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Overview of Reviews

The Cochrane Library and procedural pain in children: an overview of reviews

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Background: Procedural pain in children is highly prevalent, a major source of pain, stress and anxiety, and can have negative short- and long-term effects. Research addressing effective pain management strategies is complex, presenting challenges for clinically relevant synthesis.

Objective: To summarize Cochrane reviews assessing the effects of various interventions used for pain in non-neonatal children undergoing painful medical procedures.

Methods: The *Cochrane Database of Systematic Reviews* was systematically searched for reviews of interventions for pain in children outside of the neonatal period, undergoing painful medical procedures. The type of data to be extracted was determined a priori, and a single author performed data extraction. The Cochrane Library was searched using the terms 'procedural pain' and 'procedures'. Reviews examining acute procedural pain in older infants, children and adolescents were included. Interventions included topical anaesthetics (eutectic mixture of local anaesthetics and amethocaine), sweet tasting substances, cognitive therapy, behavioural therapy and combined cognitive-behavioural therapy(CBT). Data on self-reported, behavioural and observer pain intensity and pain distress were extracted.

Main results: Four systematic reviews were included in the overview. There was evidence that self-reported pain [risk ratio (RR) 0.63; 95% confidence interval (CI) 0.45–0.87], behavioural measures of pain (RR 0.71; 95% CI 0.52–0.96) and all pain scales combined (RR 0.69; 95% CI 0.55–0.87) were significantly less with amethocaine than with eutectic mixture of local anaesthetics. Results of trials of other interventions are reported in this article but heterogeneity of the combined effects is high.

Authors' conclusions: Amethocaine provides superior pain relief when compared with eutectic mixture of local anaesthetics for the procedure of intravenous cannulation. From the data contained in this overview, there is no current evidence of benefit supporting the use of 12% sucrose for older infants and toddlers or sweet gum for toddlers undergoing needle pain. Potentially efficacious nonpharmacological interventions may include distraction, hypnosis, combined cognitive-behavioural interventions, non-nutritive sucking and video distraction; however, further research is required as results are mixed. An integrated approach using multiple modalities encompassing both the physiological and psychological aspects of pain is compelling and warrants further study in paediatrics.

Keywords: children, Cochrane Library, distress, interventions, meta-analysis, needle, pain, procedures, overview

Editors' Note: *Overviews of reviews, compiling evidence from multiple Cochrane reviews into one accessible and usable document, are a regular feature of this journal. Our aim for each overview is to focus on the treatment question, 'which treatment should I use for this condition?', and to highlight the Cochrane reviews and their results in doing so. It is our hope that the overview will serve as a 'friendly front end' to the Cochrane Library, allowing the reader a quick overview (and an exhaustive list) of Cochrane reviews relevant to the clinical decision at hand.*

Plain language summary

Children experience pain for multiple reasons in the healthcare setting; short painful procedures to help with diagnosis and treatment are one of the most common. Pain in children is stressful for the child,

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family and caregivers and effects of under-treatment can be negative and long-lasting. The experience of pain for a child is complex and is usually accompanied by anxiety, fear and behavioural changes. While research into the best management of children's pain is improving, much work is still needed.

This overview is intended to summarize the systematic reviews of interventions studied to decrease paediatric pain that are currently available in the Cochrane Library. Given their unique physiology, research relevant to the management of newborns in the first month of life is not reviewed here. Four reviews relevant to the management of children's pain are currently available.

Several approaches can help to decrease the pain experienced by children in the hospital or clinic setting. Topical numbing creams can reduce the pain from needles for tests or treatments. Specifically, amethocaine was found to be more effective with quicker onset of effect than eutectic mixture of local anaesthetics (EMLA), although new topical anaesthetics warrant further study. There is no evidence that sweet tasting substances are effective for children outside the neonatal period from the studies in this overview. Behavioural therapies such as distraction and hypnosis are effective, inexpensive and can be used in conjunction with pharmacological analgesics with minimal resource use. Further research is required to study the additive effects of medical and psychological therapies in the treatment of children's procedural pain, as it stands to reason that combining the therapies might confer further benefit.

Background

Description of the condition

Under-treated paediatric pain is an increasingly recognized major health problem. It is highly prevalent and is one of the most common reasons for healthcare encounters (1–4). The World Health Organization and key paediatric and pain societies have advocated for optimizing pain treatment in children (5).

Over the last half-century, painful experiences from procedures related to prevention and diagnosis of disease in children has increased such that recent generations of children experience routine procedural pain in a manner and volume that is new to the human experience. Locations for these routine painful experiences are diverse and include the school setting, the public health clinic, the emergency department and inpatient wards. The average child in developed countries receives a minimum of 18 skin-puncturing injections by the age of 16, in simply following the currently recommended vaccination schedule; the majority of these injections occur in the developmentally critical first 6 years of life.

Common settings for procedural pain in children include acute care settings such as general emergency departments, intensive care units, burn care units and dental clinics as well as those settings involved in routine preventative care such as immunization clinics. Children with chronic complex disease are a particularly vulnerable population, frequently incurring painful procedures as both inpatients and outpatients. Common brief procedures for diagnosis or therapy include venipuncture, intravenous catheterization (IVC), capillary blood sampling, urinary catheterization, intramuscular (IM) injections, lumbar puncture (LP), laceration repair, nasogastric tube insertion, nasal aspiration, joint aspiration and burn dressings. Other more specialized brief procedures include bone marrow aspiration, central line insertion, central port access, arterial puncture/cannulation, biopsies and endotracheal intubation. Unfortunately, reviews of diverse settings, including those specializing in the care of children, repeatedly demonstrate poor management of acute pain (1). Thus, the need for ongoing research, education and knowledge translation for and in these settings is imperative.

Prompt and effective prevention or treatment of pain in children is important for their immediate comfort as well as their optimal life-long development. Poor pain management has a negative impact on quality of life, the effects of which may be evident even years after the painful experience (6–8). A growing body of research describes harmful, permanent effects resulting from procedural pain on immune function, neurophysiology, healthcare behaviour and attitudes (9). These lasting effects from early childhood pain result in large economic costs to society. Young age at the time of the painful experience, frequency of painful exposures and memory of painful exposures are all thought to affect the magnitude of these sustained negative sequelae (10–13).

Our understanding of pain has significantly evolved over the last three decades, from a time when clinicians believed that small infants were unable to feel pain to our current understanding that the youngest of humans, with their immature nervous systems, in fact likely suffer the greatest impact from painful experiences (10,14–16). There has also been an evolution of our understanding of the biopsychosocial and developmental complexities of children's pain, and accordingly, how a multifaceted approach is needed to most comprehensively manage it (17). Pain has both sensory and emotional components, making its assessment and management in children challenging, where manifestations of anxiety can sometimes be difficult to distinguish from those of pain. Pain and anxiety are closely intertwined and both require appropriate attention for effective management.

Our understanding of children's pain has matured, and we now recognize that seemingly similar procedures can have differing pain intensities requiring varied interventions for different children (18,19). Trials have demonstrated the lack of effectiveness of commonly used analgesics such as acetaminophen to prevent pain for some short procedures (20–22). Our

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previous trust that systemic analgesia with powerful medications such as opioids would provide an easy cover-all method of pain treatment has been revised with our discovery that procedural pain benefits from targeted local pain relief, and the knowledge that side effects from systemic analgesia can be serious enough to warrant selective and cautious use of those drugs in many situations (23–27).

The ideal analgesic for short procedures should be safe and effective with quick onset and offset and minimal or no side effects. It should help to facilitate accomplishment of the procedure with minimal pain and maximal safety. We summarize the evidence surrounding various interventions for the management of procedural pain in children available in the Cochrane Library.

Description of the interventions

Pharmacological interventions

For procedural pain, focused local analgesia is essential and can optimize pain relief. While multiple general analgesics have been described for paediatric pain, many are inadequate when used alone for painful procedures (20–22) and may best be used as adjuncts to analgesia targeted specifically to relieve procedural pain. Furthermore, with the conceptual evolution of a multimodal analgesic approach, procedural analgesia can be augmented with appropriate combinations of procedure-targeted analgesics, nonpharmacological strategies, general analgesics and/or anxiolytics (17,28–33). Several interventions (such as lidocaine jelly for urethral catheterization) are highly procedure-specific, whereas others, such as sucrose, have broader applicability. In general, the strength of evidence surrounding the efficacy of these interventions is highly variable across procedures and all continue to be areas of ongoing study. However, these interventions are considered safe, easy to use, and with minimal side effects. Given the significant implications of undertreated pain in children, there is an inherent responsibility for healthcare providers to take all measures to minimize pain (34–38).

How the interventions might work

Topical anaesthetics

Topical anaesthetics have been shown to be effective for decreasing the pain from venipuncture, IVC insertion, immunization needle pain, LP, otitis media and neonatal circumcision. Some studies suggest that topical anaesthetics alone may not adequately address deeper tissue pain such as that from IM injection or LP. A wide variety of topical anaesthetics exist and include liposomal lidocaine (Maxilene), EMLA, tetracaine adrenaline and cocaine (TAC), amethocaine (Ametop), lidocaine-epinephrine-tetracaine (LET) gel vapocoolant sprays and ice.

The amino amide local anaesthetics (amethocaine and EMLA) alter depolarization of neurons by reversibly blocking cell membrane fast voltage-gated sodium channels. Amethocaine (4% tetracaine gel) requires only 30 minutes of application, does not require an occlusive dressing to ensure effectiveness and has a duration of 4–6 hours (39). EMLA cream contains an equal mixture of prilocaine and lidocaine and provides anaesthesia for 1–2 hours after application is removed. Time to onset for penetration of intact cutaneous tissues is at least 60 minutes and an occlusive (40–41) dressing is required to prevent loss of effectiveness through dehydration of the cream. The effect of both creams wears off in several hours after application. These creams should only be used on small areas of intact skin, and not on wounds, mucous membranes, eyes or ears. With EMLA use, methemoglobinemia may be a concern, and case reports of this disorder exist in children and adults with large surface area application (42,43). Common adverse effects may include pallor, erythema, oedema and vasoconstriction in the area of application.

Other topical anaesthetics with even shorter onset time such as liposomal lidocaine are now widely available. Further, the use of adjuncts such as iontophoresis (a technique using a small electric charge to deliver a medicine or other chemical through the skin) can further reduce onset time of these creams (44). Needle-free jet injection of local anaesthesia into the epidermis is a recent alternative to topical creams and provides the advantage of onset of analgesia within 1–3 minutes of application. The J-Tip device uses pressurized carbon dioxide to rapidly force 1% lidocaine into the subcutaneous tissue and recent paediatric studies of this intervention have demonstrated minimal discomfort with rapid provision of analgesia (45–47). Vapocoolant sprays, such as ethyl chloride (Pain-Ease), provide the advantage of immediate onset but results supporting the analgesic effectiveness in children have been mixed (48–51). Vapocoolant sprays including ethyl chloride, fluorohydrocarbon and alkane mixtures are thought to provide a temporary interruption of the pain sensation through activation of ion channels or desensitization of receptors involved with pain transmission (50–52). The rapid cooling of the skin surface secondary to evaporation of the volatile liquid spray has been reported to evoke discomfort and anxiety in some children. Some children are also alarmed by the noise from spray administration. Thus while vapocoolant sprays provide the advantage of immediate onset, results supporting the analgesic effectiveness in children have been mixed (48,49,51,53). Overall, there are a number of topical anaesthetic options for the treatment of procedure-related dermal pain that are available to clinicians.

Sucrose and other sweet-tasting solutions

Sweet-tasting solutions that have been examined in numerous randomized controlled trials (RCTs) have

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included sucrose, glucose and fructose. The effect of sucrose is thought to be related to the effect of the sweet taste on the brain, as opposed to the carbohydrate content of the sucrose (54). Taste-induced analgesia is thought to be modulated by endogenous opioid activity (55–58). However, debate about this mechanism is emerging through findings that administration of opioid antagonists may not interfere with the analgesic effect of oral glucose, as well as the lack of development of tolerance with repeated glucose administration (59–61). Other proposed mechanisms include an analgesic effect through non-opioid endogenous pain inhibiting systems, activation of dopamine release and initiation of the sucking response. Bypassing the tongue by administration of sucrose via nasogastric tube into the stomach has been demonstrated to be ineffective for pain relief, suggesting that the contact of sucrose with the taste buds of the tongue is important for the analgesic effect (57).

