A systematic review of effectiveness of interventions applicable to radiotherapy that are administered to improve patient comfort, increase patient compliance, and reduce patient distress or anxiety

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ABSTRACT

Objectives

The aim of this review was to search existing literature to identify comfort interventions that can be used to assist an adult patient to undergo complex radiotherapy requiring positional stability for periods greater than 10 minutes. The objectives of this review were to; 1) identify comfort interventions used for clinical procedures that involve sustained inactivity similar to radiotherapy; 2) define characteristics of comfort interventions for future practice; and 3) determine the effectiveness of identified comfort interventions. The Preferred Reporting Items for Systematic Reviews and meta-analyses statement and the Template-for-Intervention-Description-and Replication guide were used.

Key findings

The literature search was performed using PICO criteria with five databases (AMED, CINAHL EMBASE, MEDLINE, PsycINFO) identifying 5,269 titles. After screening, 46 randomised controlled trials met the inclusion criteria. Thirteen interventions were reported and were grouped into four categories: Audio-visual, Psychological, Physical, and Other interventions (education/information and aromatherapy). The majority of aromatherapy, one audio-visual and one educational intervention were judged to be clinically significant for improving patient comfort based on anxiety outcome measures (effect size ≥0.4, mean change greater than the Minimal-Important-Difference and low-risk-of-bias). Medium to large effect sizes were reported in many interventions where differences did not exceed the Minimal-Important-Difference for the measure. These interventions were deemed worthy of further investigation.

Conclusion

Several interventions were identified that may improve comfort during radiotherapy assisting patients to sustain and endure the same position over time. This is crucial for the continual growth of complex radiotherapy requiring a need for comfort to ensure stability for targeted treatment.

Implications for practice

Further investigation of comfort interventions is warranted, including tailoring interventions to patient choice and determining if multiple interventions can be used concurrently to improve effectiveness.

INTRODUCTION

Positioning and immobilisation of patients are crucial for reproducible and accurate delivery of radiotherapy in both radical and palliative settings to ensure tumour control while avoiding healthy tissue toxicity[1-2]. Recent studies have shown that comfort in patients receiving radiotherapy for prostate cancer can be determined by treatment position[3] and a strong association was observed between comfortable patient positioning and improved treatment accuracy in patients' receiving radiotherapy for breast cancer[4]. As more complex treatment techniques like stereotactic ablative body radiotherapy (SABR) becomes standard, and treatment times are extended above 10 minutes, the comfort of patients is an important consideration[5-6]. It is also hypothesized that there is an association between patient comfort and radiotherapy treatment time[7] and one limitation to technical radiotherapy advancements is managing the patient's tolerability of immobilisation to complete the procedure while also achieving comfort[8]. Hypothetically, not providing a comfort intervention might increase the treatment time in radiotherapy.

To assist with identification and development of suitable comfort interventions, there is a need to consider what patient comfort is and means. Patient comfort is defined holistically as a state of having met the basic human needs for ease, relief, and transcendence in four contexts[9-11]. In radiotherapy procedures the role and purpose of holistic comfort interventions aim to make the procedure more tolerable to patients and ensure compliance reducing discomfort, anxiety, distress and claustrophobia. Comfort has been explored in a few studies including a focus group of patients with head and neck cancer receiving radiotherapy[2]. Their experiences reflected the definition of holistic comfort[9-11] and indicated that therapeutic radiographers may not fully appreciate their level of discomfort. A survey of 100 head and neck cancer patients who had received radiotherapy found that a quarter were anxious and that interventions were required including better patient preparation/education[12]. In UK and European guidelines, recommendations on how to manage patient comfort during radiotherapy are limited[2,13-14]. Greater evidence of comfort intervention effectiveness is required to inform national radiotherapy practice and guidelines.

Interventions such as communication with professionals and music were reported to reduce distress in up to 86% of patients receiving radiotherapy for head and neck cancer[15]. A previous systematic review explored the efficacy of holistic comfort interventions during invasive paediatric nursing procedures such as venepuncture, port access and intramuscular injection[16]. The review grouped comfort interventions into four categories: music, amusement and entertainment, caregiver facilitation and a multifaceted approach and supported the use of various distraction methods to reduce anxiety, distress, fear and pain during procedures[18]. Further studies have investigated interventions ranging from music to self-hypnosis and deep breathing exercises[17-18]. Thus, there are

promising procedural comfort interventions that may be applicable in radiotherapy. A limited number of interventions have been investigated to manage patient comfort during radiotherapy[19-20].

The aim of this review was to search existing literature to identify comfort interventions that can be used to support an adult patient to undergo clinical procedures that requires a patient to sustain the same position over a period greater than 10 minutes. The current estimated time cut off set at 10 minutes was deployed to capture procedures that would replicate the radiotherapy phase after positioning when patients must remain still during pre-treatment verification and treatment delivery such as SABR or palliative radiotherapy. The focus above 10 minutes was set to ensure a breadth of clinical procedures were included that would be more representative of radiotherapy. The objectives of this review were to: 1) identify comfort interventions that are used for clinical procedures that involve sustained inactivity similar to radiotherapy; 2) record the characteristics of the comfort interventions for future practice; and 3) determine the effectiveness of the comfort interventions.

METHODS

Protocol and registration

A review protocol was developed and prospectively published in PROSPERO (CRD42017059688) in line with the Centre of Reviews and Dissemination[21].

Information sources

The review was structured and reported according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement[22] and the Template for Intervention Description and Replication (TIDieR)[23] Guide.

Search

Five databases, AMED, CINAHL EMBASE, MEDLINE and PsycINFO, were searched to identify relevant text in titles, abstracts and key words to develop search terms. The literature search used the same databases and refined terms (electronic supplement A). The search was restricted to title and abstract fields to avoid retrieving non-related papers from the subject headings.

Selection criteria for eligible primary research was defined according to the Participant(P), Intervention(I), Control(C), Outcome(O) and Studies(S)[24] framework:

(P) Adult patients (≥18 years) undergoing a clinical procedure that required alignment, stabilisation, immobilisation and having to sustain, endure or tolerate the procedure while conscious over a period greater than 10 minutes. Clinical procedures included those where patients must remain stable and unwanted movement is critical. In the surgical and radiotherapy setting, unwanted

movement could result in collateral damage such as the laceration or irradiation of surrounding normal tissue respectively and potentially poorer outcomes for patients.

(I) Interventions to aid comfort; ease, relieve, relief, reduce distress/anxiety, relax, calm, alleviate, distract, or transcend a patient/service user immediately before or within a clinical procedure which requires alignment, stabilisation, or immobilised and has to sustain, endure or tolerate the procedure while conscious.

(C) Usual standard of care or comparator (another intervention)

(O) Assessments of patient comfort, psychological well-being, patient satisfaction and quality of life outcomes.

(S) Randomised controlled trials (RCTs) and controlled clinical trials (CCTs).

Studies published in English between 2000 and January 2019 were included to focus on contemporaneous practice. The searches were initially performed in August 2017 and updated in January 2019. Following removing of duplicates, two researchers independently reviewed the titles and abstracts initially and then full texts to identify papers that met the eligibility criteria. A consensus meeting was held, and concordance was achieved on 95% of the full texts. A third reviewer arbitrated on inclusion of the remaining 5% (n=4) of full texts.

Data extraction

Data was extracted from each paper by one researcher using a data extraction form based on the TIDieR checklist and guidelines[23] and reviewed by a second researcher. The data extraction form included: authors, year of publication, study design, setting, participants, clinical procedures, outcome measures, main outcomes (measured before and after clinical procedure delivery, or as a mean change), and delivery characteristics of the comfort interventions.

Risk of bias

The Cochrane Risk of Bias Checklist (Version 5.1.0) was used to assess risk of bias (RoB) in RCTs[25]. Six areas of ROB were assessed (random sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessment; incomplete outcome data; and selective reporting) with each area given either "low," "high," or "unclear" risk of bias[25]. To reduce the effect of human factors in assessing RoB[27-28] an online software RoBotReviewer™ which aims to semi-automate evidence synthesis using machine learning was used[28-29] alongside review by the researchers. International clinical trials registers were accessed to determine selective reporting bias; if not registered then studies were judged unclear for RoB. For CCTs the RoB was assessed using Risk-of-Bias-In-Non-Randomised-Studies-of Interventions. For this review, studies were judged

not acceptable if there was high risk for selection bias in both domains because randomisation is a crucial attribute of well-designed RCTs. Studies judged high risk in one area of selection bias, or another RoB component were deemed acceptable but treated with caution, and not included in the data synthesis.

Data synthesis

Only validated outcome measures were included in the synthesis and were reported separately for intervention and comparator groups. Where available, the change in outcome measures from before to after clinical procedures was calculated as mean differences, percentage change, Cohen's D effect size (normalised distribution) or r-effect size (non-normalised distribution) with 95% confidence intervals (CI)[30-31]. Studies were selected for the Cohen's D or r-effect size analysis dependant on whether the data followed a normal distribution[32-33], confirmed by the reported use of Kolmogorov-Smirnov (KS) or Shapiro-Wilk (SW) test for normality or assumed based on the use of parametric tests[37-38]. Where mean and standard deviations (SD) were not reported, an estimation from either inter quartile range or p-value was calculated[34-37]. Meta-analysis was not conducted because of the clinical heterogeneity in the study populations, healthcare settings, interventions and comparator types.

To determine whether comfort interventions make an important difference to the patients, the clinical significance of studies was assessed to supplement statistical significance[30-32]. In this review, clinical significance was determined using effect size and the minimal importance difference (MID). Effect sizes were interpreted using the following criteria: small effect (≤ 0.4), medium effect (≥ 0.5 ≤ 0.7) or large effect (≥ 0.8)[38]. Minimal important differences (MID) of validated outcome measures were identified from the literature[39-42]. A comfort intervention was considered to demonstrate clinical significance when the effect size exceeded 0.4, mean differences were greater than the MID and RoB was acceptable.

RESULTS

Study selection

Database searches initially identified 5269 titles (Figure 1). After removing duplicates (n=191), 5078 titles and abstracts were screened, and 4994 papers were removed leaving 84 papers for full review. Of these, 38 papers were excluded for reasons listed in Figure 1. One CCT was excluded because it used a parallel cross over design with potential for cross contamination between intervention and comparator groups. In total 46 papers were included in the review[43-88].

Study characteristics (electronic supplement B & C).

