30mins or 45mins before procedure, or EMLA given 30mins before procedure. Interventions included ice for 3mins, ice for 5mins, ethyl chloride, or refrigerant spray (compsed of alkanes)	methylparaben, lidocaine + NaCHO3, bupivicaine, lidocaine 1%, Rapydan patch, Ametop cream, Buffered lidocaine, EMLA, Ethylchloride and chloropocaine also effective][e] 1409: N= 4 studies n=335 patients (intervention and control groups not identified) 1) pain scores after EMLA® (X: 2.6; SD: 1.8) and placebo (X: 2.9; SD: 1.8). 2) pain scores after tetracaine 4% application (X: 16; SD: 23.3) or placebo (X: 20.7; SD: 18.5). 3) pain scores after applying tetracaine (X: 26.2; SD: 32.6) or placebo (X: 23.8; SD: 27.4). 4) pain scores after application of EMLA® (X: 2.4) and placebo (X: 3). n=5 studies 1) No differences between pain	1409: data not reported separately	Dichloro dichlorotetrafluoroethane and Diclofenac patch showed a negative direction of effect 1409: Pain scores were lower in all 4 studies comparing topic anesthetic to placebo. Pain scores were lower in 3 studies comparing ice to placebo. No difference was observed for coolant spray.		1409: Vallejo de la Hoz et al. (2019)

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									scores after applying ethyl chloride 2) Differences between scores of pain after applying ice (X: 13.8; SD: 16.9) or common technique (X: 25; SD: 23). 3) Differences between significant ($p < 0.001$) pain with ice (X: 3.1; SD: 1.7) and not ice (X: 4.6; SD: 1.6). 4) No differences between scores of pain after applying ethyl chloride (Me = 2; IQR 1-4.5) or placebo (Me = 2; IQR 1-5). 5) pain scores after applying coolant spray (X: 4.8; SD: 1.8) and placebo (X: 4.9; SD: 1.8).			
							9141: Multiple - USA, UK, Canada, Australia, Turkey, New Zealand	**Non-pharmacological Interventions** 9141: Vapocoolant Spray (1,1,1,3,3,-Pentaflouropropane and 1,1,1,2-tetrafluoroethane, Ethyl chloride, and COLD spray) Control: placebo spray/ no treatment	9141: Sample sizes varied from 41-300 participants among the studies (intervention vs. control group n not specified). Total n=1410. Overall: 6 studies, n=517, SMD [95%	9141: (not specified)	9141: Vapocoolant spray showed a reduction in pain during PVAD insertion compared to placebo spray/no treatment (OR 4.62, 95% CI 1.84 to 11.63; I^2=82.3%). Participants have an odds of 4.62 to experience less pain when given vapocoolant.		9141: Zhu et al. (2018)

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									CI]: −0.61[−0.96, −0.26], I² 70.6, Specified by type: 2 studies, n=172, SMD (95% CI) −0.31(−0.93, 0.31), I² 75.9) 3360: n total = 873 adults Music Therapy studies: n=121, SMD= -0.57 [95% CI, - 1.82, 0.68 Visual Distraction studies: n=86, SMD= -0.10 [95% CI, - 0.48, 0.27 Verbal Signal studies: n=287, SMD= - 0.97 (95% CI, - 1.26, - 0.68) Breathing Intervention studies: n=69, SMD= - 0.82 [95% CI, - 1.21,- 0.43]) 2142: n=2 studies Ice: n=1 study, 107 participants, VAS 5.3 ± 7.1 Vapocoolant Spray: Study 1: n=90 participants, VAS	3360: Control Group (Music Therapy studies): n=76 Control Group (Visual Distraction studies): n=91 Control Group (Verbal Signal studies): n=104 Control Group (Breathing Intervention studies): n=69 2142: Ice: n=1 study, 95 participants, VAS 8 ± 10.6 Vapocoolant Spray: Study 1: n=95 participants, VAS	When specified by type, 1,1,1,3,3-Pentafluoropropane and 1,1,1,2-tetrafluoroethane vs. no vapocoolant had a small reduction in pain. 3360: There were mixed results – music demonstrated a small but positive effect in the reduction of pain, visual distraction had little to no effect on the a reduction of pain, verbal signals had a mixed effect[f], and breathing techniques showed a greater positive effect on the reduction of pain. 2142: Ice applied to the skin for 30 seconds was shown to reduce pain during needle insertion and administration of the tetanus vaccine compared to usual care (no treatment) in study 1. In the studies examining vapocoolant spray, both studies demonstrated a positive direction of effect		3360: Boerner et al. (2015) 2142: Hall et al. (2020)
							3360: Multiple countries: Germany, Turkey, USA (4 studies), Australia (2 studies), UK, Austria 2142: Multiple: Canada, Iran, USA, India	3360: 3 studies explored a *verbal signal of pain* (i.e. "sting" or "sharp scratch"), 2 studies explored *music distraction*, 2 studies explored *visual distraction* (looking through a kaleidoscope), and 2 studies explored *breathing interventions* (i.e. "cough trick" and the Valsalva maneuver) for adults undergoing vaccination or related common needle procedures (i.e. venipuncture, PVAD insertion). 2142: Adults over 18 years of age undergoing vaccine injections in any setting (i.e. hospital or community). All studies used ice or vapocoolant as an intervention. The comparator groups were usual care/no intervention.					