A recent small RCT of 24% sucrose versus water in 59 newborn infants undergoing heel lance using nociceptive brain activity readings (via electroencephalography and electromyography) as the primary outcome measures showed that recorded nociceptive brain activity did not differ significantly between the two groups. Interestingly, this study demonstrated a significant lowering of the pain score in the sucrose group, but despite this, the authors concluded that the ability of sucrose to reduce clinical observational pain scores after the painful event should not be interpreted as pain relief. The results of this single, small RCT have not been accepted as practice-changing but rather as hypothesis-generating (62–67). Experts in the field strongly advocate for the use of sucrose prior to short painful procedures (68). Ideally, the sucrose must be administered slowly, over 2 minutes, over the surface of the tongue to be effective. The analgesic effect is further improved when sucrose is combined with a sucking stimulus such as a pacifier (29,55). Onset of action may be as early as 10 seconds, with peak action in 2 minutes and duration of effect for only 5–10 minutes (69). The effect of sucrose has largely been studied in the neonatal population but evidence for an analgesic effect beyond the neonatal period is increasing (29,61,70,71). Mechanistic understanding about the effect of sucrose is generally derived from studies of the neonatal population and the potential effects and underlying mechanisms in children outside of the neonatal period are uncertain.

Nonpharmacological interventions

Nonpharmacological interventions generally target pain and distress by attempting to alter pain signals through modification of cognitive and affective pathways. They serve to reduce fear and anxiety, empower patients by participation in their own care and enhance patient cooperation. These interventions also optimize coping skills and the clinical environment. These techniques are non-invasive, inexpensive, require little equipment and in most cases brief training.

Nonpharmacological interventions can be divided into four major areas: physical techniques, environmental modification, cognitive interventions and behavioural interventions. Physical techniques include counter-stimulation, pinching, rubbing, cold or vibration (72), and refinement of injection technique (73). Environmental modifications include provision of a quiet area, dimming of lights, calm low voices, choice language use and minimal exposure to unfamiliar staff. Just as age influences pharmacological management in terms of drug safety and approval, nonpharmacological analgesic interventions have strong age and developmental considerations, as well. Interventions should be tailored and age-appropriate. Parent and caregiver education and preparation surrounding the use of these interventions is of utmost importance for success (73).

It should be noted that several nonpharmacological interventions draw from both cognitive and behavioural schools of thought and thus, cognitive–behavioural therapies (CBT) are often used in a combined manner. As pain and anxiety are inextricably linked for children, CBT is frequently examined for both states together. The majority of research studying CBT for management of pain and anxiety has been conducted for preschool-aged and older children.

Cognitive interventions

Cognitive therapy (CT) has long been thought to be effective in the management of procedure-related pain. This therapy attempts to identify and modify beliefs and negative emotions about a situation and, as such, facilitate positive coping behaviours. Some of these therapies are complex and require specially trained personnel to guide patients through them; however, simplified versions of this therapy have been adapted for use in areas with fewer personnel resources (74–76). The therapies include hypnosis, imagery, thought stopping, suggestion, coping self-statements and memory. These therapies may be combined with behavioural interventions for increased effect.

Hypnosis is an altered state of consciousness involving a narrowing of attention and suspension of critical judgement (77). Well-designed and carefully worded therapeutic suggestions allow the child to think concretely and optimize perceptual, sensory and performance abilities. Physiological processes otherwise thought to be inaccessible to voluntary control can be altered by the hypnotic process (77,78). Evidence supporting the effectiveness of hypnosis for medical procedures exists (79–82), yet barriers to its clinical use in many settings still exist. The success of hypnosis relies on the ability of the practitioner to correctly choose words that lead to relaxation and positive imagery and poor choice of words can lead to distress or failure of the technique. Institutions with specialized staff such as child life specialists may be best suited to provide this therapy. Thus, while some level of training is ideal, quick bedside hypnotic techniques such as the magic glove are relatively uncomplicated and

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quick to administer. The 'magic glove' technique may be particularly useful for the older child. It involves the concept of visualizing less sensation in an arm (the procedural arm) covered by an imaginary glove (77).

Suggestion is the provision of verbal or nonverbal reminders that the intervention will reduce pain or distress of the procedure. *Coping skills training* occurs when the child is provided with and is encouraged to repeat or think through some positive self-coping statements such as 'I can do this' or 'this will be over soon'. *Modelling* includes viewing positive coping behaviours during a staged or successful procedure by another child (as viewed on video). *Memory alteration* strategies include helping the child reframe negative memories into positive ones. *Thought stopping* is when the child repeats, 'stop' during times of distress or pain and helps to facilitate a sense of control over the child's own emotions. *Imagery* is a technique whereby a child is encouraged to imagine or describe a pleasant or favourite object or experience (day at the beach, enchanted forest, favourite holiday, etc.). Older children more capable of abstract thinking may experience alleviated physiological effects of pain and anxiety through guided imagery and relaxation and self-coping statements.

Behavioural interventions

Behaviour therapy is based on Pavlov's classical therapy and Skinner's operant conditioning, in which people learn to change their behaviour, without focusing on the underpinnings or explanations for the behaviour (83,84). These interventions include procedural preparation, distraction, breathing exercises, blowing out air, progressive muscle relaxation, modelling, rehearsal, desensitization, flooding, positive reinforcement, parent and staff coaching and training, and virtual reality (VR). Some behavioural therapies may be easier to use than CT in busy clinical settings.

Procedural preparation can include verbal instruction, leaflets, videos, play-modelling, tours and instruction on coping strategies. Preparation should be age-appropriate and generally increases the child's and parent's understanding of the reason and benefits of the procedure as well as possible undesired effects and concurrent attempts to mitigate those effects. Preparation is thought to desensitize the child and may be of most effect if provided several days before the procedure (85–88). Effective preparation can be more challenging in the acute care setting such as an emergency department when preparation time is short. If provided too close to the intervention, with not enough time to process the information, some children may experience increased distress. However for other children, less time to worry, with the provision of good information for understanding, may serve to be effective in distress reduction. Predictive child characteristics for accurate tailoring of such interventions are unclear.

Distraction is increasingly used in the clinical setting and includes use of movies, conversation, music and physical techniques. The distraction intervention is thought to help decrease pain, as explained by the gate-control theory of pain (89). In this theory, afferent pain signals emerge through large slow-conducting fibres from a pain source, the information from which is either closed to the brain at the spinal cord level if influenced by other competing distracters, or progresses through the open 'gate' to the brain if attention is fully focused on the pain at hand. The 'pain gate' can be shut by stimulating competing small touch nerve fibres from other mechanoreceptor sites through activities such as counter pressure, massage, ice or through release of modulating pleasure neurochemicals via other mechanisms. Distraction is short-acting and pain awareness will quickly recur when the child is no longer distracted. Numerous distracters have been examined and show some evidence of efficacy including bubbles, toys, music, party blowers, cartoons, positive imaging, pinwheels, books, kaleidoscopes, arithmetic and parental coaching models (90).

Virtual reality integrates real-time computer graphics, auditory, visual and tactile stimuli, body tracking devices and other sensory input devices to immerse patients in a computer-generated interactive virtual environment (91,92). The virtual environment is presented through a head mounted display and interaction occurs with use of motion-tracking devices attached to the hands or feet. The most effective VR experience provides the patient with a feeling of complete physical and sensory immersion in the virtual environment, and systems with more complex sensory environments including touch and smell are thought to deepen the sense of immersion (93,94). Haptic (tactile) feedback is sometimes provided using small devices that vibrate against gloved skin or within input devices. VR is thought to engage the sensorimotor system more fully than simple distractive stimuli and has the ability to present synchronized stimulations to multiple sensory channels and distract the patient's attention away from the painful stimulus (95–98). VR applications are more commonly used in the mental health field to treat phobias, anxiety disorders and schizophrenia (99). Applications for rehabilitation of traumatic brain injury, stroke and dementia also exist. However, a small number of studies investigating use of VR for pain management in children have recently been published and show some promise of benefit (100–104).

Music is thought to be distractive, relaxing and anxiolytic, although the exact underlying mechanism is unknown. The effect of music may be related to the past musical experiences of the listener and choice of music played, and patient-specific predictive factors for tailoring therapy are largely unclear. A few small functional magnetic resonance imaging studies have demonstrated consistent signalling in anxiolytic brain areas when familiar (versus unfamiliar) music is played. Music is thought to induce endocrine changes with decreased cortisol level and different gender-related testosterone changes. Hormonal alterations may in turn alter inflammatory mediators, neuron

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receptor expression and ultimately influence neuroplasticity. In paediatrics, several systematic reviews reveal benefit of music for children undergoing painful procedures (105–107). However, effect sizes are variable and studies are very heterogeneous across settings, interventions, procedures and outcomes.

Progressive Muscle Relaxation Training involves the technique of alternately tensing (for 10 seconds) and relaxing the muscles (for 20 seconds) progressively over the muscle groups from head to toe. The benefit is thought to be derived from the focus brought to the difference between the feelings of tension and the warmth, heaviness and relief of muscle relaxation.

Breathing exercises: The voluntary control of breath can modulate autonomic nervous system functions, including cardiac vagal tone, as measured by heart rate variability, vigilance and attention, chemoreceptor and baroreflex sensitivity, as well as the level of central nervous system excitation. Deep breathing can activate the parasympathetic nervous system and induce altered states of consciousness (108–109). Specialized techniques include breathing deeply into the abdomen (belly breathing), breathing against airway resistance, physical postures, holding the breath at different parts of the breath cycle, or breathing alternately through both nostrils or only one nostril (110–112).

Parental/caregiver interventions

Parent presence and interaction may have varied effect depending on development of child and individual effects such as parent and child temperament. In general, infants and young children will benefit from parental presence and interaction. However, notably anxious parents may serve to increase a child's own anxiety (113–115). Parental preparation regarding their tone of voice, choice of language, involvement in promoting coping behaviours results in less distressed parents, which in turn promotes coping and decreased anxiety in the child (86,87). Parental input with calm non-emotive relaxed voices, appropriate choice of language, nonprocedural talk, humour, and prompting of self-coping behaviours, distraction, relaxation can be of benefit (116,117). Interestingly, parental use of empathetic statements, verbal reassurance, apologizing, bargaining, intellectualizing, explaining or catastrophizing (118,119) usually serves to increase anxiety in children. An explanation for this is that the latter approach reflects the parent's emotional interpretation of events and in turn heightens the child's focus on the emotional aspects of the situation.

For infants

Cognitive–behavioural interventions that potentially alter an infant's ability to perceive pain are described separately here. Owing to the unique developmental stage of infancy, interventions in this age group always involve parent or caregiver interaction and are performed best when these individuals are educated regarding these techniques beforehand. Cognitive strategies largely include distraction such as toy-mediated (showing or interactive physical play) or video- and audio-mediated (short movies/cartoons and/or music) interventions. Behavioural strategies for infants are more numerous and generally include either direct or indirect interaction of the caregiver with the infant's body. Examples include rocking/holding, kangaroo care (skin-to-skin contact), swaddling/facilitated tucking, non-nutritive sucking, breastfeeding, touch/massage, parental voice and/or presence. Other interventions, described in the literature but less well-examined, include provision of familiar or pleasant smells throughout a painful procedure (olfactory stimulation), variations of position during procedures, variations of order of injections (most painful last for immunizations) and provision of formula throughout procedures (120).

Non-nutritive sucking: The placement of a pacifier in an infant's mouth will stimulate sucking behaviour without the benefit of nutrition. The initiation of the sucking reflex has been shown to have a calming and analgesic effect on neonates and infants. Sucking is thought to stimulate the release of serotonin from the brainstem, which may modify the perception of pain (121–123). This may occur through release of cholecystokinin, an opioid-modulating substance (124). Generally, the analgesic effect is greater when sucking and sucrose are combined than with sucking alone (29,56). The serotonin effects from sucking are improved with warmth from maternal skin and eye contact, as well as familiar smells and sounds.

Why it is important to do this overview

Children and their caregivers rightly expect optimal pain management from their healthcare providers. While knowledge surrounding effective pain management strategies continues to improve, we know that pain management is still insufficient and progress in this arena is slow (125–127). Reasons for this are variable but a core issue is the insufficient number and quality of RCTs of analgesic interventions in the paediatric pain literature. It is important to provide summative overviews of the progress in the development of this field to aid clinical knowledge translation and to further guide the maturity of high quality research. This overview provides a comprehensive synopsis of the evidence currently available in the Cochrane Library pertaining to paediatric procedural pain management and may be useful to busy clinicians, patients/families, educators and policy-makers.