The studies included consisted of 46 RCTs with a total of 5782 patients [43-88]. The age of participants ranged between 18 and 80 years. The study design of RCTs included; two-arm parallel, multiple arm parallel, and mixed factorial multiple/ parallel arm study designs.

Clinical procedures

Nineteen different clinical procedures were identified. The two most common clinical procedures were observational investigations such as bronchoscopy/hysteroscopy (n=14) and interventional radiology (n=13).

Outcome measures

Most studies reported an anxiety outcome measure (n=44) and 29 studies used the State-Trait Anxiety-Inventory (STAI) aligning to psychological wellbeing. The STAI examines feelings 'at the present moment' and gives a score between 20 and 80, with a higher score indicating greater anxiety levels[89]. One study used a 6-item short STAI which is stated to be more sensitive to fluctuations in anxiety[90]. One study used the anxiety Visual-Analogue-Scale (VAS-A)[41-42], and another study used the Beck-Anxiety-Inventory (BAI) and Hamilton-Anxiety-Scale (HAS) and non-validated numeric rating scales for comfort, satisfaction, willingness to repeat and experience of the environment[91]. Only validated anxiety measures including the STAI, the VAS-A, the BAI and the HAS, reported before and after clinical procedures, were included in the data synthesis. For the STAI, the MID was set at 10[39-40]. The MID was set at 46 for the VAS-A[41], 8.8 for the BAI and 8.2 for the HAS[42].

Comfort interventions (electronic supplement B).

Thirteen comfort interventions were identified and grouped into the four categories (Table 1): Audio-visual, Psychological, Physical, and Other Interventions (education/information and aromatherapy). Comfort interventions were delivered before the clinical procedure in 10 studies, during the clinical procedure in 19 studies and both before and during the clinical procedure in 17 studies.

- Audio-visual technology interventions include audio only (n =20)[43-48,55,60-61,64,66, 68,70-74,77,82,84,86], audio-visual (n= 6)[50,51,53,60,69,88], virtual reality (n =2)[67,85] and visual only (n=1)[88]. The interventions were used for the purpose of improving (dis)comfort, reducing anxiety, distraction, improving well-being and relaxation. A wide range of music genres were used ranging from classical to easy listening popular music, chants and nature sounds. The delivery features ranged from music

or video players, loudspeakers or earphones to headsets and goggles for virtual reality. Interventions were delivered by professionals and/or self-administered by patients.

- Psychological interventions include breathing techniques (n=1)[80], cognitive behavioural therapy (n=1)[79], distraction (n=1)[64], empathetic attention (n=4)[49,60,65,76] and hypnosis (n=4)[57,65,76,81]. The interventions were used for the purpose of reducing discomfort, anxiety and pain, or improving satisfaction and relaxation. The delivery features ranged from face to face to audio players. Interventions were delivered by therapists or self-administered by patients via audio players.
- Physical interventions includes massage (n=2)[75,80], therapeutic touch (n=1)[54], reflexology (n=2)[56,78] and stress balls (n=1)[60]. The interventions were used for the purpose of reducing discomfort, anxiety, distress and pain, or improving satisfaction. The delivery was face to face with professionals.
- Other interventions includes education/information (n=4)[43,62-63,87] and aromatherapy (n=5)[52, 58, 59,78,83]. The interventions were used for the purpose of improving experience and satisfaction or reducing anxiety and psychophysiological arousal/parameters. Interventions were delivered by a range of personnel and methods.

Some studies with multiple arm parallel designs investigated interventions that crossed the above categories (n=5)[45,64,73,75,80].

Cochrane Risk of bias for included studies

Each of the included RCTs had areas where the ROB was high, low, and unclear (Fig.2). 38% of RCTs had a low overall risk of bias. Low risk for random sequence generation and concealment was reported in 77% and 32% of studies respectively. Blinding of professionals or participants to the allocated comfort intervention was reported in 6% of studies, whilst blinding of outcome assessment was completed in 36%. 81% of RCTs were judged unclear for selective reporting because trials were not registered. 3 RCTs were deemed unacceptable due to high risk of selection bias and were not included in the data synthesis[59, 67,69].

Effectiveness of comfort interventions

Only anxiety outcomes were synthesised as the outcome measures were validated and reported before and after clinical procedure (Table 2). This resulted to exclude another 17 RCTs[45-46,49,54,58,61-62, 65,70,72,74,76,78-79, 84-86]. 26 RCTs were included in the data synthesis.

Audio-visual technology interventions includes studies of audio alone[44, 47-48, 50, 55, 60, 64, 66, 68, 71,73,77, 82, 88, ,audio-visual[50-51, 53, 60] and visual[88] interventions with data available for synthesis.

Audio: six out of eleven studies of audio interventions reported statistical significance favouring the intervention ($p<0.05$)[44, 47, 55, 60, 73]. The mean difference in anxiety exceeded the MID in one intervention and with a medium effect size was judged clinically significant[71]. Medium to large effect sizes were observed in all eleven studies.

Audio-visual: three out of four audio-visual interventions studies reported statistically significance favouring the intervention ($p<0.05$) [51, 53, 60]. The mean difference in anxiety exceeded the MID in two studies[50-51]; one had a small effect size[51] and one favoured the comparator group[50]. Medium to large effect sizes were observed in all other studies[50, 51, 53, 60, 88].

Visual: one visual intervention study favoured the intervention statistically ($p <0.05$) [88]. The mean difference in anxiety did not exceed the MID but had a large effect size[88].

Only one study investigating music interventions was deemed clinically significant[71].

Psychological interventions with data available for synthesis included distraction[64], empathetic attention[60] and hypnosis[57, 81] interventions.

Distraction: one study did not show a statistically significant effect for distraction intervention[64]. The difference in mean anxiety did not exceed the MID[64], and the effect size favoured the comparator group.

Empathetic attention: one study reported statistical significance favouring the intervention[60] ($p<0.05$). The mean difference in anxiety did not exceed the MID, and while it had a large effect size, it was deemed not clinically significant.

Hypnosis: two studies reported statistical significance favouring hypnosis interventions[57, 81]($p<0.05$). Both had large effect sizes but the mean difference in anxiety did not exceed the MID in either study [57, 81].

No intervention in this category was considered clinically significant.

Physical interventions were used in three studies with data available for synthesis and involved physical touch: reflexology[56], massage[75], and stress balls[60].

Two out of three studies reported statistical significance favouring the intervention ($p<0.05$) [56, 60]. The mean difference in anxiety exceeded the MID in one study[75] with large effect sizes in the other two[56, 60]. None of the physical interventions were judged clinically significant[56, 60, 75].

Other intervention studies with data available for synthesis involved education/information[63, 83] and aromatherapy[52, 83] interventions.

Education/ information: three studies evaluated the effects of education/information interventions [43, 63, 87.] After the clinical procedure one studies reported statistical significance favouring the intervention ($p<0.05$)[63].The mean difference in anxiety did not exceed the MID in two studies [43, 63,]and small to large effects sizes favouring the comparator were observed. One study investigating a multi-media information and instruction intervention deemed to be clinically significant[87].

Aromatherapy: two studies evaluated the effects of aromatherapy essential oil interventions with different methods of diffusion[52, 83]. One study reported statistical significance favouring the intervention ($p<0.05$)[52] and the other did not[83]. The difference in mean anxiety exceeded the MID in both studies[52, 83]. Medium to large effect sizes were observed in both studies and were deemed clinically significant[52, 83]. These two studies investigating Lavandula angustifolia, Citrusaurantium L, Lavender-sandalwood, and Orange-peppermint aromatherapy were deemed clinically significant[52, 83.]

DISCUSSION

The aim of this review was to identify effective comfort interventions to support patients undergoing clinical procedures that require a patient to sustain the same position over a period greater than 10 minutes. Thirteen comfort interventions were identified which ranged from aromatherapy to virtual reality delivered before and during nineteen different clinical procedures in 46 studies. Anxiety outcomes were synthesised as the outcome measures were validated and reported before and after clinical procedure in 26 studies.

The findings of the review showed that many comfort interventions produced statistically significant improvement in anxiety outcomes but did not demonstrate clinical significance as defined for this study. Aromatherapy[52, 59, 83] used in colonoscopy, interventional radiology and minor surgery demonstrated both statistical and clinical significance and could be used in radiotherapy with careful consideration of application. Aromatherapy using vaporising systems may be contraindicated because of the potential for skin irritation or allergies linked to radiation induced skin toxicity or for vapour damage to radiotherapy equipment. A clothing tab infused with aromatherapy oils, found to be favourable in previous clinical trials[92], may be more appropriate in radiotherapy . Audio and audio-visual interventions demonstrated medium to large effect sizes[44,47,48,51,53,55,60,67,68,71,73,77,82,88] with several showing clinical significance that warrant further investigation in radiotherapy. A number of radiotherapy departments have audio-visual technology available to support their patients and audio interventions have been successfully tested in radiotherapy. For example, Chen et al[93] reported that music therapy reduced pre-radiotherapy anxiety only but did not examine the effect during the clinical procedure and for this reason, was not included in our synthesis. Audio interventions may be contraindicated in radiotherapy at times where constant communication

between radiographers and patients is required such as verbal instructions to patients on performing deep inspiration breath hold or where an audio device such as earphones or audio pillows attenuates the radiation beam. Devices may be impractical due to an immobilisation mask. Visual interventions may not be so easily accommodated during some radiotherapy techniques but some interventions such as decorative wall colour or murals may be a pragmatic option.

Three psychological interventions and two physical interventions provided immediately before or during the clinical procedure demonstrated medium to large effect sizes[57,60,81]. Psychological interventions provided as part of the preparation for radiotherapy have been studied and cognitive behavioural therapy and hypnosis have been shown to significantly (p = .0035) improve breast cancer patient general experiences[94]. Similarly, massage provided during a course of radiotherapy treatment reduced anger anxiety and depression in patients with breast cancer receiving radiotherapy ($p < 0.001$)[95]. This review focused on interventions that could be delivered within radiotherapy sessions. Psychological interventions could be readily adopted if self-administered using an audio player. Use of empathetic interventions encouraging social interaction could be challenging to deliver. However Gibbon et al[96] found that patient orientated communications skills training for the radiotherapy multi-disciplinary team resulted in significantly more empathetic interaction (p = 0.037).

Distraction using physical devices such as stress balls could be implemented with care taken not to disrupt the desired position for accurate radiotherapy. One intervention providing educational information via DVD demonstrated clinical significance[87] and could be implemented in a radiotherapy department. These interventions could also be applicable to clinical procedures including brachytherapy where there is need to develop non-pharmacological interventions[97] and paediatric radiotherapy where general anaesthesia could be reduced[98].