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									4.1 ± 5.4 Study 2: n=93 participants, pain scale mean of 2.2 (out of 10)	8 ± 10.6 Study 2: n=92 participants, pain scale mean of 3.1 (out of 10)	(favouring vapocoolant over control groups) for reducing pain during vaccination.		
								Additional RCTs identified: **Pharmacological Interventions**					
							16001: Iran	16001: EMLA cream or diclofenac gel - 1 mL of 5% EMLA cream (25 mg of lidocaine and 25 mg of prelocaine per gram) applied 60 minutes before the chemotherapy. For diclofenac gel, 1 mL of gel was applied, and the exact same approach as EMLA cream was applied. Control: placebo cream (1mLof vitamin A +D cream).	16001: n=100 (not specified how many per group) Mean pain intensity: 5.59 ±2.10 in the EMLA cream method, 5.88 ± 1.93 in the diclofenac gel method (out of total score of 10)	16001: Not specified	16001: Both the EMLA cream and diclofenac gel reduced pain compared to the placebo. There were little to no differences when comparing EMLA to diclofenac gel.		16001: Salar et al. (2018)
							1100: China	1100: 2mL of EMLA cream was applied to patients by nurses in group 2 (30 mins) and group 3 (60 mins). Control: placebo *Note: All participants in both studies were oncology patients undergoing chemotherapy.*	1100: n total=361, EMLA group 1: n=106, EMLA group 2: n=122 Mean pain scores: EMLA (60mins): 0.69 ± 0.98 EMLA (30mins): 1.11 ± 1.14	1100: n=133 Placebo: 1.91 ± 1.40	1100: The difference in mean pain score in the EMLA 60min group was 1.22 less than the control group, and the difference in mean pain score in the EMLA 30min group was 0.8 less. Both the EMLA groups showed a positive effect, with the EMLA 60min group being the strongest effect in reducing pain.		1100: Yin and Jiang (2018)

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							256: Iran	256: Group one patients received an EMLA cream patch (2 mg/10 cm2), group two patients received a transdermal diclofenac patch (TDP) (Diclofenac 100mg/50cm2). Control (group 3): placebo.	256: EMLA: n=61, Diclofenac: n=50 Mean VAS Scores: EMLA: 38.77 ± 23.28 TDP: 39.40 ± 21.60	256: n=43, 86.41 ± 22.49	256: All patients (100%) in the control group experienced pain in response to PVAD insertion, compared with 83.6% and 96% of patients in the EMLA and the TDP groups, respectively. However, the mean of the VAS score was significantly decreased in the EMLA and TDP groups compared with the control group. Intravenous cannulation pain in the EMLA group was lower than the TDP group.		256: Babaieasl et al. (2019)
							405: India	405: Group II (Ketoprofen) received a 20 mg ketoprofen transdermal patch. Control: placebo patch	405: n=100 Median pain score (inter quartile range): 2(2)	405: n=100 Median pain score (inter quartile range): 6(2)	405: The severity of pain as assessed by the VAS scores; the ketoprofen group had lower median pain scores with a median difference of 4 (positive direction of effect).		405: Kumar et al. (2018)
							8550: Netherlands	8550: All the included participants received two PVAD insertions: the first one in the right elbow, followed by insertion in the left elbow. The lidocaine spray was applied to one elbow and the placebo spray to the other elbow according to the randomization sequence.	8550: n=17 Visual Analogue Scale [median (interquartile range)] (mm): lidocaine: 18.0 (5.0–34.5)	8550: n=17, 21.0 (11.0–30.5) (Note: participants acted as their own control; n total =17 adults)	8550: There were no clinically (i.e. difference of ≥20mm on the VAS) or statistically significant differences between the lidocaine spray and the placebo conditions (difference: −9.0–11.0). The		8550: Datema et al. (2019)