Objectives

The objective of this overview is to summarize Cochrane reviews assessing the effects of various

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interventions for pain in children (excluding the neonatal group) undergoing various short painful medical procedures performed commonly during their medical care.

Methods

Criteria for considering reviews for inclusion

All Cochrane reviews assessing effects of an intervention for pain in children undergoing acute painful procedures were considered. Acute needle-related procedures are ubiquitous in varied medical units such as the emergency department, intensive care, inpatient and clinics and are commonly performed by a variety of medical practitioners. However, certain procedures are highly population-specific, and authors of this review made a decision to exclude those; these include circumcision, dental procedures, retinopathy of prematurity treatment and procedural sedation. Circumcision removes a large part of skin and the authors felt that the pain was likely quite different from that of needle punctures and other quick procedures. Specialized procedures such as treatment for retinopathy of prematurity were also considered unique to a specific population and setting. Dental procedures were excluded for similar reasons of specialized setting, practitioners and procedures. Procedural sedation was also excluded from this overview, as, while very appropriate for procedural analgesia in many cases, it is complex with mixed outcome measures (including measures of effectiveness of sedation) and there is a large body of research literature available, warranting its own separate overview.

The authors of this overview focused on older infants/toddlers and older children, as these groups were felt to be more clinically relevant to practitioners in acute care settings. Preterm infants are a subgroup being treated and/or convalescing in the neonatal intensive care unit, where procedures (such as treatment for retinopathy of prematurity) are often specialized owing to the unique needs of this patient population. Similarly, neonates in maternity units are distinct in the types of procedures and care they receive. Therefore, two reviews were excluded as they focused on neonates.

Trials were excluded if it did not meet the inclusion criteria, did not measure pain, were non-English, or were a duplicate of a trial reported in the included reviews.

Search methods for identification of reviews

The Cochrane Database of Systematic Reviews was searched for all reviews that assessed the effect of an intervention on pain in children aged 19 years and younger undergoing painful procedures. A number of terms were used in the search including 'procedural pain' and 'procedures'.

Types of outcome measures

The following a priori outcomes were specified for inclusion in this overview:

1. Self-reported pain
2. Observer-reported pain
3. Behavioural measures of pain
4. Pain distress (including anxiety, fear and distress) – self-reported, observer-reported and behavioural measures.

Physiological measurements of pain were excluded as it was felt they reflected proxies of pain, which have been poorly validated, rather than self-reported or behavioural (observer and behavioural) measurements of pain (128,129).

Data collection and analysis

Selection of reviews

All authors applied the inclusion criteria via discussion to reviews resulting from the electronic search. Four reviews (two on circumcision, one on retinopathy of prematurity and one on procedural sedation) were excluded. Six reviews initially met the criteria for inclusion.

The search update for potential relevant trials was conducted in March 2012 in the MEDLINE database for four of the included reviews with date of completion earlier than January 2010. Updated searches were carried out according to the search strategies outlined within each review (see Appendix 1). No language or document type restrictions were applied. A search update was conducted in the EMBASE database, in addition to the MEDLINE database, for one review (130) because of the lack of detail reported in the search strategy for this review and thus, subsequent lack of studies found in the former database. Three authors (SA, SC and AW) screened the records for new trials that met the inclusion criteria within the reviews. See Appendix 1 for detailed search strategies.

Data extraction and management

AW extracted the following data from the included reviews: population, intervention, comparison and outcomes, methodological quality of included trials and quantitative data. A research team member independently verified data extraction. When a discrepancy was detected in the data, both individuals examined the original data source for accuracy and reached consensus.

Data synthesis

Data were summarized according to original reporting strategies in the respective reviews.

For dichotomous data, one review (130) reported risk ratios (RR). For continuous data, two reviews (120,131) reported data in standardized mean differences (SMD) using the generic inverse method for

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a random effects model. One review (132) reported mean differences using the random effects model.

Review Manager 5.1 was used to pool the data. For those trials which did not report means and/or standard deviations, means were imputed with medians, and SDs were imputed with inter-quartile range (IQR) where SD = IQR/1.35. Data were pooled when more than one observer rated the same pain scale (as per Uman *et al*. (131)), where pooled mean = [(mean1 × N1) + (mean2 × N2)/(N1 + N2)] and pooled SD = square root of [(SD12 (N1 − 1) + SD22 (N2 − 1))/ N1 + N2 − 2]. Overall effects (such as *p* values) were reported when a summary statistic could not be derived.

Results

Description of included reviews

The current overview includes four reviews (120, 130–132), consisting of 46 trials (44 unique trials), and 13 additional new trials. In the Uman review (131), three trials were excluded from this overview as they were single trials and meta-analyses were not conducted for these studies. In the Pillai Riddell review (120), 11 of the 51 trials were included in this overview as they met the criteria for older infants/toddlers and older children.

While this overview had a non-neonatal focus, a few trials (29,70,133) from the Pillai Riddell review (120) did include a small amount of data from neonates (aged 0 months and older). As this data was minimal, could not be removed from the dataset, and contributed valuable information to the age group of interest, the authors decided to include these.

The population was divided into two groups, as defined by the respective reviews: older infants/ toddlers (range 0–48 months of age), and older children (range 3 months to 19 years of age). Procedures included in the reviews and additional trials included IVC, blood sampling (venipuncture or finger prick), subcutaneous (SC) and IM injection, finger and heel lance, urethral catheterization, port access, LP and bone marrow aspiration.

Characteristics of the reviews and newly added trials are summarized in Tables 1 and 2, respectively.

Methodological quality of included trials

Several quality assessments were used to determine the trials to be included in each review. Two reviews (130,131) used the Oxford Quality Scale of the Jadad scale. One (130) used the Cochrane ABCD concealment of allocation scale from the Cochrane Handbook, and one (132) used the Cochrane Risk of Bias assessment tool. Because of the psychological nature of the interventions and methodological issues with blinding in most trials, the Pillai review (120) utilized the Yates Quality of Study Design and Methods Scale.

Allocation concealment was reported for all trials in the Uman review (131) with a significant number of trials being unclear on how participants were allocated to groups. Blinding, withdrawals and treatment fidelity were poorly reported. All of the trials in the Lander review (130) had unclear reporting of allocation concealment and only one RCT adequately described their method of randomization. While only one trial did not employ blinding, those which did use blinding reported poorly on the description. All four trials in the Harrison review (132) had unclear risks of random sequence generation and selective outcome reporting, with low or unclear risks of allocation concealment and incomplete data reporting. Two of the trials had high risk of blinding bias and two had high risk of other potential risk of bias. Two of the 11 trials from the Pillai Riddell review (120) had high risk of bias in their total quality scores, and although the remaining trials had overall low risk scores, all but one trial had high risks of bias in blinding, outcome reporting and other potential sources of bias.

Summaries of the quality assessments are reported in Appendix 2 (Tables A4–A7).

Effect of interventions

Older infants/toddlers (range from 0 to 48 months of age among included trials)

The summary of findings are summarized in Table 3.

Sucrose interventions One review (132) examined the effect of sweet substances on behavioural measurements of pain. The review authors used a subgroup of children from two trials ranging from 13 months to 48 months of age undergoing injections for immunizations. Randomization and selective outcome reporting was unclear and indications for high risk of other potential biases existed for these studies. Despite a sensitivity analyses to remove an outlier trial, a comparison of 2 mL 12% sucrose to water showed no significant effects on crying duration or the Children's Hospital of Eastern Ontario pain scale, with significant heterogeneity ($I^2 = 90\%$) reported.

Sucking-type interventions An examination of non-nutritive sucking (120) showed evidence for non-nutritive sucking on reducing the distress compared to the nontreatment group [SMD −0.89; 95% confidence interval (CI) −1.53 to −0.25]. Swallowing water prior to venipuncture did not yield a significant difference compared to the no-treatment group. Both interventions were conducted in a small sample of children in a single trial.

Parental/caregiver interventions There were no statistically significant effects between rocking or holding, touch or massage, or structured parental involvement and control groups on measurements of pain reactivity (directly after the procedure) for these interventions. One study with a larger sample of children aged 0 to 36 months undergoing venipuncture, IVC or urethral

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Table I. Characteristics of included reviews

Review	Date assessed as up-to-date	Population	Procedures analysed under review	Intervention	Comparison	Outcomes included in present review
Pillai *et al.* (120)	24 July 2011	Preterm, term and older infants up to 3 years undergoing painful acute procedures	Heel-stick, vaccine/vitamin needle, venipuncture, needle, diaper change (preterms), endotracheal suctioning and weighing procedure (preterms)	Nonpharmacological interventions (excluding breastmilk, sucrose and music): contextual strategies; cognitive strategies (toy and video-mediated distraction); direct or indirect behavioural strategies (kangaroo care, swaddling/tucking, rocking/holding, non-nutritive sucking, swallowing water, simulated rocking and water, touch/massage, structured parental involvement, maternal voice and parent presence)	No treatment control	Pain response: pain reactivity (response right after painful stimulus); pain-regulation (response after initial pain response period)
Uman *et al.* (131)	26 July 2006	Children and adolescents aged 2–19 years undergoing needle-related procedures. Studies including patients with needle-phobia or undergoing surgery (except if needle insertion occurred before surgery and outcomes were assessed before surgery) were excluded.	Venipuncture (for immunization or blood sampling), intravenous (IV) insertion, lumbar puncture and bone marrow aspiration	Cognitive interventions (cognitive distraction, imagery, hypnosis, preparation/education/information, thought-stopping, suggestion, coping self-statements, memory change, parent training); behavioural interventions (behavioural distraction, progressive muscle relaxation training, breathing exercises, modeling, rehearsal, desensitization, positive reinforcement, parent training, parent coaching, medical staff coaching, virtual reality); cognitive–behavioural (combined) interventions (combination of above interventions)	Any of the following: nonspecific-treatment or attention-placebo control and routine or standard care	Self-reported and observer-reported pain and distress (anxiety, stress, fear); behavioural measures of pain and distress; physiological measures of pain and distress (heart rate, respiratory rate, blood pressure, oxygen saturation, cortisol levels, transcutaneous carbon dioxide tension)

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Table I. (*Continued*)

Review	Date assessed as up-to-date	Population	Procedures analysed under review	Intervention	Comparison	Outcomes included in present review
Harrison *et al.* (134)	4 August 2011	Children aged 1 – 16 years undergoing needle-related procedures including venipuncture, heel lance, finger lance, subcutaneous (SC) or intramuscular injection (IM), lumbar puncture, suprapubic bladder aspiration	IM or SC injections, blood sampling via venipuncture or finger prick	Orally administered sweet tasting substances of any concentration and volume (sucrose, glucose, fructose and nonsucrose sweeteners), with or without a pacifier and with or without additional comfort measures (cuddling, holding, etc.), distraction methods (toys, visual/verbal distraction) or pharmacological strategies (topical anaesthetics)	Oral water, milk, or other nonsweet substances. Use of pacifiers, positioning, cuddling, distraction and topical anaesthetics could be used.	Pain intensity (pain scores); behavioural, physiological and contextual indicators; self-reported pain; observational pain scores (parents, clinicians, staff); physiological responses; behavioural characteristics; other clinically important outcomes from trials; adverse events; choking, spitting up and vomiting
Lander *et al.* (130)	4 April 2006	Children younger than 18 years of age undergoing venipuncture or IV cannulation	IV cannulation, venipuncture	Amethocaine; eutectic mixture of local anaesthetics (EMLA)	Each trial compared the two interventions but may also include one of the following comparisons: placebo, no-treatment, other topical anaesthetics	Self-reported pain; observer-reported pain, ease of needle procedure (could be assessed by person performing procedure, by number of needle stick attempts or by time needed for the procedure), for different application durations, skin change (erythema)

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Table II. Characteristics of additional studies