One gap observed from the studies is the effect of combining interventions as a 'comfort package' to enhance effectiveness. Simmons et al[80] investigated four interventions to support patients undergo cataract surgery with favourable results for combined interventions. Similarly, a systematic review by Bice et al[19] found statistically significant differences favouring multifaceted (more than one intervention) interventions in most studies included in their review. Further research investigating a comfort intervention package (multiple interventions) may provide greater effectiveness for patients during radiotherapy treatment.

Some methodological aspects of the systematic literature review and reviewed studies warrant further consideration. Firstly, anxiety outcome measures may not be the most suitable measure of comfort. The current review included studies with interventions that aimed to comfort, or to

alleviate or reduce discomfort, anxiety and distress of clinical procedures. Comfort can be viewed holistically within physical, sociocultural, psychospiritual and environmental contexts that are not reflected in anxiety measures. There are limited comfort outcome measures, however the recently validated Radiotherapy-Experience-Questionnaire could be considered for measuring comfort in radiotherapy[99]. Going forward, use of comfort outcome measures within all specialties is required for generating new evidence and confirming treatment effects of comfort interventions.

For the purposes of this review, clinical significance of the anxiety measures was demonstrated with a medium or above effect size (≥ 0.4) and mean differences greater than the MID. However, the availability of information about MID specific to the outcome measures reported in this review was limited. The MID level of 10 for the STAI was based on a population of smokers; in a non-smoking population the MID maybe higher or lower[40]. Similarly, the MID for the BAI and HAS was based on a sample of patients with Parkinson's [42]. Further work is required for MID development in appropriate populations to assist with determining clinically effective interventions.

The research quality of the reviewed studies was an issue and a meta-analysis was not conducted due to this factor and because of the challenges of defining the nuances of comfort, clinical procedures and interventions. 8 RCTs were deemed unacceptable due to a high risk of selection bias and were not included in the data synthesis. Many studies did not register with an international clinical trial register which affected the assessment of selective reporting; these studies were therefore judged as having unclear RoB. Although there were some methodological challenges, a rigorous review process was followed and a semi-automated machine learning programme, RoBotReviewer™ [28-29], was used for Cochrane RoB to increase the rigour of this review by reducing the impact of human factors during data extraction. Combining the use of semi-automated extraction with manual assessment was useful and future reviews should consider using machine or deep learning systems to improve the rigour and quality of data extraction[100].

To our knowledge, this is the first systematic review that could support the further investigation of comfort interventions in radiotherapy. Given the limited recommendation of how to manage patient comfort during radiotherapy from national and European guidelines[2,9], the findings of this review and further investigation of comfort interventions will provide the evidence required for future guidelines. Given the perpetual increase in new effective treatment options and technology available in radiotherapy, it is essential that the community embraces and implements comfort interventions ensuring the best outcomes for patients.

CONCLUSION

The majority of aromatherapy interventions were clinically significant and they can be potentially considered for radiotherapy that require patients to sustain and endure the same position over time similar to these clinical procedures. There was limited evidence for other comfort interventions, although most effect sizes favoured the intervention, suggesting important benefit to patients. Further investigation of these comfort interventions is warranted, including tailoring interventions to patient choice and determining if multiple interventions could be used concurrently to improve their effectiveness. This is crucial for complex radiotherapy that necessitates more demand and attention to patient comfort to ensure stability for targeted treatment.

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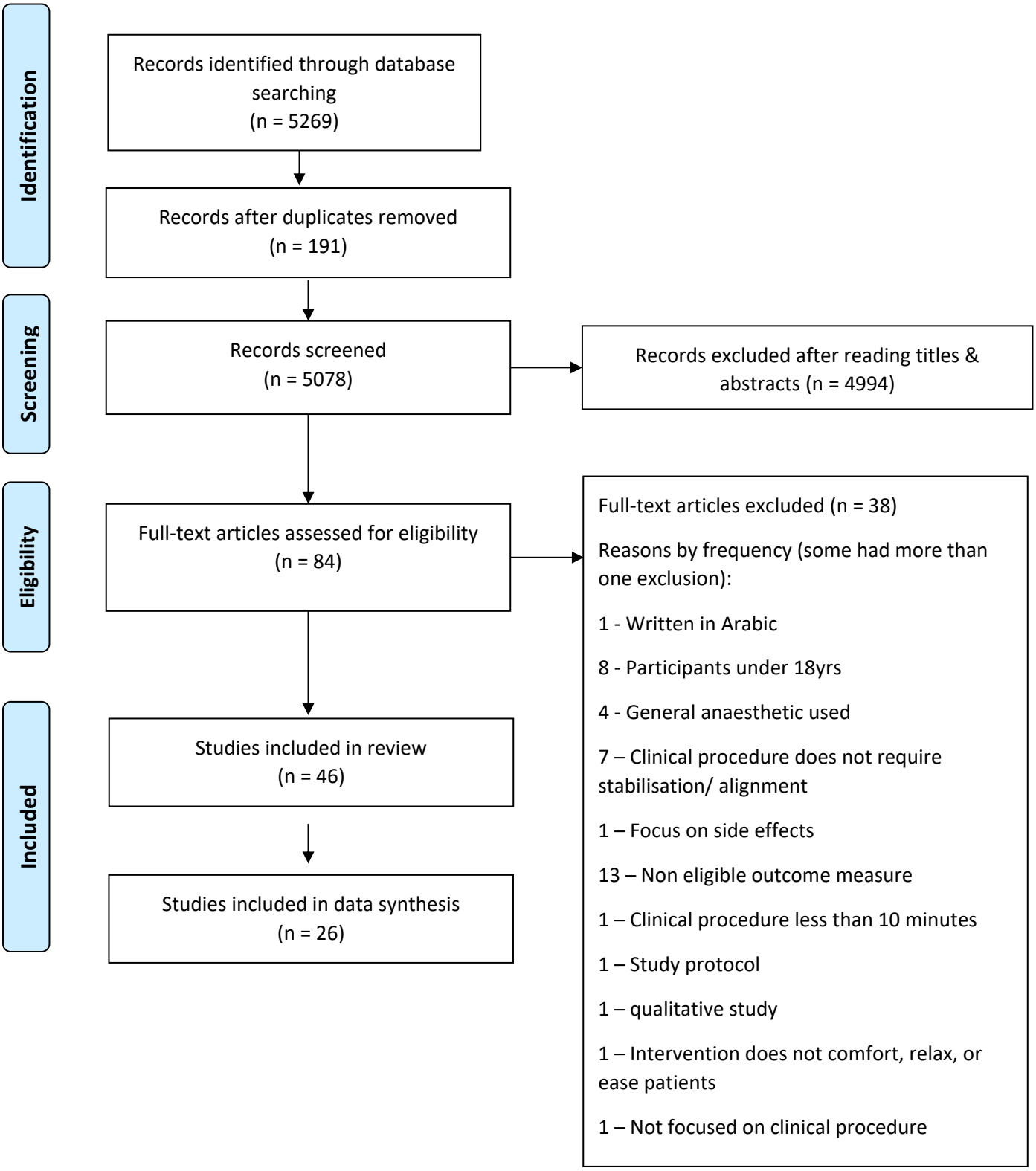

Figure 1. Flow diagram of the strategy search.

Table 1 – Intervention delivery characteristics

Comfort intervention	Rationale	Materials	Delivery features	Delivered by
AUDIO-VISUAL TECHNOLOGY INTERVENTIONS				
Audio →	♦Reduce anxiety[43-48,55, 60, 64, 66, 71-73, 77, 84, 86, 88], discomfort[48], stress[61], pain[42, 60, 64, 71-72, 77], heart rate[68], analgesics/ anxiolytics[71] Improve satisfaction[48, 60, 74], compliance[48, 82, 92], relaxation[42, 70-71], comfort[70-71], wellbeing[59], reactive hyperaemia index[74]	♦A range of music genres. [42, 44-48, 55, 60-61, 64, 68, 70-73, 77, 82] ♦ Vedic chants[73] ♦ Nature sounds ♦ Music therapy (meditative, relaxing)[66, 68, 74, 86]	♦Music player (e.g. CD player/computer)[44-48, 60-61, 64, 68, 70-73, 77, 82, 86, ♦ Loudspeaker[70-72, 82] ♦ Earphones[45-48, 60-61, 64, 68, 73, 77] ♦Cushion with speaker[74, 86] ♦Not specified[42,55, 68] ♦Most at 50-80bpm[42, 44-48, 55, 60-61, 64, 68, 70-73, 77, 82]	♦Technician[42] ♦Music therapist[45] ♦Research nurse[44] ♦Student nurses[46] ♦Nurses[46-47,55,60, 70] ♦Investigators[48, 55] ♦Physicians[42, 46] ♦CT technologists[68] ♦Study personnel[86] ♦Not specified[50, 61, 64, 66, 68, 72-74, 77, 82, 84, 88]
Audio-visual →	♦Reduce anxiety[50-53, 60] ♦Reduce pain[50-52,60] ♦Improve experience[52-53] ♦Improve satisfaction[52] ♦Tolerate procedure[69]	♦Nature sounds such as a waterfall[50-51, 88] ♦Nature scene such as a mountain stream, tropical beach, general landscape scenery and animation[50-51,69, 88] ♦ Videos included documentaries and movies[60, 88] ♦ Comedies, documentaries and panel-based quiz shows ♦Iranian music[69]	♦Music player (e.g. CD player/computer)[50-51, 69] ♦ loudspeaker ♦ Earphones[50-52, 69] ♦ Wall or ceiling mounted murals of nature scenes with/without lighting[50-51,53,69, 80]. ♦Video goggles connected to DVD[52-53] ♦ Wall mounted monitor connected to DVD ♦ Projector connected to DVD[60]	♦Standard clinic staff[51] ♦Nurse[52,60] ♦Not specified[50, 52-53, 69]
Visual →	♦Distraction from pain, anxiety, and tolerate procedure[88]	♦Scenery, animation, to film[88]	♦Monitor with DVD player (no sound)[88]	♦Not specified[88]
Virtual reality (VR) →	♦Reduce pain[85] ♦Reduce anxiety[85] ♦Reduce opioid use[67]	♦ Throwing/shooting snowballs at objects by clicking a computer mouse button[67, 85]	♦Headset goggles, earphones, DVD player, VR system[67] ♦ VR group donned a VR helmet and track ball hand controller[85]	♦Nurses[67] ♦Not specified[85]