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								Each dose of spray consisted of 0.1 ml liquid with the same colour and appearance.			lidocaine group showed lower pain scores (median difference of 3).		
							3191: USA	3191: The active system contained 0.5 mg of lidocaine hydrochloride monohydrate powder (particle size 40 mm) and medical-grade helium ("*needle free powder lidocaine delivery system*"). Control: sham placebo	3191: n=345 Age group adjusted mean pain VAS (mm): 11.6	3191: n=348 Age group adjusted mean pain VAS (mm): 16.2	3191: Treatment with the active system resulted in a reduction in pain VAS scores (difference between age group adjusted Lean Squares Means (LSM) = 4.63±1.55 mm) during venipuncture or PVAD insertion, which represents a 28% relative reduction compared with sham placebo.		3191: Zempsky et al. (2016)
							662: India	662: 10mls of fentanyl 2 µg/kg or 10mls of 0.9% saline (placebo group) given over 10min using a syringe infusion pump prior to CVAD placement procedure. Scores for pain were recorded at rest by an anesthesia resident at 5 times points:	662: n=26 *Note: Raw data (pain scores) unavailable; broken link to Figure containing data.*	662: n=25	662: Fentanyl was able to reduce procedure specific pain at T2, T3 and T10 time points in comparison to placebo group. Comparison between groups revealed that placebo group had the highest pain scores after local anesthetic injection, which was significantly attenuated by addition of study drugs in fentanyl group. Similarly, for subsequent procedural steps (T3, T10 and T60) fentanyl group had a lower pain score compared with placebo, but reached significance level only for T3 and T10 steps.		662: Samantara y and Rao (2014)
							541: Italy	541: Intervention group 1= Cryoanalgesia Intervention group 2= Anesthetic cream	541: Median arterial puncture pain (IQR) cryoanalgesia 3	541: Median arterial puncture pain (IQR) 6	541: Lower pain scores were observed in the cryoanalgesia and		541: Pagnucci et al (2020)

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								Intervention group 3= subcutaneous infiltration with mepivacaine. Control= The participants in this group did not receive any type of local anesthetic, **Non-Pharmacological Interventions**	(2.0–3.9) anestheitic cream 5 (4.2–5.9) mepivacaine 1 (0.6–1.3)	(4.0–7.0)	mepivacaine groups. Marginally lower scores were observed in the anesthetic cream group.		
							1568: Turkey	1568: Participants were divided into three intervention groups: coughing group, spirometry group, and use of a stress ball group; PVAD insertion was performed for each group during the intervention, and the pain levels felt by the individuals were assessed using the visual analog scale by a nurse who was blinded to the procedure. Control: no intervention	1568: n total = 124 Mean pain scores: **Coughing group:** n=31, 19.5 mm (SD: 13.6) **Spirometry group:** n=31, 28.3 mm (SD: 20.2) **Stress ball group:** n=31, 32.1 mm (SD: 23.8)	1568: **Control group:** n=31, 45.5 mm (SD: 19.5)	1568: All interventions were positive in reducing pain when compared to the control group. The mean difference in pain scores was 26mm lower in the coughing group compared to control group, 17.2mm lower in the spirometry group, and 13.55mm lower in the stress ball group, demonstrating that the coughing group had the greatest effect in reducing pain.		1568: Yılmaz and Gunes (2017)
							50: USA	50: Buzzy device - a plastic vibrating motor with a detachable ice pack placed over the injection site for 30 seconds; immediately before injection it is moved approximately 5 cm proximal to the site and held in place throughout the remainder of the vaccine procedure. Control group : no	50: n=250 Buzzy post-procedure pain: 0.87 ± 0.07	50: n=247, 1.12 ± 0.10	50: Positive effect - Participants receiving the Buzzy device during IM injection rated their post-procedure pain significantly lower (mean difference of 0.25) than the control group on average.		50: Redfern, Micham, Seegert & Chen (2019)

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№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Country	Intervention	Intervention	Control			
								intervention.					
							1882: Turkey	1882: Buzzy device - the ice wings of the Buzzy device were placed approximately 5 centimeters above the intervention site from 1 minute before the procedure until the end of the needle location process (venipuncture). When the device was operated, it applied vibration and cold to the site. Placebo Control Group - the Buzzy device wings were at room temperature (unfrozen) and with the vibration switch remaining off. Non-intervention control group: no intervention was implemented before the procedure, and the standard venipuncture procedure was used.	1882: n=30 Mean pain scores: 20.93 ±15.1	1882: placebo: n=30, 35.40± 11.4 non-intervention: n=30, 35.23 ± 19.3	1882: Positive effect - There were lower mean pain scores in the experimental groups compared to the control groups (14.47 lower in the intervention vs. placebo, and 14.3 lower in the intervention vs. non-intervention group). The results of advanced analysis indicated a significant difference between the mean pain scores of the experimental group and members of the placebo control and nonintervention control groups.		1882: Yılmaz, Heper, & Gozler (2017)
							15646: Turkey	15646: The Buzzy device was placed directly on the injection site for about 30 seconds and then the device was pushed 3 cm above the injection site and with the device still working (with the stimulations of cold and vibration), the standard injection protocol was applied (IM injection). Control: no intervention	15646: n=33 Post-injection mean pain score: 4.67 ±4.94	15646: n=32, 17.69 ±9.85	15646: An analysis of the pain mean scores found that the post-injection pain mean score of the application group was significantly lower than that of the control group (difference in pain mean scores of 13.02).		15646: Sahin & Eser (2018)