Author	Total number of participants	Age	Intervention (*N*)	Pain measurement	Data analysis
Balan (139)	150 children undergoing venepuncture at tertiary care centre	5–12 years	**Intervention:** EMLA (50); **Intervention:** Indian classical instrumental music (50); **Control:** Placebo cream + earphone with no music (50)	**Self-report pain:** VAS——— 0, 1, 5 min **Observer-reported pain:** VAS Parent——— 0, 1, 5 min Investigator——— 0, 1, 5 min Observer——— 0, 1, 5 min	**Analysed:** Distraction • Self-report pain——— 0 min • Observer-reported pain——— 0 min [pooled means (SDs) for parent, investigator and observer] Mean (SD) derived from median and inter-quartile range (IQR); cannot use data for EMLA as it does not compare EMLA with amethocaine
Berberich (134)	41 children undergoing immunizations	4–6 years	**Intervention (20):** Multifaceted distraction method: Verbal suggestion of diminished sensation (ethyl chloride on arm with verbal suggestion of coolness and reduced sensation), horseshoe-shaped plastic gripper, and watch a vibrating instrument travel down arm and say a word once it reaches the elbow **Control (21):** Office-routine control group	**Self-reported pain:** FPS-R **Observer-reported distress:** FPS-R **Behavioural measures of pain:** FLACC	**Analysed:** Distraction • Self-reported pain • Observer-reported distress • Behavioural measures of pain Used reported means, calculated SDs from range
Caprilli (141)	108 children undergoing venipuncture	4–13 years	**Intervention (54):** Live music by professional musician **Control (54):** Standard medical care	**Behavioural measures of distress:** OSBD-A—before, during, after **Self-reported pain:** Wong-Baker FACES scale—after	**Analysed:** Distraction • Behavioural measures of distress—during procedure Reported *p* value for Wong-Baker FACES Scale—no analysis due to missing SDs and range
Gold (90)	20 children undergoing IV placement for MRI or CT scans	8–12 years	**Intervention (10):** Virtual reality (VR)—Street Luge virtual environment via a head-mounted display **Control (10):** Standard of care (1) Topical anaesthesia spray prior to procedure (2) Standard of care + VR	**Self-reported pain:** FPS-R—pre, post Wong-Baker FACES Pain Rating Scale—pre, post	**Analysed:** Virtual reality • Self-reported pain (FPS-R)—post-intervention
Kristjansdottir (135)	118 adolescents undergoing immunization	13–15 years	**Intervention:** (1) Music with headphones (38) (2) Music without headphones (41) **Control:** Standard care (39)	**Self-reported pain:** VAS—right after procedure	**Analysed:** Distraction • Self-report pain for music with headphones versus control

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Table II. (*Continued*)

Author	Total number of participants	Age	Intervention (*N*)	Pain measurement	Data analysis
Liossi (81)	45 children undergoing regular venepunctures as part of cancer status monitoring	7–16 years	**EMLA (5% 1 mL) (15) –** applied for 60 min prior to procedure **EMLA + hypnosis (15) –** taught self-hypnosis **EMLA + attention (15) –** met therapist for same duration as hypnosis group	**Self-reported pain:** VAS—T1, T2, T3 **Self-report anxiety:** VAS—T1, T2, T3 **Behavioural measures of distress:** PBCL observer—T1, T2, T3	**Analysed:** Hypnosis • Self-report pain—T1; • Self-report anxiety—T1; • Behavioural measures of distress—T1 Used EMLA + Hypnosis vs. EMLA only
Marec-Bérard (142)	124 children with cancer undergoing lumbar puncture	2–18 yrs	**Intervention (62):** Positioning pillow **Control (62):** No intervention	**Self-reported pain:** VAS (subgroup analysis 6 years and older) Intervention $N = 38$ Control $N = 34$ **Behavioural measures of anxiety:** LeBaron scale (8-item scale on behaviour)	**Analysed:** Cognitive–behavioural therapy • Self-reported pain • Behavioural measures of pain Imputed means from medians, calculated SDs from range
Newbury (146)	679 children undergoing venous cannulation	3 months–15 years	**Intervention:** Amethocaine (337) EMLA (342) **Convenience cohort observed from distress Amethocaine (33); EMLA (32)**	**Convenience cohort: Self-reported pain:** FLACC	Missing means (SDs)—only reported *p* values for change in scores in the Before-During and During-After groups.
Nguyen (137)	40 children with leukaemia undergoing lumbar puncture	7–12 years	**Intervention (20):** Earphones with music **Control (20):** Earphones without music	**Self-report pain:** NRS—before, during, after **Self-report anxiety:** STAI-short—before, after	**Analysed:** Distraction Self-report pain—during Self-report anxiety—after
Nilsson (104)	42 children with cancer undergoing insertion of SC venous port device or venous puncture	5–18 years	**Intervention (21):** VR **Control (21):** No treatment	**Self-report pain:** CAS—before, during, after **Self-report anxiety:** FAS—before, during, after **Behavioural measures of pain:** FLACC—before, during, after	Reported medians and *p*'s to test for differences between groups *no analysis due to missing SDs and range
Noguchi (136)	62 children receiving childhood vaccinations	4–6.5 yrs	**Intervention:** Musical story (21) Nonmusic/spoken (21) **Control:** Standard care/control (20)	**Self-reported pain:** FPS—after **Observer-reported pain:** FPS—observer (after) **Behavioural measures of distress** OSBD—observer (during)	**Analysed:** Distraction • Self-reported pain—after • Observer-reported pain—after • Behavioural measures of distress—during Used data from music versus standard care/cotrol groups

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Table II. (*Continued*)

Author	Total number of participants	Age	Intervention (*N*)	Pain measurement	Data analysis
Wang (140)	300 children undergoing venepuncture for IV treatment	8–9 years	**Intervention (100/100):** Audiovisual distraction (100)—choice of 10 cartoon videos Psychological interventions (100)—explain before venepuncture; therapeutic touch; encouragement; guided imagery **Control (100):** No intervention	**Self-reported pain:** VAS **Cooperative behaviour:** CBSCV—cooperative behaviour scale of children in venepuncture	**Analysed:** Distraction • Self-reported pain CBT-combined • Self-reported pain Only data for VAS was used
Windich-Biermeier (138)	50 cancer patients undergoing port access/venipuncture (non-emergent needlestick)	5–18 years	**Intervention (22): Standard care (see below) + self-selected distracter:** (1) I-Spy book (2) Bubbles (3) Music table (4) VR glasses (5) Nintendo Gameboy **Control (28): Standard care** (1) Explanation of procedure (2) Parental presence (3) Topical EMLA or Fluori-Methane	**Self-report pain:** CAS—immediately after **Self-report fear:** Glasses Fear Scale Child—immediately after Parent—before, after Nurse—before, during, after **Behavioural distress: OSBD** Nurse—before, during, after	**Analysed:** Distraction • Self-reported pain Observer-reported distress—pooled means(SDs) for parent and nurse (after) *could not be conducted due to missing control data Behavioural distress—after *could not be conducted due to missing control data

catheterization in the Pillai Riddell review (120) examined parent presence and structured parental involvement on pain regulation (crying measured after the first 30 seconds post-procedure), but found no difference between either interventions and the respective control groups.

Distraction interventions The distraction interventions were assessed in children aged between 2 months and 3 years, all undergoing venipuncture. No evidence of a significant effect was found for toy distraction on a behavioural pain scale measured either directly after or beyond 30 seconds post-procedure. There was evidence that video distraction decreased pain on behavioural measures directly after (SMD −0.70; 95% CI −1.13 to −0.27), and 30 seconds after the procedure (SMD −0.84; 95% CI −1.20 to −0.47).

Older children (range from 3 months to 19 years of age among included trials)

Sweet-tasting interventions All the sweet-tasting substance interventions came from one review (132). The two trials examining sweetened gum (a combination of sweeteners approximately as sweet as a 15–30% sucrose solution) versus unsweetened gum were conducted on children undergoing venipuncture, finger prick or IM injection. There was no evidence of a significant difference between intervention and control groups before or during procedure in self-reported measures of pain intensity using the Colour Analogue Scale or the Faces Pain Scale.

Topical anaesthetic interventions There was evidence that self-reported pain (RR 0.63; 95% CI 0.45–0.87), behavioural measures of pain with a sensitivity analysis (RR 0.71; 95% CI 0.52–0.96), and all pain scales combined (RR 0.69; 95% CI 0.55–0.87) were significantly less with amethocaine than with EMLA. There was evidence that amethocaine was effective in reducing pain intensity and distress when applied for 30–60 minutes (RR 0.61; 95% CI 0.41–0.91), for manufacturer's recommended times (RR 0.64; 95% CI 0.46–0.89) and for application over 60 minutes (RR 0.70; 95% CI 0.51–0.96). There was evidence that amethocaine was better than EMLA at reducing procedural pain with IVC (RR 0.70; 95% CI 0.55–0.88). Evidence of less erythema (redness) upon EMLA removal was noted, when compared to amethocaine.

Distraction/coaching interventions With the exception of one comparison, all of the interventions involving distraction or coaching yielded very high levels of heterogeneity ranging from 63 to 97%. The original review (131) showed evidence that *distraction* interventions reduced self-reported pain among 634 children in nine trials (SMD −0.24; 95% CI −0.45 to −0.04). A further seven trials examining distraction interventions were added to the meta-analysis. Three trials (134–136) comprised of children (aged 4 to 15 years)

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Table III. Summary of findings

(a) Older infants/toddlers – range from 0 to 48 months of age

A. Sucrose interventions versus water or no treatment

Sucrose interventions	Type of needle-related procedure(s)	Measurement of distress	Studies (participants)	Effect estimate MD [95% CI]	I^2 (%)	Significant
Sucrose (2 mL 12% sucrose) versus water or no treatment—behavioural measures of pain	SC or IM injections	Crying time (seconds); CHEOPS	2 (80)	−32.45 [−116.91, 52.01]	93	NS
Sucrose (2 mL 12% sucrose) versus water or no treatment*—behavioural measures of pain	SC or IM injections	Crying time (seconds); CHEOPS	2 (73)	−25.39 [−96.15, 45.36]	90	NS

*Sensitivity analysis reported: removal of seven patients (age 19 months or older) from one study due to significant heterogeneity between studies.

B. Sucking-type interventions versus no treatment control

Sucking-type interventions	Type of needle-related procedure(s)	Measurement of distress	Studies (participants)	Effect estimate SMD [95% CI]	I^2 (%)	Significant
Non-nutritive sucking-related versus no treatment control-distress regulation	Venipuncture	FLACC	1 (41)	−0.89 [−1.53, −0.25]	—	Favours non-nutritive sucking
Swallowing water 20 min prior versus no treatment control-distress regulation	Venipuncture	Cry	1 (30)	0.00 [−0.72, 0.72]	—	NS

C. Parental/caregiver interventions versus no treatment control

Parental/caregiver interventions	Type of needle-related procedure(s)	Measurement of distress	Studies (participants)	Effect estimate SMD [95% CI]	I^2 (%)	Significant
Rocking/holding versus no treatment control-pain reactivity	Venipuncture	NFCS	1 (106)	0.23 [−0.15, 0.62]	—	NS
Touch/massage-related vs/no treatment control-pain reactivity	Venipuncture	PIPP	1 (20)	−0.21 [−0.84, 0.41]	—	NS
Structured parent involvement versus no treatment control-pain reactivity	Venipuncture	NFCS; MBPS	3 (209)	−0.26 [−0.70, 0.17]	60	NS
Parent presence versus no treatment control-pain regulation	Venipuncture, IVC or urethral catheterization	Cry (Hertz)	1 (278)	0.00 [−0.24, 0.23]	—	NS
Structured parent involvement versus no treatment control-pain regulation	Venipuncture, IVC or urethral catheterization	Cry (Hertz)	1 (288)	0.02 [−0.21, 0.25]	—	NS

D. Distraction interventions versus no treatment control

Distraction interventions	Type of needle-related procedure(s)	Measurement of distress	Studies (participants)	Effect estimate SMD [95% CI]	I^2 (%)	Significant
Toy distraction versus no treatment control-pain reactivity	Venipuncture	MBPS	3 (259)	−0.10 [−0.35, 0.14]	0	NS

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Table III. (*Continued*)

D. Distraction interventions versus no treatment control

Distraction interventions	Type of needle-related procedure(*s*)	Measurement of distress	Studies (participants)	Effect estimate SMD [95% CI]	I^2 (%)	Significant
Video distraction versus no treatment control-pain reactivity	Venipuncture	MBPS; VAS	1 (90)	−0.70 [−1.13, −0.27]	—	Favours video distraction
Toy distraction versus no treatment control-pain regulation	Venipuncture	MBPS	1 (133)	−0.08 [−0.50, 0.33]	0	NS
Video distraction versus no treatment control-pain regulation	Venipuncture	MAISD	1 (126)	−0.84 [−1.20, −0.47]	—	Favours video distraction