Comfort interventions	Rationale	Materials	Delivery features	Delivered by
PSYCHOLOGICAL INTERVENTIONS				
Breathing techniques →	♦Reduce discomfort, pain & anxiety[80]	♦Verbal coaching and slow breathing instructed[80]	♦Face to face[80]	♦Nurses[80]
Cognitive behavioural therapy →	♦Improve relaxation[79]	♦ Live guided imagery[79] ♦ Recorded guided imagery[79]	♦ Face to face[79] ♦ CD player[79]	♦Trained therapist[79]
Distraction →	♦Reduce pain & anxiety[64]	♦ Participant reads a book[64]	♦ A book[64]	♦Research nurses[64]
Empathic attention →	♦Reduce pain[60, 76] ♦Reduce anxiety[49, 60, 76] ♦Improve satisfaction[60] ♦Reduce discomfort[65] ♦Reduce adverse effects[65]	♦ Verbal empathy[49,65,76] & touch[49] ♦ Non-verbal attention[76] ♦Engage in conversation[60, 76] ♦Attentive listening, Perception of control, Emotionally neutral, Avoid negative suggestion[76]	♦ Face to face [49, 60, 65, 76]	♦Nurse[60] ♦Medical student[65, 76] ♦Psychology graduate[65, 76] ♦Therapist[49]
Hypnosis →	♦Reduce pain[76, 81] ♦Reduce anxiety[57, 76, 81] ♦Reduce discomfort & Reduce adverse effects[65]	♦ Progressive relaxation, visualisation, & deep trance[57,65, 81]	♦ Face to face[, 65, 81] ♦Self hypnosis[57,76]	♦Nurse[65, 76] ♦Medical student[65, 76] ♦Psychology graduate[65, 76] ♦Not specified[57] ♦Social worker[81]

Comfort interventions	Rationale	Materials	Delivery features	Delivered by
PHYSICAL INTERVENTIONS				
Massage, therapeutic touch & reflexology→	♦Reduce pain[75,80] ♦Reduce anxiety[56, 75, 78] ♦Reduce diststress[54] ♦Reduce discomfort[54,80]	♦ Massage[75,80] ♦ "energy repatterning" hand movements over parts of the patient's anatomy (often the torso) where energy field abnormalities are detected[54] ♦ Three reflexology acupressure points for the pituitary gland, heart and solar plexus were stimulated by hand[56,78]	♦ Face to face light finger[80] & 20 minutes Effleurage strokes across different parts of the body Massage[75] ♦ Face to face Kriegler and Kunz Therapeutic touch Massage[54] ♦ Face to face foot reflexology (both feet) for 10 minutes[56,78]	♦Nurse[80] ♦Four trained practitioners[54] ♦Massage therapist[75] ♦Reflexologist[56,78]
Distraction →	♦Reduce pain, anxiety and improve patient satisfaction[60]	♦Stress balls[60]	♦ Stress balls manipulated during clinical procedure by participant[60]	♦self-directed by patientt[60]

Comfort interventions	Rationale	Materials	Delivery features	Delivered by
OTHER INTERVENTIONS				
Education/ information →	♦Improve experience[43] ♦Reduce anxiety[62, 87] ♦Reduce psychophysiological arousal[63] ♦Increase satisfaction[87]	♦Participant watches live examination[63] ♦ Video education/ information[43] ♦Audio information about procedure[62] ♦Instructional Accessibility-enhanced multimedia informational education (AEMIE)[87]	♦ Monitor screen of examination[63] ♦ Monitor screen with DVD player[43, 87] ♦Music player & headphones[62] ♦Head mounted display with headphnes[63]	♦Radiographer[43] ♦Research assistant[62] ♦Nurse[63, 87]
Aromatherapy →	♦Reduce anxiety [52, 58-59, 83] ♦Reduce physiology parameters[59, 78]	♦Lavandula angustifolia Miller, citrus aurantium L. essencses[52] ♦ Lavender oil, grapefruit oil, and Osmanthus fragrans+B7 oil for diffusion[58] ♦Neroli essences were poured on gauze[59] ♦ Essential oils lavender/sandalwood on tab or orange/peppermint on tab[83]	♦ Participants inhaled aroma from the tissue paper for 20 minutes from a 20cm distance[52] ♦ Diffuser used[58] ♦ Delivered via handhold-nebulizer with oxygen mask which pneumatically pump the oil into the mask; the oxygen masks were placed on the participants nose to smell for five minutes[59] ♦Tabs placed on participant gown[83]	♦Study researchers[52] ♦Endoscopist[58] ♦Nurse[83] ♦Not specified[59,78]

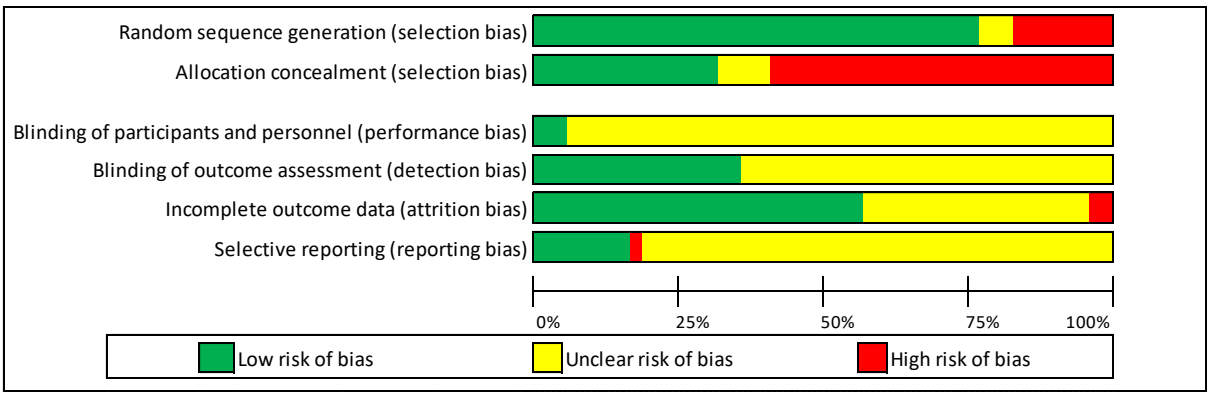

Figure. 2. Cochrane risk of bias summary of randomised controlled trials (n=46)

Table 2 – Clinical significance of interventions before & after clinical procedures (based on anxiety outcome measures)

Source	Comfort intervention category	Outcome measure		Mean difference Before-after clinical procedure				Mean difference between groups	% difference between groups	Effect size with CI (95%)	Intervention Clinically significant
		Type	Minimal important difference (MID)	Intervention Group Mean difference	≥MID	Comparator Group Mean difference	≥MID				
Angioli R, et al 2014[44]	Audio-visual technology interventions	STAI	10	3.4	X	1.1	X	2.2	66%	4.2 (3.8 to 4.5)	No
Buffum MD, et al 2006[47]		STAI	10	3.4	X	1.1	X	2.2	66%	4.1 (3.5 to 4.6)	No
Chlan L, et al 2000[48]		STAI	10	2.4	X	-1.6	X	4.0	167%	0.7 (0.2 to 1.2) *	No
Hayes A, et al 2003[55]		STAI	10	4.4	X	1.5	X	2.9	66%	1.2 (0.9 to 1.5)	No
Hudson BF, et al 2015[60](music)		STAI	10	0.0	X	-2.3	X	2.3	102%	1.3 (1.7 to 1.0)	No
Kwekkeboom KL, et al 2003[64]		STAI	10	4.1	X	7.0	X	-2.9	-71%	-5.0 (-3.8 to -6.2)	No
LEE WL, et al 2017[66]		STAI	10	5.3	X	-0.7	X	5.9	88%	5.6 (4.6 to 6.6)	No
Ng MY, Et al 2016[68]		STAI	10	2.0	X	1.2	X	0.8	41%	0.6 (0.3 to 0.9)	No
Nilsson U, et al 2009[71]		Short STAI	10	14.7	✓	14.3	✓	0.4	2%	0.5 (0.5 to 0.5) *	Yes
Padam A, et al 2017[73]		STAI	10	1.9	-	1.4	X	0.5	26%	0.4 (0.0 to 0.7)	No
		STAI	10	3.8	X	1.4	X	2.4	63%	2.6 (2.1 to 3.1)	No
Shabanloei R, et al 2010[77]		STAI	10	9.7	X	5.8	X	3.9	40%	3.6 (2.9 to 4.3)	No
Sobana R, et al 2015[82]		Short STAI	10	6.1	X	0.1	X	6.1	99%	2.0 (2.6 to 1.3)	No
Diette GB, et al 2003[50]		STAI	10	13.5	✓	12.0	✓	1.5	11%	-1.8 (-1.3 to -2.4)	No
Drahota A, et al 2008[51]		STAI	10	13.5	✓	12.0	✓	1.5	11%	0.2 (-0.3 to 0.6) *	No

Source	Comfort intervention category	Outcome measure		Mean difference Before-after clinical procedure				Mean difference between groups	% difference between groups	Effect size with CI (95%)	Intervention Clinically significant
		Type	Minimal important difference (MID)	Intervention Group Mean difference	≥MID	Comparator Group Mean difference	≥MID				
Fang AS, et al 2016[53]		STAI	10	6.1	X	0.1	X	6.1	99%	2.0 (2.5 to 1.5)	No
Hudson BF, et al 2015[60] (DVD)		STAI	10	2.3	X	-2.3	X	4.6	199%	3.3 (3.8 to 2.8)	No
Xiaolian J, et al 2015[88]		STAI	10	5.0	X	4.1	X	0.8	17%	0.7 (0.3 to 1.0)	No
		STAI	10	2.5	X	-2.3	X	4.7	7%	3.3 (3.8 to 2.8)	No
Hızlı F, et al 2015[57]	**Psychological interventions**	BAI	8.8	3.0	X	-1.9	X	4.8	38%	0.9 (0.6 to 1.2) *	No
		HAS	8.2	4.6	X	-2.8	X	7.4	40%	0.9 (0.6 to 1.3) *	No
Snow A, et al 2012[81]		VAS-A (0-100mm)	46	22.0	X	13.0	X	9.0	41%	0.7 (1.2 to 0.3)	No
Kwekkeboom KL, et al 2003[64]		STAI	10	6.3	X	7.0	X	0.7	11%	-1.2 (-0.5 to -1.9)	No
Hudson BF, et al 2015[60]		STAI	10	2.5	X	-2.3	X	4.7	193%	3.3 (3.8 to 2.8)	No
Heidaria F, et al 2017[56]	**Physical interventions**	STAI	10	4.4	X	1.5	X	2.9	66%	1.0 (0.9 to 1.0) *	No
Rosen J, et al 2013[75]		STAI	10	6.5	X	8.6	X	-2.1	-32%	-0.2 (0.5 to -0.9)	No
		STAI	10	12.1	✓	9.5	X	2.6	21%	0.2 (0.9 to -0.4)	No
Hudson BF, et al 2015[60]		STAI	10	3.0	X	-2.3	X	5.3	176%	2.4 (2.8 to 1.9)	No
Ahlander BM, et al 2018[43]	**Other: Education/ information**	STAI	10	6.5	X	1.1	X	5.4	83%	-1.0 (-1.4 to-0.6)	No
Kola S, et al 2013[63]		STAI	10	-4.0	X	4.5	X	-8.5	212%	1.0 (-1.2 to -0.7)*	No
			10	6.2	X	3.5	X	2.7	44%	0.4 (-0.3 to 1.1)*	No
			10	-6.2	X	4.5	X	-10.7	-173%	-1.0 (-1.3 to-0.5)*	No
			10	4.1	X	3.9	X	0.1	3%	0.0 (-0.3 to 0.4) *	No