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							7024: India	7024: Experimental group 1 - given dry heat (hot water bag) temperature 120-140 degrees Farenheit for 7mins on the peripheral cannulation site, prior to PVAD insertion. Experimental group 2 - given moist heat (moist warm towel) 110-115 degrees Farenheit over site for 7mins. Control group - no intervention prior to PVAD insertion.	7024: group 1: n=20 group 2: n=20	7024: n=20	7024: Majority (95%) of the sample had mild level of pain in experimental group 1, and 75% in group 2 had moderate level of pain during PVAD insertion. The least pain was experienced by the patients in experimental group 1 compared to group 2 and control.		7024: Jisha et al. (2017)
							3281: Iran	3281: Acupressure group - blood samples were taken from the right arm with an intervention (massage of the real points of acupressure) and from the left arm using routine venipuncture. All blood samples were taken by an experienced nurse, and acupressure was performed by trained researcher. Placebo group - blood samples were taken from the right arm with an intervention (massage of the false points of acupressure) and from the left arm using the routine method. Control group - blood	3281: n=60 Mean pain score (SD): 2.42 (1.48)	3281: placebo group: n=66, 3.27 (1.86) control group: n=61, 3.26 (1.35)	3281: The Games-Howell post hoc analysis revealed there were significant differences between the acupressure and placebo groups and between the acupressure and control groups. Patients who received acupressure during blood sampling experienced lower levels of pain than patients in the other 2 groups (mean difference of 0.85 lower in acupressure compared to placebo, 0.84 lower in acupressure compared to control).		3281: Hosseinabadi, Biranvand, Pournia, & Anbari (2015)

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								samples were taken from the 2 arms using routine venipuncture methods. 382: Intervention Group I (Hot Application) Before the PVC was inserted, the researcher applied a hot application to the catheter insertion site (inner surface of the forearm) using a hot pack for 1 minute. Intervention Group II (Cold Application) Before PVC was inserted, the researcher applied a cold application to the catheter insertion site (inner surface of the forearm) using a cold pack for 1 minute. Control= no pain management	382: Turkey	382: Pain Score During PVC insertion hot 0.7±1.1; 0.0 (0.0-1.0) cold 1.1±1.4; 1.0 (0.0-2.0)	382: Pain Score During PVC insertion control 2.2±1.9; 2.0 (0.0-3.2)	382: Pain scores were less in both hot and cold groups compared to control. There was no difference between hot and cold groups.		382: Korkut, Karada, Dogan (2020)
							507: Turkey	507: Buzzy cold vibrating device Control: no pain management	507: N=50 Visual analog scale mean (SD): 1.04 (0.96)	507: N=50 Visual analog scale mean (SD) 5.32 (1.64)	507: Pain was less in the intervention group compared with the control group.		507: Cetin and Cevik (2019)
							524: Turkey	524: Distraction cards group- Cards containing approximately six optical illusion pictures were shown to the patients and as a method of distraction during the PIC insertion procedure they were asked what they saw in these cards. VR group- Underwater 3D audial videos were played	524: Distraction group N=40 Mean SD pain score 3.32 ± 2.81 N=40 VR Mean SD pain score 3.50 ± 2.84	524: Control group (n = 40) mean SD 4.72 ± 3.15	524: Pain scores were lower in both distraction groups compared with control. There was no difference in pain score between VR and distraction cards groups.		524: Basak et al (2019)

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								with visual reality (VR) goggles during PIC insertion until the procedure was completed. Control: no distraction					
							525: France and Belgium	525: Hypnosis group In the hypnosis group, the clinicians applied classical non-verbal hypnotic tools adapted to the subject and indirect suggestion of comfort by body language. Control group= Neutral group Or Nocebo group	525: Hypnosis group (n=89) Pain after peripheral intravenous cannulation 1.5 (1.9) [0-9]	525: Pain after peripheral intravenous cannulation Neutral group (n=92) 3.5 (2.3) [0-9] Nocebo group (n=91) 3.8 (2.5) [0-10]	525: pain after PIVC, was lower in the hypnosis group compared with the neutral and nocebo groups		525: Fusco et al (2020)
							554: Turkey	554: Aromatherapy The patients in the lavender group were administered aromatherapy inhalation of lavender essential oils before needle insertion into an implantable venous port catheter. Similarly, aromatherapy inhalation of eucalyptus essential oils was administered to the eucalyptus group before needle insertion. Control= no intervention	554: Lavender group: n=41 mean VAS Score: 2.37 +/- 1.62 Eucalyptus group: n=41 mean VAS score: 3.19 +/-1.8	554: n=41 Control mean VAS Score: 3.69 +/-1.55	554: Pain scores were lower in the lavender group compared to control. There was no difference control and eucalyptus group.		554: Mutluay & Ozdemir (2019)
							764: Iran	764: Aromatherapy with peppermint essence Three drops of peppermint were poured on a piece of cotton and attached to the collar of the subjects' cloth 10cm from their nose. Control= distilled water	764: n=40 mean pain score 2.95±0.98 (95% CI 2.635-3.265)	764: n=40 mean pain score 3.42±1.33 (95% CI 2.997-3.853)	764: Pain scores were lower in the aromatherapy group compared to the control group (Mean Difference: -0.475 +/- 0.249 (-1.067-0.117)).		764: Akbari et al. (2019)