(*b*) Older Children – range from three months up to 19 years of age

A. Sucrose-based interventions – sweet gum versus unsweetened gum

Sucrose-based interventions	Type of needle-related procedure(*s*)	Measurement of pain	Studies (participants)	Effect estimate MD [95% CI]	I^2 (%)	Significant
Sweet gum versus unsweetened gum before procedure—behavioural measures of pain	Blood sampling (venipuncture or finger prick), IM injection	CAS	2 (111)	0.24 [−0.69, 1.18]	0	NS
Sweet gum versus unsweetened gum before procedure—behavioural measures of pain	Blood sampling (venipuncture or finger prick), IM injection	FPS	2 (111)	−0.15 [−0.61, 0.30]	0	NS
Sweet gum versus unsweetened gum during procedure—behavioural measures of pain	Blood sampling (venipuncture or finger prick), IM injection	CAS	2 (103)	0.86 [−0.12, 1.83]	0	NS
Sweet gum versus unsweetened gum during procedure—behavioural measures of pain	Blood sampling (venipuncture or finger prick), IM injection	FPS	2 (103)	0.23 [−0.28, 0.74]	0	NS

B. Topical anaesthetic interventions – Amethocaine versus EMLA

Topical anaesthetic interventions	Type of needle-related procedure(*s*)	Measurement of pain	Studies (participants)	Effect estimate RR [95% CI]	I^2 (%)	Significant
Amethocaine versus EMLA—all pain scales combined	IVC; venipuncture	5-point behavioural scale; observed verbalization, movement and self-report; VAS; OSBD; PCT; undefined pain scale	5 (420)	0.78 [0.62, 0.98]	44	Favours amethocaine
Amethocaine versus EMLA*—all pain scales combined	IVC; venipuncture	5-point behavioural scale; observed verbalization, movement and self-report; VAS; OSBD; PCT	4 (354)	0.69 [0.55, 0.87]	0	Favours amethocaine
Amethocaine versus EMLA—self-reported pain	IVC; venipuncture	VAS; OSBD; PCT	2 (80)	0.63 [0.45, 0.87]	0	Favours amethocaine
Amethocaine versus EMLA—behavioural measures of pain	IVC; venipuncture	5-point behavioural scale; observed verbalization, movement and self-report; VAS; OSBD; undefined pain scale	4 (360)	0.83 [0.62, 1.12]	53	NS

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Table III. (*Continued*)

B. Topical anaesthetic interventions – Amethocaine versus EMLA

Topical anaesthetic interventions	Type of needle-related procedure(s)	Measurement of pain	Studies (participants)	Effect estimate RR [95% CI]	I^2 (%)	Significant
Amethocaine versus EMLA*—behavioural measures of pain	IVC; venipuncture	5-point behavioural scale; observed verbalization, movement and self-report; VAS; OSBD	3 (294)	0.71 [0.52, 0.96]	0	Favours amethocaine
Amethocaine versus EMLA—short application time (30–60 min)	IVC	Observed verbalization, movement and self-report; self-report 3-pt pain scale	2 (134)	0.61 [0.41, 0.91]	0	Favours amethocaine
Amethocaine versus EMLA—manufacturer's recommended application times	IVC; venipuncture	Observed verbalization, movement and self-report; VAS; OSBD; PCT; undefined pain scale	4 (200)	0.84 [0.60, 1.16]	62	NS
Amethocaine versus EMLA—manufacturer's recommended application times*	IVC; venipuncture	Observed verbalization, movement and self-report; VAS; OSBD; PCT	3 (134)	0.64 [0.46, 0.89]	0	Favours amethocaine
Amethocaine versus EMLA—long application times (over 60 min)	IVC	5-point behavioural scale; VAS; OSBD	2 (240)	0.70 [0.51, 0.96]	0	Favours amethocaine
Amethocaine versus EMLA—IV cannulation	IVC	5-point behavioural scale; observed verbalization, movement and self-report; PCT	3 (320)	0.70 [0.55, 0.88]	0	Favours amethocaine
Amethocaine versus EMLA—undifferentiated needle	IVC; venipuncture	VAS; OSBD; undefined pain scale	2 (100)	1.78 [0.70, 4.54]	79	NS
Amethocaine versus EMLA—erythema after removal of drugs	IVC; venipuncture	VAS; OSBD; PCT	2 (86)	14.83 [2.28, 96.36]	0	Favours EMLA

*sensitivity analyses reported with removal of one trial due to outlier and poor quality of pain measurement.

C. Distraction/coaching interventions versus control/standard care (interventions for which new trials were added are shaded)

Distraction/coaching interventions	Type of needle-related procedure(s)	Measurement of pain	Studies (participants)	Effect estimate SMD [95% CI]	I^2 (%)	Significant
Distraction versus control/standard care—self-reported pain	Venipuncture; IVC; port access; lumbar puncture	FPS; FACES Scale; Glasses Fear Scale; VAS; Oucher Pain Scale; Wong-Baker FACES Pain Scale; FPS-R; CAS; NRS; OSBD	16 (1183)	−0.51 [−0.85, −0.17]	87	Favours distraction
Distraction versus control/standard care—self-reported distress	Venipuncture; IVC; finger capillary puncture; port access; lumbar puncture	Glasses Fear Scale; VAS for anxiety; 8-item picture test of anxiety; STAI	5 (280)	−0.29 [−0.79, 0.22]	75	NS
Distraction versus control/standard care—behavioural measures of pain	Venipuncture	CHEOPS; CFCS; FLACC	3 (193)	−0.56 [−1.40, 0.27]	86	NS
Distraction versus control/standard care—behavioural measures of distress	Venipuncture; IVC; bone marrow aspiration	OSBD-R; Modified Frankl Behaviour Rating Scale; CAMPIS; PPQ-R; PBRS-R; 5-point rating scale; OSBD-A; OSBD	5 (237)	−0.30 [−0.77, 0.17]	63	NS

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Table III. (*Continued*)

C. Distraction/coaching interventions versus control/standard care (interventions for which new trials were added are shaded)

Distraction/coaching interventions	Type of needle-related procedure(s)	Measurement of pain	Studies (participants)	Effect estimate SMD [95% CI]	I^2 (%)	Significant
Distraction versus control/standard care—observer-reported distress	Venipuncture; IVC; finger capillary puncture	Modified Frankl Behaviour Rating Scale; PPQ-R; OSBD-R; GDS; direct observations; 4-point scale; FPS-R; VAS; OSBD	7 (326)	−0.98 [−2.12, 0.16]	95	NS
Parent coaching + distraction versus control/standard care—behavioural measures of distress	Venipuncture; IVC	CAMPIS; OSBD; BAADS; VAS; distress ratings; PPQ-R; OSBD-R	2 (104)	−0.58 [−1.48, 0.32]	80	NS
Nurse coaching + distraction versus control/standard care—self-reported pain	Venipuncture	FACES scale; VAS	2 (138)	−1.13 [−3.52, 1.25]	97	NS
Nurse coaching + distraction versus control/standard care—behavioural measures of distress	Venipuncture	5-point Likert scale; CAMPIS-R; VAS	2 (138)	−0.53 [−0.87, −0.19]	0	Favours nurse coaching + distraction
Nurse coaching + distraction versus control/standard care—observer-reported distress	Venipuncture	5-point Likert scale; CAMPIS-R; VAS	2 (138)	−0.79 [−2.73, 1.14]	96	NS

D. Hypnosis-type interventions versus control/standard care (interventions for which new trials were added are shaded)

Hypnosis-type interventions	Type of needle-related procedure(s)	Measurement of pain/distress	Studies (participants)	Effect estimate SMD [95% CI]	I^2 (%)	Significant
Hypnosis versus control/standard care—self-reported pain	Bone marrow aspiration; lumbar puncture; venipuncture	Pain self-report; 6-point faces rating scale; Wong-Baker FACES Pain Scale; VAS	5 (176)	−1.69 [−2.76, −0.62]	88	Favours hypnosis
Hypnosis versus control/standard care—self-reported distress	Bone marrow aspiration; lumbar puncture; venipuncture	Fear Self-Report; Pain Self-Report; VAS	5 (176)	−2.60 [−4.06, −1.15]	91	Favours hypnosis
Hypnosis versus control/standard care—behavioural measures of distress	Bone marrow aspiration; lumbar puncture; venipuncture	PBRS-R; 5-point Likert scale; 5-point rating scale; PBCL	6 (193)	−1.36 [−2.16, −0.56]	82	Favours hypnosis
Suggestion versus control/standard care—self-reported pain	Intramuscular injection; venipuncture	Loebach & Schroeder 1979 tool (adapted); VAS; FPS	3 (238)	−0.20 [−0.55, 0.15]	40	NS

E. Preparation/information interventions versus no preparation/nontreatment control

Preparation/information interventions	Type of needle-related procedure(s)	Measurement of pain/distress	Studies (participants)	Effect estimate SMD [95% CI]	I^2 (%)	Significant
Preparation/information versus no preparation/nontreatment control—self-reported pain	Venipuncture	VAS; Oucher scale	2 (154)	−0.22 [−1.20, 0.76]	88	NS
Preparation/information versus no preparation/nontreatment control—observer-reported distress	Venipuncture	Procedure questions; GDS; 5-point scale of distress	2 (154)	−0.15 [−0.88, 0.57]	79	NS

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Table III. (*Continued*)

F. Virtual reality interventions versus control/standard care (interventions for which new trials were added are shaded)

Virtual reality interventions	Type of needle-related procedure(s)	Measurement of pain	Studies (participants)	Effect estimate SMD [95% CI]	I^2 (%)	Significant
Virtual reality versus control/standard care—self-reported pain	Lumbar puncture; IVC for MRI or CT scans	VAS; FPS-R	2 (50)	−0.28 [−0.84, 0.28]	0	NS

G. Cognitive–behavioural therapy combined interventions versus control/standard care (interventions for which new trials were added are shaded)

CBT interventions	Type of needle-related procedure(s)	Measurement of pain/distress	Studies (participants)	Effect estimate SMD [95% CI]	I^2 (%)	Significant
Cognitive–behavioural therapy combined versus control/standard care—self-reported pain	Venipuncture; bone marrow aspiration; IVC prior to MRI; lumbar puncture	FACES scale; 6-point faces rating scale; self-report; VAS;	7 (489)	−0.63 [−1.21, −0.05]	87	Favours cognitive–behavioural therapy
Cognitive–behavioural therapy combined versus control/standard care—observer-reported pain	Venipuncture	VAS; parent and nurse ratings of child distress	2 (81)	−0.10 [−0.54, 0.34]	0	NS
Cognitive–behavioural therapy combined versus control/standard care—self-reported distress	Venipuncture; bone marrow aspiration; IVC prior to MRI	Computer smiley faces; 6-point faces rating scale; self-report anxiety and pain; STAI-C	4 (156)	−0.75 [−1.75, 0.25]	87	NS
Cognitive–behavioural therapy combined versus control/standard care—behavioural measures of distress	Venipuncture; bone marrow aspiration; IVC prior to MRI; lumbar puncture	CAMPIS; OSBD; BAADS; CAMPIS-R; CAMPIS-SF; PBCL; behavioural distress scores; MRI distress ratings; MRI Behaviour Checklist; LeBaron Scale	7 (401)	−0.55 [−0.90, −0.20]	63	Favours cognitive–behavioural therapy
Cognitive–behavioural therapy combined versus control/standard care—observer-reported distress	Venipuncture; IVC prior to MRI	5-point Likert scale; CAMPIS-R; VAS; CAMPIS-SF; parent and nurse ratings; behavioural distress scores; MRI distress ratings; MRI behaviour checklist	4 (197)	−0.88 [−1.65, −0.12]	84	Favours cognitive–behavioural therapy

H. Overall Effect for those trials where a summary statistic could not be derived

Trial	Interventions	Type of needle-related procedure(s)	Measurement of pain	No. of participants	Overall effect	Authors' conclusion
Caprilli (143)	Music versus control	Venipuncture	Wong-Baker FACES scale	Music (54); Control (54)	$p = 0.048$	Significant effect of the presence of musicians over self-reported pain
Newbury (148)	Amethocaine versus EMLA	Non-urgent IVC	FLACC Observer—before, during, after VAS Observer—before, during, after	Amethocaine (33); EMLA (32)	$p > 0.05$	No statistical significance in the VAS scores or the FLACC scale.
Nilsson (107)	Virtual reality versus control	Insertion of SC venous port device or venous puncture	CAS FAS FLACC	VR (21); Control (21)	**Before-during** Intervention group CAS $p = 0.018$ FAS $p = 0.028$ FLACC $p = 0.163$	

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Table III. (*Continued*)

H. Overall Effect for those trials where a summary statistic could not be derived						
Trial	**Interventions**	**Type of needle-related procedure(s)**	**Measurement of pain**	**No. of participants**	**Overall effect**	**Authors' conclusion**
					Control group CAS $p = <0.001$ FAS $p = 0.028$ FLACC $p = 0.001$ **During-after** Intervention group CAS $p = 0.003$ FAS $p = 0.008$ FLACC $p = 0.027$ Control group CAS $p = 0.004$ FAS $p = 0.001$ FLACC $p = < 0.001$	No significant differences between intervention and control groups;

undergoing immunizations. Two trials (137,138) were completed for oncology patients aged 5–18 years. One trial (139) examined children aged 5–12 years undergoing venipuncture at a tertiary care centre, and one (140) examined children aged 8–9 years undergoing venipuncture for intravenous (IV) treatment. Whenever possible, self-reported pain during procedure was extracted for analysis. When this was not available, scores reported on pain scales directly after the procedure was preferred over pre-procedural or other endpoint scores. The resultant effect estimate (SMD −0.51; 95% CI −0.85 to −0.17) showed some evidence that distraction reduced self-reported pain in a total of 16 studies involving 1183 children.