Source	Comfort intervention category	Outcome measure		Mean difference Before-after clinical procedure				Mean difference between groups	% difference between groups	Effect size with CI (95%)	Intervention Clinically significant
		Type	Minimal important difference (MID)	Intervention Group Mean difference	≥MID	Comparator Group Mean difference	≥MID				
Wu KL, et al 2014[87]		STAI	10	16.3	✓	10.2	✓	6.2	38%	0.9 (0.6 to 1.2) *	Yes
				13.5	✓	10.2	✓	3.3	25%	0.5 (0.0 to 1.0) *	Yes
Eslami J, et al 2018[52]	Other: Aromatherapy	STAI	10	12.8	✓	-1.0	X	13.8	92%	5.9 (4.7 to 7.1)	Yes
		STAI	10	13.7	✓	-1.0	X	14.7	93%	9.0 (4.7 to 10.7)	Yes
Hu PH, et al 2010[59]		STAI	10	11.0	✓	7.1	X	3.9	35%	0.3 (-2.6 to 2.1) *	No
Trambert T, et al 2014[83]		STAI	10	14.2	✓	2.9	X	11.3	79%	0.5 (-2.4 to 3.3) *	Yes
		STAI	10	6.5	X	2.9	X	3.6	55%	0.2 (-2.8 to 3.1) *	No

Electronic Supplement A – Search and Mesh terms

COMFORT	CLINICAL PROCEDURE	INTERVENTION	RESEARCH DESIGN
((((((uncomfortable).ti,ab OR (discomfort*).ti,ab OR (anxiety OR anxious).ti,ab OR exp ANXIETY/ OR (distress*).ti,ab OR (stress*).ti,ab OR exp "STRESS, PSYCHOLOGICAL"/ OR (fear*).ti,ab OR exp FEAR/ OR (fright*).ti,ab OR (scare*).ti,ab OR (emotion*).ti,ab OR (tension OR tense*).ti,ab OR (misapprehen*).ti,ab OR (apprehens*).ti,ab OR (panic).ti,ab OR exp "PANIC DISORDER"/ OR (claustrophob*).ti,ab OR exp "PHOBIC DISORDERS"/)	Radiotherapy* "radiation therap*" exp RADIOTHERAPY/ ((procedur*).ti,ab OR exp "SURGICAL PROCEDURES, OPERATIVE"/ OR ("local anaesthe*").ti,ab OR ("regional anaesthe*").ti,ab OR ("conscious surgery").ti,ab OR ("awake surgery").ti,ab OR (surgery).ti,ab OR (immobil*).ti,ab OR (invasive).ti,ab OR exp "MINIMALLY INVASIVE SURGICAL PROCEDURES"/)) [DT 2000-2018]" NOT ((child*).ti,ab OR (paediatric* OR pediatric*).ti,ab))	AND (((ease*).ti,ab OR (comfort*).ti,ab OR (transcend*).ti,ab OR (relax*).ti,ab OR exp RELAXATION/ OR (relieve OR relief).ti,ab OR (alleviat*).ti,ab OR (distract*).ti,ab OR (calm*).ti,ab) AND ((intervention*).ti,ab OR (treat OR treatment*).ti,ab OR (therap*).ti,ab OR (technique*).ti,ab OR (hypnosis).ti,ab OR exp HYPNOSIS/ OR exp "MIND-BODY THERAPIES"/))) AND	(("randomised control trial*").ti,ab OR ("randomized control trial*").ti,ab OR exp "CONTROLLED CLINICAL TRIALS AS TOPIC"/ OR exp "NON-RANDOMIZED CONTROLLED TRIALS AS TOPIC"

Electronic Supplement B – Characteristics of included studies

Sources	Setting	Design	Study participants	Comfort Intervention	Clinical procedure	Clinical procedure timings (minutes)
Ahlander BM, et al 2018[43]	Outpatient: diagnostic imaging department at 1 hospital	RCT - two-arm parallel design	49 video information 48 comparator	Education/ information; administered before procedure	Cardiovascular magnetic resonance imaging	40 – 80
Angioli R, et al 2014[44]	Outpatient: gynaecology day surgery at 1 hospital	RCT - two-arm parallel design	185 music 187 comparator	Audio: administered during procedure	Hysteroscopy	10 – 30
Argstatter H, et al 2006[45]	Outpatient: cardiology day surgery at 1 hospital	RCT - multiple arm parallel design	28 music 28 coaching 27 comparator	Audio & coaching; administered before & during procedure	Intracardiac catheterization	30 – 40
Björkman I, et al 2013[46]	Outpatient: endoscopy department at 1 hospital	RCT - two-arm parallel design	60 music 60 comparator	Audio; administered before & during procedure	Colonoscopy	30
Buffum MD, et al 2006[47]	Outpatient: interventional radiology department at 1 hospital	RCT - two-arm parallel design	89 music 81 comparator	Audio; administered before & during procedure	Vascular angiography	30 – 60
Chlan L, et al 2000[48]	Outpatient: endoscopy department at 1 hospital	RCT - two-arm parallel design	30 music 34 comparator	Audio; administered during procedure	Flexible sigmoidoscopy	10 -20
Choi SM, et al 2016[49]	Outpatient: bronchoscopy department at 1 hospital	RCT - multiple arm parallel design	89 verbal empathy 88 verbal empathy & touch 90 comparator	Empathic attention; administered before procedure	Impacted mandibular third molar removal	20
Diette GB, et al 2003[50]	Outpatient: endoscopy department at 1 hospital	RCT - two-arm parallel design	41 audio-visual 39 comparator	Audio-visual; administered before & during procedure	Flexible bronchoscopy	15 - 45
Drahota A, et al 2008[51]	Outpatient: nail surgery clinics at 1 hospital & 1 community centre	RCT - two-arm parallel design	78 audio-visual 74 comparator	Audio-visual; administered before & during procedure	Minor surgery	60
Eslami J, et al 2018[52]	Outpatient: urology department at 1 hospital	RCT - multiple arm parallel design	30 aromatherapy: lavandula angustifolia miller essence 30 aromatherapy: citrus aurantium L. 30 comparator	Aromatherapy; administered before & during procedure	Laparoscopic cholecystectomy	30

Sources	Setting	Design	Study participants	Comfort Intervention	Clinical procedure	Clinical procedure timings (minutes)
Fang AS, et al 2016[53]	Outpatient: interventional radiology (IR) department at 1 hospital	RCT - two-arm parallel design	39 video glasses 44 comparator	Audio-visual; administered during procedure	Interventional radiology	20 - 30
Frank LS et al 2007[54]	Outpatient: day surgery at 1 hospital	RCT - two-arm parallel design	42 therapeutic touch 40 comparator	Massage/ therapeutic touch & reflexology; administered before & during procedure	Stereotactic core breast biopsy	30 - 60
Hayes A, et al 2003[55]	Outpatient: gastrointestinal diagnostic centre at 1 hospital	RCT - two-arm parallel design	100 music 98 comparator	Audio; administered before & during procedure	colonoscopy or esophagogastroduodenoscopy	15 - 30
Heidaria F, et al 2017[56]	Outpatient: coronary angiography department at 1 hospital	RCT - two-arm parallel design	45 h& reflexology 45 comparator	Therapeutic touch; administered before procedure	Coronary angiography	30 - 40
Hızlı F, et al 2015[57]	Outpatient: urology day surgery at 1 hospital	RCT - two-arm parallel design	32 hypnotherapy 32 comparator	Hypnosis; administered before procedure	Transrectal ultrasound-guided prostate needle biopsy	30
Hozumi H, et al 2017[58]	Outpatient: colonoscopy department at 1 military hospital	RCT - multiple arm parallel design	72 vehicle (placebo) 71 lavender 71 grapefruit 74 osmanthus fragrans 73 comparator	Aromatherapy; administered during procedure	Colonoscopy	30
Hu PH, et al 2010[59]	Outpatient: colonoscopy at 1 hospital	RCT - two-arm parallel design	14 neroli aromatherapy 13 comparator	Aromatherapy; administered before procedure	Colonoscopy	30
Hudson BF, et al 2015[60]	Outpatient: private clinic specializing in minimally invasive treatment of venous conditions	RCT - multiple arm parallel design	84 music 80 DVD 78 interaction 80 stress ball 76 comparator	Audio, audio-visual, interaction & stress ball; administered during procedure	Minimally invasive surgery of venous conditions	60
Jiménez-Jiménez M, et al 2013[61]	Outpatient: angiography & vascular surgery department at 1 hospital	RCT - two-arm parallel design	40 music 40 comparator	Audio; administered during procedure	Varicose vein crossectomy with great saphenous vein versus Stripping	20 - 30
Kekecs Z, et al 2014[62]	Outpatient: cataract surgery department in 1 hospital	RCT - two-arm parallel design	34 education & therapeutic suggestion 50 comparator	Education/ information; administered before procedure	Cataract surgery	30 - 45