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Patient Comfort (assessed with validated pain scales including VNRDS, VAS, and a 10-point Likert Scale)													
4	RCT	Very Serious[g]	Serious[h]	Not serious	Not serious	Not detected[i]					All studies demonstrated minimal to no differences in patient comfort levels when given pharmacological or non-pharmacological pain management interventions.	⊕⊕◯◯ Low	
							662: India 3191: USA 50: USA	**Pharmacological Interventions** 662: 10mls of fentanyl 2 µg/kg given over 10min using a syringe infusion pump prior to CVAD placement procedure. Control: 10mls of 0.9% saline (placebo group) 3191: The active system contained 0.5 mg of lidocaine hydrochloride monohydrate powder (particle size 40 mm) and medical-grade helium ("needle free powder lidocaine delivery system"). Control: sham placebo **Non-pharmacological Interventions** 50: Buzzy device - a plastic vibrating motor with a detachable ice pack placed over the injection site for 30	662: n=26 T10 Mean VAS: Fentanyl: 4 (approximated from figure) 3191: n=345 Mean VAS ±SD=4.1±8.9 50: n=250 Only participants who received the	662: n=25, T10 Mean VAS: 5 3191: n=348 Mean VAS±SD= 2.4±5.5 50: n=247 (Note: control group not asked to rate	662: There was minimal to no effect on procedure related discomfort between the groups for all procedural steps except for T10 (10 min after the procedure), mean difference of 1 (lower score meaning greater comfort in fentanyl group). 3191: The mean comfort level of study device actuation demonstrated good tolerance in both the active system group and in the sham placebo group (mean difference of 1.7). The majority of patients treated with the active system (324/345 [94%]) or sham placebo (340/348 [97%]) reported a comfort VAS score of 15 mm. 50: Participants receiving the intervention did not		662: Samantaray and Rao (2014) 3191: Zempsky et al. (2016) 50: Redfern, Micham, Seegert & Chen

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								seconds Control group: no intervention	intervention (Buzzy) were asked to rate discomfort caused by coldness of the ice pack and vibration of the device separately on a 10-point Likert scale (specific values not reported).	discomfort).	report discomfort because of the coldness of the ice pack (median 1.0, IQR = 1.0) or because of the vibration of the device (median 1.0, IQR = 0)		(2019)
							525: France and Belgium	525: Hypnosis group In the hypnosis group, the clinicians applied classical non-verbal hypnotic tools adapted to the subject and indirect suggestion of comfort by body language. Control group= Neutral group Or Nocebo group	525: comfort after peripheral intravenous cannulation Hypnosis 8.5 (1.7) [2-10]	525: Comfort after peripheral intravenous cannulation neutral 7.7 (2.2) [1-10] nocebo 7.2 (2.1) [1-10]	525: Comfort after PIVC insertion was higher in the hypnosis group compared with both the nocebo and neutral groups.		525: Fusco et al (2020)
Fear/Anxiety (assessed with: NRS or VAS)													
2[i]	SR (of RCTs)	Serious[k]	Not Serious[l]	Not Serious	Not Serious	Not detected	9141: Multiple -	**Non-pharmacological Interventions** 9141: Vapocoolant Spray	9141: n=168 (intervention and	9141: Not	All reviews demonstrated minimal to no differences in patient fear/anxiety levels when given pharmacological or non-pharmacological pain management interventions. In addition, 7 RCTs were identified. There were mixed results for anxiety- some studies reported less anxiety in the intervention group while others reported no difference. 9141: A total of 168 patients	⊕⊕⊕◯ MODERATE	9141: Zhu

Quality assessment							Study Details		No. of Participants		Reported effects/outcomes	Certainty	Reference
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Country	Intervention	Intervention	Control			
							USA, UK, Canada, Australia, Turkey, New Zealand 3360: USA 50: USA	(1,1,1,3,3,-Pentaflouropropane and 1,1,1,2-tetrafluoroethane, Ethyl chloride, and COLD spray) Control: no treatment or placebo 3360: 2 studies explored *music distraction*, and 2 studies explored *visual distraction* (looking through a kaleidoscope) for adults undergoing vaccination or related common needle procedures (i.e. venipuncture, PVAD insertion). *Note: Other studies included in this review did not pertain to fear/anxiety outcome.* ***Additional RCTs identified:*** **Non-Pharmacological Interventions** 50: Buzzy device - a plastic vibrating motor with a detachable ice pack placed over the injection site for 30 seconds. Control group – no intervention before vaccine.	control group n not specified) Mean VAS: 0.52mm, 95% CI -0.18 to 1.23mm; I^2 = 80.6%) 3360: n total = 374 adults Music therapy studies: n=121, SMD= -0.25 [95% CI, -0.61, 0.10] Visual distraction studies: n=86, SMD= -0.05 [95% CI, -0.50, 0.40] 50: n=250 Pre-vaccine anxiety score: 1.53 ± 0.13 3281: n=60	specified 3360: Control group (music therapy studies): n=76 Control group (Visual distraction studies): n=91 50: n=247, 1.48 ± 0.15	in two studies were combined to analyze patients' anxiety due to spray using the VAS. No difference in patients' anxiety due to spray was observed between vapocoolant spray and placebo spray/no treatment. 3360: Both music and visual distraction showed little to no effect on the reduction of fear/anxiety. 50: The mean anxiety reported by participants on VAS before the vaccination showed little to no effect between the intervention and control groups. Pre-vaccine anxiety scores were 0.05 higher in the Buzzy group compared to the control group (mean		et al. (2018) 3360: Boerner et al. (2015) 50: Redfern, Micham, Seegert & Chen (2019)