Two additional trials (137,138) examining *distraction* in oncology patients were added to the meta-analysis for self-reported distress, showing no evidence of a significant difference between intervention and control groups on self-reports of distress.

One new trial (134) was added to the meta-analysis for behavioural measures of pain. There was no evidence of a significant difference between distraction and control groups in behavioural pain scores in the three trials totalling 193 children.

Two new trials (136,141) were added as they examined *music distraction* on behavioural measures of distress on pain. The final five studies of 237 children did not show evidence of a significant difference between intervention and control groups in behavioural measures of pain.

Three new trials (134,136,139) were extracted for data on observer-reported distress. All children in these studies underwent venipuncture. Both studies (136,139) were only extracted for pain scores during the procedure. There was no evidence that distraction reduced observer-reported distress scores in a total of seven trials with 326 children.

Combined parent coaching and distraction did not show significant evidence of a difference compared to control groups. Combined nurse coaching and distraction showed evidence of reducing behavioural measures of distress (SMD −0.53; 95% CI −0.87 to −0.19) but did not show significant effect on self-reported pain or observer-reported distress.

Hypnosis-type interventions *Hypnosis* interventions were conducted among children undergoing bone marrow aspiration or LP for cancer in one review (131). One new trial (81) of 45 children aged 7–16 years undergoing venipuncture as part of cancer monitoring was added to the meta-analysis, only utilizing pain and distress scores immediately following the procedure (T1). There was evidence that hypnosis reduced self-reported pain (SMD −1.69; 95% CI −2.76 to −0.62), self-reported distress (SMD −2.60; 95% CI −4.06 to −1.15) and behavioural measures of distress (SMD −1.36; 95% CI −2.16 to −0.56). There was no evidence that *suggestion* interventions differed from control groups in reducing self-reported pain. All of the studies examining hypnosis-type interventions yielded high I^2 scores, indicating significant heterogeneity across studies.

Preparation/information interventions The *preparation/information* interventions were conducted among two trials of children aged 3–12 years undergoing venipuncture. There was no evidence of a significant

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difference between intervention and control groups in self-reported pain or observer-reported distress.

VR interventions Only one trial in the Uman review (131) examined VR intervention for 30 children aged 10–19 years undergoing LPs for cancer treatment. The effect estimate was not selected for reporting in the review because of having only a single trial in the analysis, and an additional trial (101) of children aged 8–12 years undergoing IV placement for magnetic resonance imaging or CT scans was added to the meta-analysis for this overview. There was no evidence that VR interventions reduced self-reported pain in these groups of children.

Cognitive–behavioural therapy interventions One review (131) examined *cognitive–behavioural* combined therapies for children undergoing venipuncture, bone marrow aspirations or IV insertions and there was no evidence from the five trials (217 participants) that these interventions reduced self-reported pain. Data from two additional trials (140,142) were added to the meta-analysis. One study (142) used a positioning pillow intervention to reduce pain among 124 children with cancer undergoing LP. The other study (140) used a combined psychological intervention on 100 children undergoing venipuncture for IV treatment. The final effect estimate in the seven trials (489 children) showed evidence that cognitive–behavioural interventions reduced self-reported pain (SMD −0.63; 95% CI −1.21 to −0.05), where a high level of heterogeneity remained.

One new trial (142) of oncologic patients was extracted for *behavioural* measures of anxiety using the LeBaron Scale, and the resultant effect estimate showed evidence that CBT reduced behavioural measures of distress (SMD −0.55; 95% CI −0.90 to −0.20).

There was no evidence of a significant difference between cognitive–behavioural intervention and control groups in observer-reported pain, self-reported distress or observer-reported distress.

Discussion

Despite our understanding of the importance of pain relief in children, and the increasing amount of high quality research into effective pain management methods, there remains a significant knowledge–practice gap in day-to-day clinical practice (126,143). Some explanations for this gap recognize the difficulties facing clinicians who aim to expediently and meaningfully synthesize a vast volume of relevant clinical research. Other related barriers to optimal paediatric pain management include insufficient physician orders, insufficient education regarding pain management and perception of pain management as a low priority in clinical management (144,145). Given the prevalence of procedural pain in children, the vast number of procedures performed and therapies available, and the wide variation in measurements of treatment effects, it is important to periodically re-evaluate the best evidence available for treatment in order to identify key changes and novel interventions.

Sweet-tasting substances

Harrison *et al*. included four trials in their review of the intervention of sucrose as analgesia for children aged 1–16 years undergoing painful procedures (132). Results revealed that the two studies comparing 2 mL 12% sucrose versus water for immunization pain in infants up to 48 months of age showed no reduction in crying time overall, although results between the two studies were conflicting when viewed in isolation. Overall, the meta-analysis sample size of 80 subjects was still small and heterogeneity between the studies remained high, even with sensitivity analysis. The heterogeneity may be in part explained by the marked differences in holding technique (maternal cuddle versus holding against examination table) and diverse cultural settings (Turkey versus USA). A synergistic effect between sucrose and maternal cuddle may explain the findings of a significant reduction in crying time from one study in Harrison's review (132) and verification of these findings would be important. Furthermore, the dose of 12% sucrose is a less sweet solution than those often recommended for use in this age group and it is possible that stronger doses or repeated doses at 2-minute intervals may have improved effect.

From this review, there is no current evidence of benefit supporting the use of 12% sucrose for older infants (two trials) and toddlers or sweet gum for toddlers (two trials) undergoing needle pain. However, only a small number of studies in this age group exist and further studies with stronger doses and/or repeat doses of sucrose, and less variation in confounding concurrent CBT strategies are warranted. Other reviews of sucrose effectiveness in infants beyond the neonatal period suggest that sucrose may provide some analgesia, resulting in procedural pain reduction, but magnitude of effects may be less marked at doses studied (140). For older infants/toddlers and older children, attention must be paid to describing the overall treatment effect, determining the age at which sucrose is ineffective, establishing concentration and dosing schedules, as well as examining the relationship between sucrose and co-analgesic interventions (132). Furthermore, intra-procedure variability in pain intensity and quality exists, and thus clarification as to the procedure-specific-applicability of sucrose for children (versus grouping variable short procedures together) in all age groups is essential.

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Topical anaesthetics

Lander *et al*. (130) compared amethocaine with EMLA for topical anaesthetic efficiency, ease of needle procedure and skin changes for venipuncture or IVC. Six trials consisting of 534 children between the ages of 3 months and 15 years were reviewed. Outcome assessments included measures of self-report and observer reports. Each of the six trials used a different pain scale, some with incorporation of behavioural measures into the pain scales. Some of the pain scales were not validated and considerable technical diversity exists surrounding the approach to measurements. Randomization was poorly described and blinding was sub-optimal in the trials, in general.

Meta-analysis results demonstrated that amethocaine provided superior pain relief when compared to EMLA for the procedure of IVC, regardless of differences in preceding application times. Data were not sufficient to draw conclusions regarding effectiveness for the procedure of venipuncture (only one trial) or in terms of ease of accomplishment of either procedure. Cost analyses, including data on drug costs, dressing costs, number of applications or cannulas required, were not performed in any of the trials and such comparisons remain lacking. Adverse reactions were reported in some trials but data were not very comprehensive. Skin blanching seemed to be associated with EMLA, while erythema was more likely with amethocaine.

An additional trial (146) from the search update reported no significant difference between the Visual Analogue Scale or Face Legs Arms Cry Consolability Scale for EMLA and amethocaine groups in 65 IVCs in children aged 3 months–15 years. Lander's (130) appears to be the only systematic review of trials of these two topical anaesthetics in children. Of note, recent trials examining either EMLA or amethocaine do so with several concurrent comparisons and may show synergistic benefits of multiple interventions (147–149). Another recent trial compares one of the newer topical anaesthetics liposomal lidocaine (Maxilene) with amethocaine showing no difference between the two (150) in terms of analgesic effect. Several reviews of other available topical anaesthetics are available (151,152).

Cognitive–behavioural interventions

Uman *et al*. (131) reviewed 25 trials of cognitive–behavioural interventions for needle-related pain and distress in 1702 children aged 2–19 years. Nine cognitive interventions, 11 behavioural interventions and various combinations of the two categories were synthesized. Outcome measures included four self-report scales of pain and distress, several global observer report scales, two pain scales and two distress scales used as behavioural measures as well as seven physiological outcome measures. Immunizations ($n = 9$), venipuncture or blood draws/sampling ($n = 8$), LP ($n = 5$), IVC ($n = 4$), bone marrow aspirations ($n = 3$) and IM injections ($n = 1$) were the procedures examined across the 25 studies. Participants included a mixture of healthy and chronically ill children in the inpatient and outpatient settings. Quality concerns included inadequate randomization and follow-up of patients and the maximum quality score was a three out of five on the Jadad scale with 15 studies receiving a score of zero. It should be noted, however, that difficulties in masking the CBT intervention, which may be inherent in trials of this nature, likely contribute to the low Jadad scores. Many of the interventions examined had only a small number of studies, each. Efficacious interventions in order of effect size were distraction ($n = 10$), hypnosis ($n = 5$) and combined cognitive–behavioural interventions. Data for the efficacy of other psychological interventions such as information/preparation, nurse coaching and distraction, parent positioning and distraction, and distraction and suggestion were limited but showed favourable trends. An additional trial retrieved from the search update supported the beneficial effects of hypnosis. For general CBT, additional trials supported the direction of a positive effect. For distraction, results were mixed but outcome measures were highly variable and difficult to align for conclusion purposes. Overall, heterogeneity across studies was high and as such, in the absence of more congruent studies, conclusions for clinical recommendations are not yet entirely clear.

Pillai Riddell *et al*. (120) examined 13 different types nonpharmacological interventions (Table 1) across 11 RCTs involving 1553 older infants aged 1 month–36 months of age. Procedures included IM and SC injection, IVC, venipuncture and urethral catheterization. Interventions for older infants included non-nutritive sucking, swallowing water, rocking, holding or both, simulated rocking, massage or touch, environmental modification, toy distraction, video distraction, structured parent involvement and parent presence. Non-nutritive sucking was found in one trial to be of benefit for pain reduction. Verification of this finding in future trials would be important. Video distraction was also found to be helpful from one large trial. No other evidence of benefit for the interventions studied was demonstrated for older infants, in this overview. Heterogeneity across studies was very large even with performance of sensitivity analyses. Most studies were of marginal/satisfactory quality and thus attention to improved reporting and methodologies in this area is important. Overall, confidence in the lack of effect for these interventions is limited and further procedure-specific research using these interventions is warranted.