Sources	Setting	Design	Study participants	Comfort Intervention	Clinical procedure	Clinical procedure timings (minutes)
Kola S, et al 2013[63]	Outpatient: colposcopy department at 1 hospital	RCT - mixed factorial & multiple parallel design	40 high-information 39 low-information 38 comparator Each group split between high & low monitors based on Miller Behavioural Style Scale	Education/information; administered during procedure	Colposcopy	10 – 20
Kwekkeboom KL, et al 2003[64]	Outpatient: oncology clinic at 1 hospital	RCT - multiple arm parallel design	24 music 14 distraction 20 comparator	Audio & distraction; administered before & during procedure	Tissue biopsy or vascular port placement	20 - 40
Lang EV, et al 2000[65]	Inpatient & outpatient: interventional radiology department at 1 hospital	RCT - multiple arm parallel design	80 attention 82 hypnosis 79 comparator	Empathic attention & hypnosis; administered during procedure	Percutaneous transcatheter diagnostic & therapeutic peripheral vascular & renal interventions	30 - 60
LEE WL, et al 2017[66]	Outpatient: diagnostic imaging department at 1 hospital	RCT - two-arm parallel design	35 meditative music 37 comparator	Audio; administered during procedure	Positron emission tomography (PET) scans	30 - 60
McSherry T, et al 2018[67]	Inpatient: burns ward at 1 hospital	RCT - two-arm parallel cross over design	10 immersive virtual reality (IVR) with first dressing change 8 IVR with second dressing change	Virtual reality; administered during procedure	Painful wound care procedures	10 - 20
Ng MY, et al 2016[68]	Outpatient: diagnostic imaging department at 1 hospital	RCT - two-arm parallel design	100 music 97 comparator	Audio; administered before & during procedure	cardiac computed tomography	15
Navidian A, et al 2018[69]	Outpatient: bronchoscopy department at 1 hospital	RCT - two-arm parallel design	30 audio-visual 30 comparator	Audio-visual; administered during procedure	Flexible bronchoscopy	15 - 45
Nilsson U, et al 2009[70]	Outpatient: percutaneous coronary intervention unit at 1 hospital	RCT - two-arm parallel design	121 music 117 comparator	Audio; administered during procedure	Coronary angiography	30 - 40
Nilsson U, et al 2012[71]	Outpatient: percutaneous coronary intervention unit at 1 hospital	RCT - two-arm parallel design	34 music 34 comparator	Audio; administered during procedure	Coronary angiography	30 - 40
Packiam VT, et al 2018[72]	Outpatient: urology department at 1 hospital	RCT - two-arm parallel design	85 music 97 comparator	Audio; administered during procedure	Transrectal prostate biopsies	10

Sources	Setting	Design	Study participants	Comfort Intervention	Clinical procedure	Clinical procedure timings (minutes)
Padam A, et al 2017[73]	Outpatient: department of physiology & gastroenterology in 1 hospital	RCT - multiple arm parallel design	67 vedic chants 66 classical music 66 comparator	Audio; administeredbefore procedure	Upper gastrointestinal endoscopy	30
Ripley L, et al 2014[74]	Outpatient: cardiac catheterization laboratory in 1 hospital	RCT - two-arm parallel design	36 music intervention 34 comparator	Audio; administered before & during procedure	Cardiac catheterization	30 – 40
Rosen J, et al 2013[75]	Outpatient: haematology/ oncology & multidisciplinary clinics at 1 hospital	RCT - multiple arm parallel design	40 massage (7 did not receive) 20 structured attention (6 did not receive)	Massage, therapeutic touch & reflexology; administered before & during procedure	Placement of vascular access devices	20 - 40
Schupp CJ, et al 2005[76]	Outpatient: radiology department in 1 hospital	RCT - mixed factorial & multiple parallel design	Low state anxiety group (<43) 37 attention 36 hypnosis 43 comparator High state anxiety group (≥43) 43 attention 43 hypnosis 34 comparator	Empathic attention & hypnosis; administered before & during procedure	Interventional radiology	20 - 30
Shabanloei R, et al 2010[77]	Outpatient: haematology & oncology research centre at 1 hospital	RCT - two-arm parallel design	40 music 40 comparator	Audio; administered during procedure	Bone marrow biopsy & aspiration	30
Shahsavari H, et al 2017[78]	Outpatient: bronchoscopy department at 1 hospital	RCT - two-arm parallel design	40 reflexology 40 comparator	Reflexology; administered before procedure	Flexible bronchoscopy	15 - 45
Shenefelt PD, et al 2013[79]	Outpatient: dermatologic surgery clinic at 1 hospital	RCT - multiple arm parallel design	13 guided imagery live induction 13 guided imagery Recorded induction 13 comparator	Cognitive behavioural therapy; administered before & during procedure	Dermatologic procedures	10 - 90
Simmons D, et al 2004[80]	Outpatient: ophthalmology department in 1 hospital	RCT - multiple arm parallel design	20 massage 20 verbal coaching & slow breathing 20 massage, verbal coaching & slow breathing 20 comparator	Massage, verbal coaching & breathing techniques; administered before & during procedure	Cataract surgery	30 - 45
Snow A, et al 2012[81]	Outpatient: cancer treatment centre at 1 hospital	RCT - two-arm parallel design	41 hypnosis 39 comparator	Hypnosis; administered before & during procedure	Bone marrow aspiration/ biopsy procedure	30

Sources	Setting	Design	Study participants	Comfort Intervention	Clinical procedure	Clinical procedure timings (minutes)
Sobana R, et al 2015[82]	Outpatient: gastrointestinal endoscopy department at 1 hospital	RCT - two-arm parallel design	30 music 30 comparator	Audio; administered before procedure	Upper gastrointestinal endoscopy	30
Trambert T, et al 2014[83]	Outpatient: breast care centre at 1 hospital	RCT - multiple arm parallel design	30 lavender-sandalwood 30 orange-peppermint 28 comparator	Aromatherapy; administered during procedure	Breast biopsy	30 - 60
Ugras GA, et al 2018[84]	Inpatient: otorhinolaryngology surgery at 1 hospital	RCT - multiple arm parallel design	45 natural sounds 45 classical Turkish music 45 classical western music 45 comparator	Audio; administered before procedure	Otorhinolaryngology surgery	15 - 720
Walker MR, et al 2014[85]	Outpatient: urology department at 1 hospital	RCT - two-arm parallel design	22 virtual reality 23 comparator	Virtual reality; administered during procedure	Cystoscopy	15 - 30
Weeks BP, et al 2011[86]	Outpatient: cardiac catheterization laboratory in 1 hospital	RCT - multiple arm parallel design	30 loudspeaker music intervention 34 focused music intervention 34 comparator	Audio; administered during procedure	Coronary angiography	30 - 40
Wu KL, et al 2014[87]	Outpatient: cardiac catheterization laboratory in 1 hospital	RCT - multiple arm parallel design	43 accessibility-enhanced multimedia informational education (AEMIE) 46 instructional DVD education 46 comparator	Education/ information; administered before & during procedure	Cardiac catheterisation	30 – 40
Xiaolian J, et al 2015[88]	Outpatient: endoscopy centre at 1 hospital	RCT - multiple arm parallel design	60 visual 60 audio-visual 60 comparator	Visual & audio-visual; administered during procedure	Colonoscopy	30

Electronic Supplement C – Data extraction table

Sources	Comfort Intervention	Outcome measures	Intervention/comparator	Main outcomes										
				Data reported before clinical procedure					Data reported after clinical procedure/ mean magnitude of reduction*					
				Mean	Median	SD/SE‡	IQR/ range	P-value	Mean	Median	SD/ SE‡	IQR/ range	95% CI	P-value
Ahlander BM, et al 2018[43]	Education/ information	STAI	Video information:	-	35	-	28, 43	*p*=0.10	-	28	-	22.5, 36	-	*p*=0.20
			comparator:	-	35	-	28, 43		-	30	-	24, 38	-	
		HAD	Video information:	-	6	-	2, 9	*p*= 0.01	-	-	-	-	-	-
			comparator:	-	6.6	-	3, 8.5		-	-	-	-	-	-
Angioli R, et al 2014[44]	Audio	STAI	Music:	39.75	-	8.94	-	*p*>0.05	27.59	-	6.3	-	-	*p*<.001
			Comparator:	39.15	-	7.42	-		32.66	-	11.6	-	-	
Argstatter H, et al 2006[45]	Audio & coaching	STAI	Music:	-	-	-	-	-	7.3*	-	9.4	-	-	*p*=0.05
			Coaching:	-	-	-	-	-	7.3*	-	9.4	-	-	
			Comparator:	-	-	-	-	-	7.3*	-	9.4	-	-	
Björkman I, et al 2013[46]	Audio	STAI	Music:	-	-	-	-	-	-	-	-	-	-	*p*=0.007†
			Comparator:	-	-	-	-	-	-	-	-	-	-	
		Relaxation	Music:	-	-	-	-	-	-	-	-	-	-	*p*=0.065†
			Comparator:	-	-	-	-	-	-	-	-	-	-	
		Wellbeing	Music:	-	-	-	-	-	-	-	-	-	-	*p*=0.006† †favours music
			Comparator:	-	-	-	-	-	-	-	-	-	-	
Buffum MD, et al 2006[47]	Audio	STAI	Music:	38.57	-	10.5	-	*p*=0.149	35.2	-	9.7	-	-	*p*=0.05
			Comparator:	36.23	-	10.5	-		35.1	-	10.59	-	-	
Chlan L, et al 2000[48]	Audio	STAI	Music:	36.9		12.5		*p*=0.28	34.5	-	10	-	-	*p*=0.002
			Comparator:	40.2		11.9			41.8	-	13.5	-	-	
		Satisfaction	Music:	-	-	-	-	-	-	-	-	-	-	*p*=0.11‡ †favours music
			Comparator:	-	-	-	-	-	-	-	-	-	-	
		Discomfort	Music:	-	-	-	-	-	4.3	-	2.1	-	-	*p*=0.026
			Comparator:	-	-	-	-	-	5.2	-	1.7	-	-	
Choi SM, et al 2016[49]	Empathic attention	VAS-A (1-10mm)	Verbal empathy:	-	30	-	10, 55	*p*=0.682	-1.2*	-	-	-	-4.1,1.8	*p*<0.05