Quality assessment							Study Details		No. of Participants		Reported effects/outcomes	Certainty	Reference
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Country	Intervention	Intervention	Control			
							3281: Iran 382: Turkey	3281: Acupressure group - blood samples were taken from the right arm with an intervention (massage of the real points of acupressure) and from the left arm using routine venipuncture. All blood samples were taken by an experienced nurse, and acupressure was performed by a trained researcher. Placebo group : massage of the false points of acupressure Control group: no intervention 382: Intervention Group I (Hot Application) Before the PVC was inserted, the researcher applied a hot application to the catheter insertion site (inner surface of the forearm) using a hot pack for 1 minute. Intervention Group II (Cold Application) Before PVC was inserted, the researcher applied a cold application to the catheter insertion site (inner surface of the forearm) using a cold pack for 1 minute. Control= no pain	Mean (SD) anxiety score: 16.44 (12.72) *right arm, with intervention 382: Anxiety Score During PVC insertion hot 0.2±0.5; 0.0 (0.0-0.0) cold 1.0±1.4; 0.0 (0.0-2.0)	3281: placebo group: n=66, 16.96 (12.36) control group: n=61, 20.50 (12.78). 382: Anxiety Score During PVC insertion control 1.6±1.4; 2.0 (0.0-3.0)	difference). 3281: There were little to no differences found in the anxiety scores of the 3 groups *after the intervention*. Anxiety scores *during blood sampling* from the right and left arms revealed a positive effect between the acupressure and the placebo groups, while no difference was found between the anxiety scores *during blood sampling* from the right and left arms in the control group. There was a mean difference of 0.52 lower anxiety scores in the acupressure group compared to placebo, and 4.08 lower in the acupressure group compared to control. 382: Anxiety scores were lower in hot and cold groups compared with control. Anxiety scores were lower in the hot group compared with the cold group.		3281: Hosseinabadi, Biranvand, Pournia, & Anbari (2015) 382: Korkut, Karada, Dogan (2020)

Quality assessment							Study Details		No. of Participants		Reported effects/outcomes	Certainty	Reference
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Country	Intervention	Intervention	Control			
								management 507: Buzzy cold vibrating device					
							507: Turkey	Control: no pain management	507: Anxiety scores After catheterization mean SD Mean state anxiety scores 40.82 ± 3.61 Mean trait anxiety scores 46.48 ± 6.44	507: Anxiety scores After catheterization mean SD Mean state anxiety scores 40.84 ± 3.80 Mean trait anxiety scores 45.98 ± 6.46	507: No difference between buzzy and control groups.		507: Cetin and Cevik (2019)
							525: France and Belgium	525: Hypnosis group In the hypnosis group, the clinicians applied classical non-verbal hypnotic tools adapted to the subject and indirect suggestion of comfort by body language. Control group= Neutral group Or Nocebo group	525: Anxiety After peripheral intravenous cannulation Hypnosis 2.3 (2.5)[0-9]	525: Anxiety after peripheral intravenous cannulation neutral 3.0 (2.9) [0-10] nocebo 3.6 (2.7) [0-10]	525: Anxiety scores were lower in the hypnosis group compared with nocebo or neutral groups.		525: Fusco et al (2020)
							554: Turkey	554: Aromatherapy The patients in the lavender group were administered aromatherapy inhalation of lavender essential oils before needle insertion into an implantable venous port catheter. Similarly, aromatherapy inhalation of eucalyptus essential oils was administered to the eucalyptus group before needle insertion. Control= no intervention	554: Lavender mean STAI-I Scores: 37.24 +/- 8.35 Eucalyptus mean STAI-I Scores: 35.24 +/- 8.43	554: Control mean STAI-I Scores: 37.73 +/- 9.09	554: There was no difference in anxiety scores between groups.		554: Mutluay & Ozdemir (2019)
							764: Iran	764: Aromatherapy with peppermint essence Three drops of peppermint were poured	764: Mean anxiety score before	764: Mean anxiety score before intervention	764: There was a great improvement in anxiety scores from pre to post in the aromatherapy group		764: Akbari