Conclusion and summary

Implications for practice

Treatment of procedural pain in children should be considered standard practice. Many convenient, safe

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and potentially efficacious modalities exist. One can argue that the use of effective anaesthesia for procedural pain should *always* be offered, except in life-threatening emergencies when delays in management are likely to result in poor outcome for the patient (5,153,154). Unfortunately, we know that despite the existence of a large body of evidence for analgesic treatments, children still continue to have their pain under-treated and under-prevented.

There is no evidence from the *Cochrane Library* that the analgesic effect of sucrose extends beyond the neonatal period or that sweet-tasting gum is an effective analgesic in toddlers. Of note, however, low concentrations of sucrose were used in the included studies in the older age group. It is possible that higher concentrations of sucrose are needed for older children. Despite the absence of definitive evidence of effect *from this review* and based on studies not included in this review, many clinical guidelines recommend the use of sucrose as a simple, low-cost, quick analgesic for infants up to 12 months of age (68,155). For correct administration the sucrose must be administered slowly over the tongue for 100–120 seconds prior to the procedure and will maintain effect for 5–10 minutes only (57). Additional measures such as skin-to-skin contact, holding, kangaroo care are unlikely to confer any harm and likely offer additional benefit which cannot be measured through our current scales (124). Design of nurse-initiated pain protocols and electronic clinical pathways may address the problem of overlooking this inexpensive, effective and efficient modality of pain management.

Amethocaine was found to be more effective for pain management and has faster onset than EMLA. It should be noted that a newer formulation of liposomal lidocaine (Maxilene) is in clinical use with even shorter onset of action and some favourable clinical trial results (150,156). Combinations of topical analgesics with other analgesic strategies may maximize benefit to the child. We know that, in reality, this and other opportunities for pain treatment in children may unfortunately be overlooked because of competing priorities. An efficient approach to pain management that includes anticipating who will likely need venipuncture at triage/nursing assessment, prescribing take-home topical preparations for patients referred for blood work, performing history, physical or counselling during the wait for onset of topical anesthesia, etc., is necessary to efficiently incorporate the use of topical anaesthetics and other analgesics into practice in essentially all cases. The need to use multiple application sites for topical anaesthetics, in case of failed IV or venipuncture attempts, must also be taken into account in cost or pain analyses.

Behavioural therapies such as distraction are *potentially* effective, inexpensive and can be used in conjunction with pharmacological analgesics without onerous resource use. Simple distracters such as toys, videos, music can be made readily available with low cost and minor inconvenience in most clinical settings. Cognitive modalities such as hypnosis and some mixed CBT are efficacious but may require specially trained personnel, such as child life specialists. Simple CBT approaches such as preparation, coping statements, relaxation, breathing techniques and guided imagery are quick, easy and readily available to all. Other psychological interventions require further study.

Implications for research

Tackling the wealth of currently available pain literature and synthesizing clinically useful applications from it can be a daunting task for the busy healthcare provider. The translation of knowledge of effective procedural pain management into clinical practice remains a challenge in both paediatric and general hospitals. Rapid and effective mechanisms for translation of and dissemination of advances in the field of pain management must be incorporated into responsible and responsive research plans.

Outcome measures

A key challenge posed by pain research is interpretation of diverse outcome measures. There are so many different potential outcomes and methods to measure these outcomes. The use of pain scales to measure pain is the most widely accepted and best validated approach to the assessment of pain in children. However, numerous pain scales exist, many of which, at first glance, seem to differ only slightly from each other, although small inter-scale differences may be meaningful. Several studies have used pain scales that have not been validated. Others have used validated scales but have not applied them in the appropriate settings. It is imperative to focus on validated, well-described and similar outcome measures across studies so that data from future trials can be meaningfully interpreted. In order to encourage simplicity of focus, future RCTs and systematic reviews should maintain strict definitions and descriptions of the procedure examined.

It is imperative that the research community focus on the best key outcome measures with very specific guidelines on how to exactly measure and interpret them, such that future trials will be well designed and subsequent data will be suitable for combination and interpretation. Currently, because of highly variable outcome measures and vaguely described procedures, many trials are simply not suitable to the formation of meaningful, clinically relevant synthesis. Developments along these lines have begun with the formation of the Pediatric Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials group (PedIMMPACT, www.immpact.org), which has recommended core outcome domains, measurements of patient satisfaction and monitoring of adverse effects for consideration in trial design for acute and chronic paediatric pain. The group has also created systematic reviews including a review of observational and

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behavioural pain measures in children, and self-report pain intensity measures in children (157,158).

Some outcome measures have been incorporated into trials seemingly because of their traditional existence and without consideration of their validity. Change in heart rate has been used widely as a surrogate measure for pain, although its aetiology can stem from multiple other sources including fever, dehydration and anxiety. Heart rate data collection methodology is highly variable and the most accurate way of collecting and interpreting this data has yet to be established. Physiological response likely varies with age and previous pain experience, amongst other variables. Several studies report dissociation between pain scale findings and physiological responses, which leads to uncertainties about the validity of this measure. Self-report is not available in young preverbal children to corroborate the validity of heart rate as a measure of pain. Several studies in adults, using self-report to help establish validity, suggest that heart rate and pain intensity do not correlate well and study of infants noted decreased heart rate in response to pain (159–161). Further research with attention to the question of the validity of heart rate and other surrogate measures, with age- and procedure-specific data, might be useful.

Other physiologic measures such as oxygen saturation, carbon dioxide saturation and blood pressure changes may be falling out of favour because of lack of positive findings in these areas, low specificity or sensitivity, or applicability only to unique sub-groups such as very premature infants. Almost all pain studies have moved away from measuring physiologic variables as primary outcome measures for children. If used as a secondary outcome, they should be interpreted with reference to, and in correlation with, validated patient-provided pain scale measurements.

The question of how to interpret behavioural measures such as crying times remains an issue. Crying time, intensity, pitch and quality have been used as surrogate measures of pain. Crying time variants have been most commonly used because of presumed ease of measurement, although exact methodology regarding how to measure and report crying time is wide ranging. Crying may not be as reliable in premature infants as in mature infants, and this data may be missed in those that would cry but cannot for therapeutic reasons (e.g. ventilator dependent). Novel attempts to objectively measure neonatal crying as a surrogate for neonatal pain via acoustic analysis have recently been performed. Further evaluation of this technology as a potential pain measurement tool may be warranted (162). A recent small but high profile study has brought the utility of electroencephalography and electromyography measurements in pain study to the forefront (64). While this study was provocative, there is no evidence, at this time, that electromyography or electroencephalography should replace patient-level validated measures of pain in children.

Procedures

In order to encourage simplicity of focus, future RCTs and systematic reviews should maintain strict definitions and descriptions of the procedure examined. For example, even venipuncture, IV catheter placement and heel lance have differing pain intensities, physical locations and durations and may require varied approaches to management. Ideally, medical procedures should be performed in a standardized manner and each unique procedure considered distinctive. Other areas for paediatric procedural pain research and synthesis include patient experience of pain during LPs, urinary catheterizations and suprapubic catheterizations. Of great importance is the need for improved monitoring and reporting of adverse effects of analgesic interventions, a factor that is key in clinical decision making surrounding an intervention.

For infants and other vulnerable populations

For infants, many specific areas still require more robust evidence: the optimal dose and concentration of sucrose; the role of pacifier; comparison of breastfeeding/milk to sucrose and the use of sweet substances and pacifiers for other procedures such as LPs and urinary catheterizations. The potential benefits and safety of adjunctive use of topical anaesthetics should be clarified. Research into psychological interventions for pain and distress in infants should not be forgotten, as results are promising. Systematic reviews in some of these areas would currently be possible and other areas require more well-designed trials. Vulnerable paediatric populations, particularly those experiencing chronic disease such as cancer, cystic fibrosis and diabetes, have unique, repeated procedural pain experiences that likely affect and may change their pain processing and responses. However, only a small body of literature concerning repeated paediatric procedural pain in chronically ill children is currently available and thus, further attention to these unique populations is urgently warranted.

Trial design

Recently, initiatives to assist researchers with the challenges inherent to trial design in paediatrics have been forthcoming (163). Berde *et al*. (129) report a consensus overview of the unique practical, ethical and scientific challenges to paediatric analgesic trial design. In addition, a series of guidance for standardization of consent and recruitment; containing risk of bias; data monitoring committees; determining adequate sample sizes; the selection, measurement and reporting of outcomes; and appropriate age groups for paediatric trials has recently been published (164–171). Clear processes for monitoring and reporting of adverse events should be incorporated at the trial design stage. A need for continued development and refinement of paediatric clinical trial standards is essential.

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As newer analgesic strategies become available and are studied, on-going systematic reviews will remain important for distillation of pertinent information. Future trials should include clear data on blinding, randomization, economic analyses, ease of procedure, singularity and details of procedure and outcome measurements. Pain assessment tools should be age-appropriate and validated in the practice setting. Achieving consensus on the best methodological approaches to pain research will make advances in this field more readily attainable.

Knowledge translation

Pain and its management is complex, with both sensory and emotional components. Currently, even in the face of a rapidly growing body of research into pain assessment, prevention and treatment, optimal pain management falls short for children. Efforts must be made to determine the most effective modalities for rapid knowledge translation to practice, particularly in the nonpaediatric (or general medical) settings, where access to new paediatric-specific knowledge may be challenging. Given the current paradigm of solid clinical evidence to support procedural pain treatment and yet an epidemic of oligoanalgesia, it would stand to reason that optimizing dissemination strategies should be prioritized in children's pain research.

Overall completeness and applicability of evidence

The evidence describing effective analgesia surrounding procedural pain for older infants/toddlers and older children, is incomplete and unclear. However, topical anaesthetics are clearly beneficial and several interventions demonstrate potential. Well-designed, multicentre trials using congruent approaches are needed to gain clarity surrounding results. In practice, given the gravity of the experience of pain and the low cost and side-effect profile of some of the simple analgesic strategies described, clinical guidelines for a multimodal approach are recommended (172–178). However, only a few studies incorporating comparisons of multimodal approaches are currently available and well-designed trials comparing various combinations of pharmacological and integrated pharmacological–behavioural strategies are warranted.

Summary of main results

From this review, there is no current evidence of benefit supporting the use of 12% sucrose for older infants and toddlers or sweet gum for toddlers undergoing needle pain. Amethocaine provides superior pain relief as compared to EMLA for the procedure of IVC regardless of differences in preceding application times. Potentially efficacious nonpharmacological interventions include distraction, hypnosis and combined cognitive–behavioural interventions. Nonnutritive sucking and video distraction were found in single trials to be of benefit for pain reduction in older infants/toddlers. From this overview, no other evidence of benefit for the interventions studied was demonstrated. Of note, heterogeneity across studies was very large even with performance of sensitivity analyses. The quality of reported studies was of marginal/satisfactory or unclear quality and thus attention to improved reporting and methodologies in this area is important. This review has been useful to outline some of the available evidence, to identify gaps and suggest directions for further research.

Authors' conclusions

From this overview, nonpharmacological interventions and sucrose use in older infants/toddlers require further procedure-specific studies using well-validated, well-recognized and congruent outcome measures. As such, the evidence is currently inconclusive for these interventions. Evidence of the effectiveness of topical anaesthetics (particularly amethocaine) is clear although as new preparations emerge, conclusions will need to be updated. Knowledge translation to the clinician and the practice setting is essential to preventing procedural pain in children. Translation of findings to practice requires wide dissemination of research findings.

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Contribution of authors

All authors contributed in the preparation of this overview. SC wrote the Abstract, Background, Discussion and Conclusion sections and reviewed articles for inclusion. AW extracted data and conducted analyses, created the tables and figures, and wrote the Methods and Results section. SA reviewed articles for inclusion and contributed to the drafting of the manuscript. SC is the primary author of this overview. All authors contributed to editing all sections of the overview and take responsibility for the manuscript.

Declarations of interest

SC and SA are authors of a study included in one of the reviews (29). There are no known conflicts of interest.

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177. The Royal Australasian College of Physicians. Guideline Statement: Management of Procedure-Related Pain in Children and Adolescents. Sydney: Royal Australasian College of Physicians; 2005.

178. The Royal Australasian College of Physicians. Guideline Statement: Management of Procedure-Related Pain in Neonates; 2005.