Sources	Comfort Intervention	Outcome measures	Intervention/comparator	Main outcomes										
				Data reported before clinical procedure					Data reported after clinical procedure/ mean magnitude of reduction*					
				Mean	Median	SD/SE‡	IQR/ range	P-value	Mean	Median	SD/ SE‡	IQR/ range	95% CI	P-value
		Satisfaction	Verbal empathy/ touch:	-	30	-	10, 55		-0.3*	-	-	-	-5.7, 1.9	
			Comparator:	-	37	-	20, 59		-0.3*	-	-	-	-2.9, 2.3	
			Verbal empathy:	-	-	-	-	-	-	-	-	-	-	
			Verbal empathy/ touch:	-	-	-	-	-	-	-	-	-	-	$p>0.05$‡ † in all groups
			Comparator:	-	-	-	-	-	-	-	-	-	-	
Diette GB, et al 2003[50]	Audio-visual	STAI	Audio-visual:	43.2	-	-	-	$p>0.05$	44.8	-	-	-	-	$p=0.084$
			Comparator:	43.8	-	-	-		45.6	-	-	-	-	
Drahota A, et al 2008[51]	Audio-visual	STAI	Audio-visual:	41.4	-	12.5	-	-	27.91	-	9.86	-	-	-
			Comparator:	39.2	-	13	-	-	27.2	-	7.44	-	-	-
Eslami J, et al 2018[52]	Aromatherapy	STAI	Lavandula angustifolia:	43.9	-	9.71	-	-	31.1	-	6.44	-	-	$P<0.001$‡
			Citrus aurantium L.:	43.9	-	7.88	-	-	30.17	-	5.59	-	-	$P<0.001$‡
			Comparator:	39.7	-	10.02	-	-	40.7	-	9.69	-	-	$P=0.975$ † Compared to comparator
Fang AS, et al 2016[53]	Audio-visual	STAI	Video glasses:	36	-	11.3	-	$p=0.40$	-7.7*	-	9.9	-	-	$p=0.0335$
			Comparator:	33.8	-	12.3	-		-4.4*	-	9.4	-	-	
Frank LS, et al 2007[54]	Massage therapeutic touch & reflexology	Nervousness	Therapeutic touch:	69.9	-	42.6	-	$p=0.76$	−41*	-	46	-	-	$p=0.77$
			Comparator:	67.1	-	34.8	-		−44*	-	41	-	-	

Sources	Comfort Intervention	Outcome measures	Intervention/comparator	Main outcomes										
				Data reported before clinical procedure					Data reported after clinical procedure/ mean magnitude of reduction*					
				Mean	Median	SD/SE‡	IQR/ range	P-value	Mean	Median	SD/ SE‡	IQR/ range	95% CI	P-value
		Tense	Therapeutic touch:	66.1	-	33.4	-	*p*=0.71	−40*	-	46	-	-	*p*=0.80
			Comparator:	69.2	-	36.7	-		−37*	-	41	-	-	
		Fearful	Therapeutic touch:	60.6	-	43.8	-	*p*=0.86	−35*	-	55	-	-	*p*=0.43
			Comparator:	67.7	-	34.8	-		−43*	-	48	-	-	
Hayes A, et al 2003[55]	Audio	STAI	Music:	36.7	-	9.1	-	-	32.3	-	10.4	-	-	*p*=0.007
			Comparator:	36.1	-	8.3	-	-	34.6	-	11.5	-	-	
Heidaria F, et al 2017[56]	Therapeutic touch	STAI	Hand reflexology:	49.82	-	1.74	-	*p*=0.78	42.67	-	1.47	-	-	*p*=0.001
			Comparator:	49.71	-	1.65	-		48.66	-	1.78	-	-	
Hızlı F, et al 2015[57]	Hypnosis	BAI	Hypnotherapy:	6	-	-	0–28	-	2	-	-	0–23	-	*p*=0.001
			Comparator:	9	-	-	0–28	-	8	-	-	0–34	-	
		HAS	Hypnotherapy:	11	-	-	2 –29	-	6	-	-	0–22	-	*p*=0.005
			Comparator:	11.5	-	-	0–31	-	11.5	-	-	1–38	-	
Hozumi H, et al 2017[58]	Aromatherapy	Anxiety VAS (1-10mm)	Vehicle (sham):	-	-	-	-	-	3	-	7‡	-	-	*P*>0.05
			Lavender:	-	-	-	-	-	3	-	6‡	-	-	*P*>0.05
			Grapefruit:	-	-	-	-	-	2	-	8‡	-	-	*P*>0.05
			Osmanthus:	-	-	-	-	-	2	-	7‡	-	-	*P*<0.05
			Comparator:	-	-	-	-	-	3	-	8‡	-	-	*P*>0.05
Hu PH, et al 2010[59]	Aromatherapy	STAI	Neroli:	41.79	-	10.28	-	*p*=0.734	30.79	-	3.89	-	-	*p*=0.079
			Comparator:	43.46	-	10.41	-		36.46	-	9.31	-	-	
Hudson BF, et al 2015[60]	Audio, Audio-visual, interaction & stress ball	STAI	Music:	38.6	-	8.78	-	-	38.6	-	10.31	-	-	*p*=0.03
			DVD:	39.86	-	10.3	-	-	37.56	-	10.28	-	-	
			Interaction:	37.74	-	9.19	-	-	35.29	-	8.94	-	-	

Sources	Comfort Intervention	Outcome measures	Intervention/comparator	Main outcomes										
				Data reported before clinical procedure					Data reported after clinical procedure/ mean magnitude of reduction*					
				Mean	Median	SD/SE‡	IQR/ range	P-value	Mean	Median	SD/ SE‡	IQR/ range	95% CI	P-value
		S-NRS	Stress ball:	41.54	-	11.0	-	-	38.54	-	8.58	-	-	
			Comparator:	39	-	7.72	-	-	41.29	-	9.72	-	-	
			Music:	4.49	-	2.71	-	-	3.79	-	2.42	-	-	
			DVD:	4.65	-	2.32	-	-	3.31	-	2.24	-	-	
			Interaction:	4.33	-	2.31	-	-	3	-	1.96	-	-	*p*=0.06
			Stress ball:	4.8	-	2.43	-	-	3.6	-	2	-	-	
			Comparator:	4.33	-	2.13	-	-	4.38	-	2	-	-	
		A-NRS	Music:	-	-	-	-	-	4.76	-	0.06	-	-	-
			DVD:	-	-	-	-	-	4.7	-	0.06	-	-	-
			Interaction:	-	-	-	-	-	4.64	-	0.06	-	-	-
			Stress ball:	-	-	-	-	-	4.7	-	0.06	-	-	-
			Comparator:	-	-	-	-	-	4.58	-	0.06	-	-	-
Jiménez-Jiménez M, et al 2013[61]	Audio	STAI Control of intraoperative stress feeling	Music:	33.7	-	9.3	-	*p*=0.78	-	-	-	-	-	-
			Comparator:	34.1	-	10	-		-	-	-	-	-	-
			Music:	-	-	-	-	-	1.31	-	0.3	-	-	*p*=0.02
			Comparator:	-	-	-	-	-	2.36	-	0.3	-	-	
Kekecs Z, et al 2014[62]	Education/ information	STAI	Education / therapeutic suggestion:	41.59	-	10.1	-	*p*=0.254	-	-	-	-	-	-
			Comparator:	44.22	-	11.5	-		-	-	-	-	-	-
		Wellbeing (scale 1-9)	Education / therapeutic suggestion:	6	-	-	3–9	*p*=0.98	6	-	-	3–9	-	*p*=0.084
			Comparator:	6	-	-	2–9		6	-	-	2–9	-	
		Calmness (scale 1-7)	Education / therapeutic suggestion:	4.5	-	-	2–7	*p*=0.37	4.5	-	-	2 –7	-	*p*=0.039
			Comparator:	4	-	-	2–7		4	-	-	3 –7	-	
			High-info.											

Sources	Comfort Intervention	Outcome measures	Intervention/comparator	Main outcomes										
				Data reported before clinical procedure					Data reported after clinical procedure/ mean magnitude of reduction*					
				Mean	Median	SD/SE‡	IQR/ range	P-value	Mean	Median	SD/ SE‡	IQR/ range	95% CI	P-value
Kola S, et al 2013[63]	Education/ information	STAI	Low monitor:	17.75	-	6.79	-	-	13.75	-	5.27	-	-	-
			High monitor:	18.94	-	7.12	-	-	12.75	-	3.26	-	-	-
			Low-info. Low monitor		-		-	-		-		-	-	-
			Low monitor:	17.39	-	6.59	-	-	13.33	-	4.41	-	-	-
			High monitor:	16.75	-	5.48	-	-	12.81	-	4.11	-	-	-
			Comparator		-		-	-		-		-	-	-
			Low monitor:	18.79	-	5.83	-	-	14.3	-	5.24	-	-	-
			High monitor:	16.89	-	5.09	-	-	13.42	-	3.43	-	-	-
Kwekkeboom KL, et al 2003[64]	Audio & distraction	STAI	Music:	36.2	-	13.0	-	-	32.1	-	12.46	-	-	-
			Distraction:	42.8	-	13.0	-	-	36.5	-	12.46	-	-	-
			Comparator:	36.2	-	13.0	-	-	29.2	-	12.46	-	-	-
Lang EV, et al 2000[65]	Empathic attention & hypnosis	Anxiety VAS (1-10)	Attention:	3.8	-	-	-	-	2.5	-	-	-	-	-
			Hypnosis:	3.8	-	-	-	-	1	-	-	-	-	-
			Comparator:	3.5	-	-	-	-	3.8	-	-	-	-	-
LEE WL, et al 2017[66]	Audio	STAI	Meditative:	40.26	-	5.68	-	*p*=0.50	34.97	-	6.73	-	-	*p*=0.02
			Comparator:	37.73	-	6.73	-		38.38	-	5.66	-	-	
McSherry, T, et al 2018[67]	Virtual reality	Anxiety VNS (1-10)	Immersive virtual reality (IVR) - 1st dressing: change	4.8	-	2.9	-	-	3.5	-	3	-	-	*P*>0.05
			IVR - 2nd dressing change:	4.1	-	2.4	-	-	3.5	-	2.6	-	-	
Ng MY, et al 2016[68]	Audio	STAI	Music:	-	10	-	7, 13	*P*=0.328	-	8	-	6, 10	-	*p*=0.721
			Comparator:	-	10	-	8, 13		-	9	-	6, 12.5	-	
Navidian A, et al 2018[69]	Audio-visual	Willingness to repeat the	Music:	-	-	-	-	-	-	-	-	-	-	*p*=0.04‡ †favours music