Quality assessment							Study Details		No. of Participants		Reported effects/outcomes	Certainty	Reference
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Country	Intervention	Intervention	Control			
								on a piece of cotton and attached to the collar of the subjects' cloth 10cm from their nose. Control= distilled water	intervention3.87±1.04 (95% CI 3.405-4.095) Mean anxiety score after intervention 2.32 ±0.97 (95% CI 2.014-2.636)	3.47±1.43 (95% CI 3.017-3.933) Mean anxiety score after intervention 2.1±1.42 (95% CI 1.643-2.557)	compared to the control group. However there was no difference between groups in post intervention groups.		et al. (2019
Patient Satisfaction (assessed with: VAS, 10-point Likert Scale, or Phlebotomy Satisfaction Evaluation Scale)													
1[m]	SR (of RCTs)	Not Serious[n]	Serious[o]	Serious[p]	Not Serious[q]	Not detected	9141: Multiple - USA, UK, Canada, Australia, Turkey, New Zealand	**Non-Pharmacological Interventions** 9141: Vapocoolant Spray (1,1,1,3,3,-Pentaflouropropane and 1,1,1,2-tetrafluoroethane, Ethyl chloride, and COLD spray) Control: no treatment or placebo spray.	9141: n=668 (n not specified in intervention vs. control groups) Mean increase in satisfaction scores: 4.62 mm (95% CI 2.23 to 9.57 mm)	9141: Not specified Mean increase in satisfaction scores: 4.62 mm (95% CI 2.23 to 9.57 mm) [individual scores not reported]	The review reported an increase in patient satisfaction when given non-pharmacological pain management interventions. Five additional RCTs were identified for the outcome of patient satisfaction. All but one study supported the review finding with higher satisfaction in the intervention groups. 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.*	⊕⊕⊕◯ MODERATE	9141: Zhu et al. (2018)

Quality assessment							Study Details		No. of Participants		Reported effects/outcomes	Certainty	Reference
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Country	Intervention	Intervention	Control			
							Additional RCTs Identified: **Non-Pharmacological Interventions** 50: USA 1882: Turkey	50: Buzzy device - a plastic vibrating motor with a detachable ice pack placed over the injection site for 30 seconds; immediately before vaccine IM injection it is moved approximately 5 centimeters proximal to the site and held in place throughout the remainder of the procedure. Control group: no intervention 1882: Buzzy device - For the individuals in the experimental group, the ice wings of the Buzzy device, frozen solid in the refrigerator. When the device was operated, it applied vibration and cold to the site. At the end of 1 minute, the device was removed and immediately afterward the vein entry procedure was implemented. Placebo Control Group - the Buzzy device wings were at room temperature (unfrozen)	50: n=250 Satisfaction mean scores: 9.11 ± 0.11 1882: n=30 Mean satisfaction score: 76.00±23.7	50: n=247, 9.09 ± 0.12 1882: placebo: n=30, 61.90 ±25.5 non-intervention: n=30, 55.26±34.8	50: Mean reported satisfaction was equivalent between control and experimental groups. 1882: There was increased satisfaction of members of the experimental group compared to the control groups.		50: Redfern, Micham, Seegert & Chen (2019) 1882: Yılmaz, Heper, & Gozler (2017)

Quality assessment							Study Details		No. of Participants		Reported effects/outcomes	Certainty	Reference
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Country	Intervention	Intervention	Control			
								and with the vibration switch remaining off. Control: no intervention					
							15646: Turkey	15646: Buzzy group – the device was placed directly on the injection site for about 30 seconds and then the device was pushed 3 cm above the injection site and with the device still working (with the stimulations of cold and vibration), the standard injection protocol was applied (IM injection). Control: No intervention	15646: n=33 Mean satisfaction score: 94.82 ± 4.97	15646: n=32, 85.06 ± 13.39	15646: The mean injection satisfaction score of the intervention group was found to be significantly higher than that of the control group (mean difference of 9.76 higher satisfaction in the Buzzy group compared to control).		15646: Sahin & Eser (2018)
							507: Turkey	507: Buzzy cold vibrating device Control: no pain management	507: Satisfaction mean (SD) 95.30 (3.89)	507: Satisfaction mean (SD) 82.12 (7.48)	507: Satisfaction scores were higher in the buzzy group compared with control.		507: Cetin and Cevik (2019)
							524: Turkey	524: Distraction cards group- Cards containing approximately six optical illusion pictures were shown to the patients and as a method of distraction during the PIC insertion procedure they were asked what they saw in these cards. VR group- Underwater 3D audial videos were played with visual reality (VR) goggles during PIC insertion	524: Distraction groups (n = 80) Mean SD 8.07 ± 2.67	524: (n = 40) mean SD 5.12 ± 3.41	524: Satisfaction was higher in the distraction groups compared to the control group. There was no difference between VR group and distraction cards group.		524: Basak et al (2019)

Quality assessment							Study Details		No. of Participants		Reported effects/outcomes	Certainty	Reference
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Country	Intervention	Intervention	Control			
								until the procedure was completed. Control: no distraction					

Acronyms:

SR = Systematic Review

RCT = Randomized Controlled Trial

EMLA = eutectic mixture of local anesthetics

CI = confidence interval

NRS = Numeric Rating Scale

VAS = Visual Analog Scale

VNRDS = Verbal Numeric Rating Discomfort Scale

[a] Five systematic reviews that included a total of 62 RCTs were included. 20 additional RCTs were identified for the outcome of patient's rating of pain; however the findings supported the results of the systematic reviews and were not GRADED separately.