Sources	Comfort Intervention	Outcome measures	Intervention/comparator	Main outcomes											
				Data reported before clinical procedure					Data reported after clinical procedure/ mean magnitude of reduction*						
				Mean	Median	SD/SE‡	IQR/ range	P-value	Mean	Median	SD/ SE‡	IQR/ range	95% CI	P-value	
		clinical procedure (% survey)	Comparator:	-	-	-	-	-	-	-	-	-	-		
Nilsson U, et al 2009[70]	Audio	Anxiety NRS (1-10)	Music:	-	2	-	0, 4	*p*=0.479	-	-	-	-	-	-	
			Comparator:	-	2	-	0, 4		-	-	-	-	-	-	
		Relaxation NRS (1-10)	Music:	-	-	-	-	-	-	8	-	5, 9	-	*p*=0.218	
			Comparator:	-	-	-	-	-	-	8	-	4, 9	-		
		Short STAI	Music:	-	-	-	-	-	-	15	-	14, 15	-	*p*=0.932	
			Comparator:	-	-	-	-	-	-	15	-	13, 15	-		
		Discomfort NRS (1-10)	Music:	-	-	-	-	-	-	0.5	-	0, 2	-	*p*=0.193	
			Comparator:	-	-	-	-	-	-	1	-	0, 3	-		
Nilsson U, et al 2012[71]	Audio	Anxiety NRS (1-10)	Music:	5.3	-	2	-	-	-	-	-	-	-	-	
			Comparator:	5.4	-	2.4	-	-	-	-	-	-	-	-	
		Enviroment NRS (1-10)	Music:	-	-	-	-	-	9	-	1.7	-	-	*p*<0.0001‡ †favours music	
			Comparator:	-	-	-	-	-	7.7	-	3	-	-		
		Relaxation NRS (1-10)	Music:	-	-	-	-	-	5.6	-	3	-	-		
			Comparator:	-	-	-	-	-	6	-	3.1	-	-		
		Discomfort NRS (1-10)	Music:	-	-	-	-	-	-	0.8	-	0–10	-		
			Comparator:	-	-	-	-	-	-	2	-	0–8	-		
Packiam VT, et al 2018[72]	Audio	STAI	Music:	33.7	-	8.9	-	*p*=0.61	-	-	-	-	-	-	
			Comparator:	34.4	-	9.9	-		-	-	-	-	-	-	
		Satisfaction VAS (0-10)	Music:	-	-	-	-	-	8.8	-	1.6	-	-	*p*= 0.29	
			Comparator:	-	-	-	-	-	8.5	-	1.9	-	-		
		Willingness to repeat VAS (0-10)	Music:	-	-	-	-	-	8.2	-	2.7	-	-	*p*= 0.92	
			Comparator:	-	-	-	-	-	8.1	-	2.2	-	-		
	Audio	STAI	Vedic chants:	40.4	-	8.8	-	-	38.5	-	10.7	-	-	-	

Sources	Comfort Intervention	Outcome measures	Intervention/comparator	Main outcomes										
				Data reported before clinical procedure					Data reported after clinical procedure/ mean magnitude of reduction*					
				Mean	Median	SD/SE‡	IQR/ range	P-value	Mean	Median	SD/ SE‡	IQR/ range	95% CI	P-value
Padam A, et al 2017[73]			Music:	41.8	-	9.9	-	-	38	-	8.6	-	-	-
			Comparator:	40.5	-	8.7	-	-	39.1	-	8.8	-	-	-
Ripley L, et al 2014[74]	Audio	Short STAI	Music:	-	-	-	-	-	8	-	-	7-11	-	*p*=0.36
			Comparator:	-	-	-	-	-	9	-	-	8-12	-	
Rosen J, et al 2013[75]	Massage, therapeutic touch & reflexology	STAI	Massage:	37.67	-	12.5	-	*p*=0.427	31.15	-	1.54	-	-	*p*=0.9720
			Attention:	40.45	-	12.9	-		31.83	-	2.23	-	-	
Schupp CJ, et al 2005[76]	Empathic attention & hypnosis	STAI	Low STAI (<43)											
			Attention:	31.1	-	6.9	-		-	-	-	-	-	-
			Hypnosis:	33.5	-	5.7	-	*p*>0.05	-	-	-	-	-	-
			Comparator:	34	-	5.5	-		-	-	-	-	-	-
		Time course of patients' anxiety self-rating (0-10)	Attention:	-	-	-	-	-	4.85	-	-	-	-	*p*>0.05
			Hypnosis:	-	-	-	-	-	1.98	-	-	-	-	
			Comparator:	-	-	-	-	-	2.03	-	-	-	-	
		STAI	High STAI (≥43)											
			Attention:	53.8	-	7.5	-		-	-	-	-	-	-
			Hypnosis:	51.1	-	6.6	-	*p*<0.05	-	-	-	-	-	-
			Comparator:	53.3	-	7.7	-		-	-	-	-	-	-
		Time course of patients' anxiety self-rating (0-10)	Attention:	-	-	-	-	-	3.84	-	-	-	-	*P*=0.06
			Hypnosis:	-	-	-	-	-	3.35	-	-	-	-	
			Comparator:	-	-	-	-	-	2.03	-	-	-	-	
Shabanloei R, et al 2010[77]	Audio	STAI	Music:	52.9	-	6.94	-	*P*=0.852	43.24	-	5.41	-	-	*P*=0.27
			Comparator:	52.18	-	7.29	-		46.42	-	7.2	-	-	
Shahsavari H, et al 2017[78]	Reflexology	Anxiety VAS (1-10mm)	Reflexology:	4.35	-	0.33	-	*p*=0.2	2.83	-	0.23	-	-	*p*>0.001
			Comparator:	3.78	-	0.29	-		4.88	-	0.34	-	-	

Sources	Comfort Intervention	Outcome measures	Intervention/comparator	Main outcomes										
				Data reported before clinical procedure					Data reported after clinical procedure/ mean magnitude of reduction*					
				Mean	Median	SD/SE‡	IQR/ range	P-value	Mean	Median	SD/ SE‡	IQR/ range	95% CI	P-value
Shenefelt PD, et al 2013[79]	Cognitive behavioural therapy	Anxiety SUD (0-10)	Guided imagery live:	3.31	-	-	0 -7		0.77	-	-	0-3	-	
			Guided imagery recorded:	3.38	-	-	0-8	*P*>0.05	0.77	-	-	0-5	-	*P*>0.05
			Comparator:	3.15	-	-	0-10		1.15	-	-	0-4	-	
Simmons D, et al 2004[80]	Massage, verbal coaching & breathing techniques	Anxiety Likert (0-10)	Massage:	-	-	-	-	-	3.65	-	-	1.7	-	-
			Verbal coaching/ slow breathing:	-	-	-	-	-	3.1	-	-	2.2	-	-
			Massage/ verbal coaching:	-	-	-	-	-	2.75	-	-	1.5	-	-
			Comparator:	-	-	-	-	-	5.85	-	-	1.9	-	-
		Discomfort Likert (0-10)	Massage:	-	-	-	-	-	4.3	-	-	2	-	-
			Verbal coaching/ slow breathing:	-	-	-	-	-	3.5	-	-	2.2	-	-
			Massage/ verbal coaching:	-	-	-	-	-	4.15	-	-	2.3	-	-
			Comparator:	-	-	-	-	-	5.95	-	-	1.9	-	-
Snow A, et al 2012[81]	Hypnosis	VAS-A (1-100mm)	Hypnosis:	-	-	-	-	-	-22*	-	18‡	-	-	*p*=0.026
			Comparator:	-	-	-	-	-	-13*	-	6‡	-	-	
Sobana R, et al 2015[82]	Audio	Short STAI	Music:	-	-	-	-	-	-6.1*	-	4.19	-	-	-
			Comparator:	-	-	-	-	-	0.06*	-	1.2	-	-	-
Trambert T, et al 2014[83]	Aromatherapy	STAI	Lavender-sandalwood:	-	-	-	-	-	-11*	-	-	35,4	-	-

Sources	Comfort Intervention	Outcome measures	Intervention/comparator	Main outcomes										
				Data reported before clinical procedure					Data reported after clinical procedure/ mean magnitude of reduction*					
				Mean	Median	SD/SE‡	IQR/ range	P-value	Mean	Median	SD/ SE‡	IQR/ range	95% CI	P-value
			Orange-peppermint:	-	-	-	-	-	-6*	-	-	-33,10	-	-
			Comparator:	-	-	-	-	-	-4*	-	-	-28,23	-	-
Ugras GA, et al 2018[84]	Audio	STAI	Natural sounds:	39.11	-	4.71	-	*p*<0.001	34.38	-	4.71	-	-	*p*<0.001
			Turkish music:	41.71	-	9.89	-		35.44	-	7.66	-	-	
			Classical music:	41.93	-	9.51	-		35.71	-	10.28	-	-	
			Comparator:	43.51	-	6.64	-		44.09	-	6.47	-	-	
Walker MR, et al 2014[85]	Virtual reality	VAS-A (1-100mm)	Virtual reality:	4.9	-	-	-	-	5.6	-	-	-	-	-
		Unpleasant VAS (1-100mm)		5.2	-	-	-	-	5.1	-	-	-	-	-
		VAS-A (1-100mm)	Comparator:	-	-	-	-	-	6.2	-	-	-	-	-
		Unpleasant VAS (1-100mm)		-	-	-	-	-	5.3	-	-	-	-	-
Weeks BP, et al 2011[86]	Audio	Anxiety NRS	Loudspeaker music:	-	-	-	-	-	2	-	-	1–9	-	*p*<0.05
			Focused music:	-	-	-	-	-	2	-	-	1–8	-	*p*<0.05
			Comparator:	-	-	-	-	-	5	-	-	1–10	-	*p*>0.05
Wu KL, et al 2014[87]	Education/ information	STAI	Accessibility-enhanced multimedia informational education:	-	-	-	-	-	16.33	-	-	-	-	*p*<0.05
			Instructional DVD education:	-	-	-	-	-	13.25	-	-	-	-	*p*>0.05
			Comparator:	-	-	-	-	-	10.16	-	-	-	-	*p*>0.05

Sources	Comfort Intervention	Outcome measures	Intervention/comparator	Main outcomes										
				Data reported before clinical procedure					Data reported after clinical procedure/ mean magnitude of reduction*					
				Mean	Median	SD/SE‡	IQR/ range	P-value	Mean	Median	SD/ SE‡	IQR/ range	95% CI	P-value
Xiaolian J, et al 2015[88]	Visual & Audio-visual	STAI	Visual:	33.35	-	10.3	-	p=0.637	28.2	-	6.93	-	-	*p*=0.169
			Audio-visual:	34.13	-	8.85	-		29.18	-	7.08	-	-	
			Comparator:	35	-	9.3	-		30.88	-	9.32	-	-	