[b] Three systematic reviews were rated as 'low risk of bias' and two systematic reviews were rated as 'unclear risk of bias' using the Risk of Bias in Systematic Reviews (ROBIS) appraisal tool. One SR (2481) assessed risk of bias (ROB) using the CONSORT (Consolidated Standards of Reporting Trails) Statement for RCTs, and the STROBE (Strengthening the Reporting of Observational studies in Epidemiology) statement for observational studies, and found that the included studies varied in quality due to lack of reporting. Another SR (9141) assessed ROB using the Jadad score, and found that 7 of the 9 included studies for adults were rated as high quality, and 2 rated as low quality. The third SR (3360) assessed ROB using the Cochrane ROB tool and found that all included RCTs had a high overall risk of bias due. Review 1409 rating studies using the Jadad score and Cochrane ROB tool. Most studies had a low risk of bias. Review 2142 assessed ROB using the Cochrant ROB tool and found that two studies had high ROB and one had unclear ROB. We downgraded by 1 due to some concerns in ROB across the SRs.

[c] The authors of one systematic review (9141) noted serious heterogeneity in the review (I^2=70%). There were also multiple interventions used across the studies, with varying effects: topical anesthetic, ice, cold spray and breathing techniques (effective), visual and music distraction (null effect). Reviewers did not downgrade for this, due to the nature of the research question.

[d] Study 3191 was industry sponsored. We did not downgrade, due to the large number of included studies for this outcome.

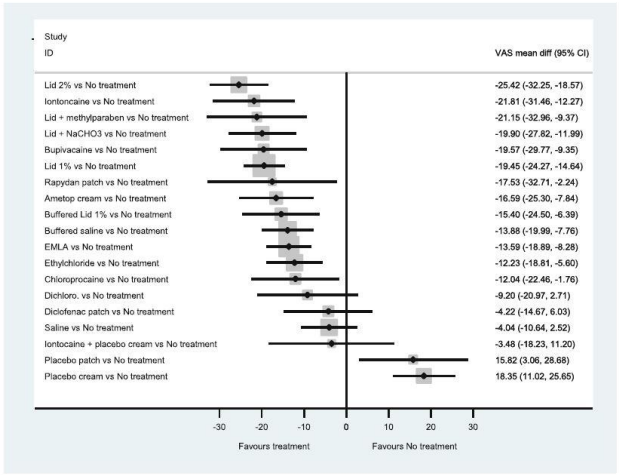

Fig. 3 NMA forest plot vs. no treatment

e

[f] Participants in 1 study reported significantly lower self-reported pain intensity than in the other 2 included studies. When data from this study was removed, a significant difference was observed in pain, with participants who received the signal about the impending procedure reporting significantly lower pain as compared with those who received the signal about the impending pain (n=199).

[g] Two studies had a 'high risk of bias' and two were rated 'some concerns' based on the Cochrane Risk of Bias 2.0 tool. Reasons for concerns were lack of a protocol or a priori plan, measurement of outcomes, and unclear randomization. We downgraded by 1.5.

[h] There was some diversity in the outcome measurement; one study measured comfort with IV insertion, one measured comfort with the pain management intervention (needle-free device). We downgrade by 0.5.

[i] Study 3191 was industry sponsored. We did not downgrade, due to the large number of included studies for this outcome.

[j] Two systematic reviews with a total of 4 RCTs were included for this outcome. An additional 7 RCTs were identified to support this finding.

[k] Both included systematic reviews had a 'low risk of bias' when rated using the ROBIS appraisal tool. One SR (9141) assessed ROB using the Jadad score, and found that 7 of the 9 included studies for adult populations were rated as high quality, and 2 rated as low quality. The other SR (3360) assessed ROB using the Cochrane ROB tool and found that all included RCTs had a high overall risk of bias due. We downgraded by 1 due to some concerns in ROB across the SRs.

[l] One of the systematic reviews (3360) noted considerable heterogeneity (reviewers did not downgrade further for this, as it was already considered when assessing risk of bias).

[m] The one included systematic review examined 4 studies related to this outcome. An additional 5 RCTs were identified in addition.

[n] The included SR (9141) assessed ROB using the Jadad score, and found that 7 of the 9 included studies for adult populations were rated as high quality, and 2 were rated as low quality. We did not downgrade.

[o] Authors noted high heterogeneity (I^2=72%). Downgraded by 1.

[p] The satisfaction outcome was reported on for adults and children combined. We downgraded by 0.5.

[q] Total number of events was >400 (n=668). We did not downgrade.