Appendix 1

MEDLINE search strategy (via OvidSP)

Table A1. Update of Uman *et al.* (131)

MEDLINE (Ovid)
1 Needles/
2 (needle* or inject*).mp.
3 (immuni* or vaccin* or inject* or (finger adj1 prick*) or (heel adj1 prick*)).mp.
4 ((lumbar adj1 puncture*) or (spinal adj1 tap*)).mp.
5 ((bone adj1 marrow adj1 aspiration) or (bone adj1 marrow adj1 biops*)).mp.
6 (intravenous or intra-venous or venepuncture* or (venous adj1 cannulation*)).mp.
7 (catheter adj3 insert*).mp.
8 (central adj1 line adj3 insert*).mp.
9 (central adj1 venous adj1 catheter adj3 insert*).mp.
10 ((local adj1 analges*) or (local adj1 anaesthe*) or (local adj1 anesthe*)).mp.
11 ((arterial adj1 puncture) or (artery adj3 puncture)).mp.
12 (arterial adj1 line*).mp.
13 (thoracocentesis or paracentesis).mp.
14 or/1–13
15 exp Pain/
16 ((needle* adj3 pain*) or (needle* adj3 distress*) or (needle* adj3 discomfort) or (needle* adj3 fear*) or (needle* adj3 fright*) or (needle* adj3 anxious) or (needle* adj3 anxiet*) or (procedure* adj3 pain*) or (intervention* adj3 pain*) or (intervention* adj3 distress*) or (procedure adj3 distress*) or (procedure* adj3 discomfort*) or (immuni* adj3 pain) or (vaccin* adj3 pain*) or (inject* adj3 pain*) or (procedure-related adj3 pain)).mp.
17 or/15–16
18 (rehears* or coping or (verbal* adj1 encourage*) or (positiv* adj1 reinforce*) or reward* or token* or (self adj1 talk*) or selftalk* or (stop adj1 signal*) or (structured adj1 attention)).mp.
19 ((cognitive* adj3 intervention) or (cognitive* adj3 therapy) or (cognitive* adj3 distract*) or (behaviour* adj3 therap*) or (behaviour* adj3 intervention) or (behaviour* adj3 therap*) or (behaviour adj3 intervention)).mp.
20 (((audiovisual or (audio adj1 visual) or visual*) and distract*) or movie* or television or (virtual adj1 reality) or (tactile adj1 stimulat*) or (behaviour* adj3 distract*) or (behaviour* adj3 distract*)).mp.
21 (tv or game* or toy*).ti,ab.
22 (cognitive adj1 behavioural adj1 intervention*).mp.
23 ((multisensory adj1 stimulation) or (multisensory adj1 stimulation)).mp.
24 Cognitive Therapy/
25 Desensitization, Psychologic/
26 Relaxation Therapy/
27 Therapeutic Touch/
28 Relaxation/
29 Breathing Exercises/
30 exp Hypnosis/
31 "Imagery (Psychotherapy)"/
32 Laughter Therapy/
33 exp Psychotherapy/
34 (desensiti* or relax* or (therapeutic adj1 touch*) or (breathing adj1 exercise*) or hypnosis or hypnoti* or hypnotherapy or image* or psychotherap* or (tactile adj1 stimul*)).mp.
35 ((autogenic adj1 training) or (auto adj1 suggestion*)).mp.
36 ((colour* or colour* or music* or play) and (therap* or distract*)).mp.
37 Behaviour Therapy/
38 or/18–36
39 exp Child/
40 exp Infant/
41 Adolescent/
42 (child* or infant* or adolescent* or adolescence).mp.
43 or/39–41
44 14 and 17 and 38 and 43

Restricted to years July 2006–April 2012.

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Table A2. Update of Lander *et al.* (130)

MEDLINE (Ovid)
1 EMLA*.mp.
2 "eutectic mixture of local anesthetics".mp.
3 "eutectic mixture of local anaesthetics".mp.
4 Lidocaine/
5 Prilocaine/
6 (or/1–3) or (and/4–5)
7 topical anesthe*.mp.
8 topical anaesthe*.mp.
9 ametop*.mp.
10 amethocaine*.mp.
11 Tetracaine/
12 or/9–11
13 (1 or 2 or 3 or (4 and 5)) and (7 or 8) and (9 or 10 or 11)
14 Humans/
15 and/13–14
EMBASE (Ovid)

Restricted to years June 2005–April 2012.

EMBASE search strategy (via OvidSP)

Table A3. Update of Lander *et al.* (130)

EMBASE (Ovid)
1 EMLA*.mp.
2 "eutectic mixture of local anesthetics".mp.
3 "eutectic mixture of local anaesthetics".mp.
4 Lidocaine/
5 Prilocaine/
6 (or/1–3) or (and/4–5)
7 topical anesthe*.mp.
8 topical anaesthe*.mp.
9 ametop*.mp.
10 amethocaine*.mp.
11 Tetracaine/
12 or/9–11
13 (1 or 2 or 3 or (4 and 5)) and (7 or 8) and (9 or 10 or 11)
14 Humans/
15 and/13–14

Restricted to years June 2005–April 2012.

Appendix 2

Table A4. Quality assessment for which the Oxford Quality Scale (Jadad 1996) scale was used

Review	Trial	Allocation concealment	Blinding (coders blinded for at least 1 measure)*	Description of withdrawals/ dropouts	Treatment fidelity&	Quality Score
Uman 2010	Blount 1992	Unclear	—	—	—	0
	Cassidy 2002	Yes	Yes	—	Yes	2
	Cavender 2004	Yes	—	—	—	2
	Cohen 1997	Yes	—	—	Yes	0
	Cohen 1999	Yes	—	Yes	Yes	3
	Cohen 2002	Yes	—	—	—	0
	Eland 1981	Unclear	—	—	—	0
	Fanurik 2000	Unclear	—	—	—	0
	Fowler-Kerry 1987	Unclear	Yes	—	—	0
	Gonzalez 1993	Unclear	Yes	—	Yes	2
	Goodenough 1997	Unclear	Yes	—	—	0
	Harrison 1991	Unclear	—	—	—	0
	Katz 1987	Unclear	Yes	—	—	0
	Kleiber 2001	Yes	Yes	Yes	Yes	3

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Table A4. (*Continued*)

Review	Trial	Allocation concealment	Blinding (coders blinded for at least 1 measure)*	Description of withdrawals/ dropouts	Treatment fidelity&	Quality Score
	Kuttner 1987	Unclear	—	—	—	0
	Liossi 1999	Yes	Yes	Yes	—	1
	Liossi 2003	Unclear	—	Yes	Yes	1
	Liossi 2006	Yes	Yes	Yes	Yes	3
	Posner 1998	Unclear	—	Yes	—	1
	Press 2003	Unclear	—	—	—	0
	Tak 2005	Unclear	—	—	—	0
	Tyc 1997	Unclear	Yes	—	—	0
	Vessey 1994	Yes	—	—	—	2
	Wint 2002	Unclear	—	—	Yes	0
	Zabin 1982	Unclear	—	—	—	0
Lander 2010	Arrowsmith 2000	Unclear	Single blind	None	—	2
	Carceles 2002	Unclear	Double-blind	None	—	NR
	Choy 1999	Unclear	Unclear	Yes	—	2
	Lawson 1995	Unclear	Single blind	Yes	—	2
	Romsing 1999	Unclear	Double-blind	Not stated	—	3
	Van Kan 1997	Unclear	No	Yes	—	2

* This was not part of the Jadad scale but was coded to compensate for the fact that double-blinding is difficult to achieve with psychological interventions

& This was not part of the Jadad scale; the study was scored on whether the study provided a description regarding treatment fidelity (whether participants actually used the intervention they were assigned to)

NR Not reported

Table A5. Quality assessment for which the Cochrane ABCD concealment of allocation scale (Cochrane Handbook - Higgins 2005) was used

Review	Trial	Randomization (adequate or inadequate description)	ABCD concealment of allocation scale (Cochrane)
Lander 2010	Arrowsmith 2000	Inadequate	—
	Carceles 2002	Adequate	ABCDE
	Choy 1999	Inadequate	—
	Lawson 1995	Inadequate	—
	Romsing 1999	Inadequate	—
	Van Kan 1997	Inadequate	—

Table A6. Risk of bias assessment for which the Cochrane 'Risk of Bias' (Higgins 2008) scale was used

Review	Trial	Random sequence generation	Allocation concealment	Blinding of intervention	Incomplete outcome data reported	Selective outcome reporting	Other potential sources of bias
Harrison 2011	Allen 1996	Unclear risk	Low risk	Low risk	Unclear risk	Unclear risk	High risk
	Dilli 2009	Unclear risk	Low risk	Low risk	Low risk	Unclear risk	High risk
	Lewkowski 2003a	Unclear risk	Unclear risk	High risk	Low risk	Unclear risk	Low risk
	Lewkowski 2003b	Unclear risk	Unclear risk	High risk	Low risk	Unclear risk	Low risk

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Table A7a. Quality assessment for which the Yates (2005) Quality of Study Design and Methods Scale was used

Review: Pillai 2011	Trial							
Bias	**Allen 1996**	**Bauchner 1996**	**Bustos 2008**	**Cohen 2002**	**Cohen 2006**	**Cramer-Berness 2005**	**Cramer-Berness 2005b**	**Curtis 2007**
Sample criteria (0–1)	Low risk (1)	Low risk (1)	Low risk (1)	High risk (0)	Low risk (1)	Low risk (1)	High risk (0)	Low risk (1)
Evidence criteria was met (0–1)	Low risk (1)	Low risk (1)	Low risk (1)	High risk (0)	Low risk (1)	Low risk (1)	High risk (0)	Low risk (1)
Attrition (0–2)	High risk (0)	Low risk (1)	Low risk (2)	High risk (0)	Low risk (1)	Low risk (1)	Low risk (2)	Low risk (1)
Rates of attrition (0–1)	High risk (0)	Low risk (1)	Low risk (1)	High risk (0)	High risk (0)	High risk (0)	Low risk (1)	Low risk (1)
Sample characteristics (0–1)	High risk (0)	Low risk (1)	High risk (0)	Low risk (1)	Low risk (1)	Low risk (1)	Low risk (1)	Low risk (1)
Group equivalence (0–1)	High risk (0)	Low risk (1)	Low risk (1)	Low risk (1)	Low risk (1)	Low risk (1)	Low risk (1)	Low risk (1)
Randomization (0–2)	Low risk (1)	Low risk (2)	Low risk (2)	High risk (0)	Low risk (2)	Low risk (1)	Low risk (2)	Low risk (2)
Allocation bias (0–1)	High risk (0)	High risk (0)	Low risk (1)	High risk (0)	Low risk (1)	Low risk (1)	Low risk (1)	Low risk (1)
Measurement bias (0–1)	High risk (0)	High risk (0)	High risk (0)	High risk (0)	High risk (0)	High risk (0)	Low risk (1)	Low risk (1)
Justification of outcomes (0–2)	Low risk (1)	Low risk (1)	Low risk (2)	Low risk (2)	Low risk (2)	Low risk (2)	Low risk (2)	Low risk (2)
Validity of outcomes for context (0–2)	Low risk (1)	Low risk (1)	Low risk (2)	Low risk (2)	Low risk (2)	Low risk (2)	Low risk (2)	Low risk (2)
Reliability and sensitivity (0–2)	Low risk (1)	Low risk (1)	Low risk (1)	Low risk (1)	Low risk (2)	Low risk (2)	Low risk (2)	Low risk (2)
Power calculation (0–1)	High risk (0)	High risk (0)	Low risk (1)	High risk (0)	Low risk (1)	Low risk (1)	Low risk (1)	Low risk (1)
Sufficient sample (0–1)	High risk (0)	Low risk (1)	Low risk (1)	High risk (0)	Low risk (1)	Low risk (1)	High risk (0)	Low risk (1)
Planned analysis (0–1)	High risk (0)	Low risk (1)	Low risk (1)	Low risk (1)	Low risk (1)	Low risk (1)	Low risk (1)	Low risk (1)
Statistics reporting (0–1)	High risk (0)	Low risk (1)	Low risk (1)	Low risk (1)	High risk (0)	Low risk (1)	Low risk (1)	Low risk (1)
Intention-to-treat (0–1)	High risk (0)	Low risk (1)	High risk (0)	High risk (0)	High risk (0)	High risk (0)	Low risk (1)	High risk (0)
Adequate control group (0–1)	Low risk (1)	Low risk (1)	High risk (0)	Low risk (1)	High risk (0)	Low risk (1)	High risk (0)	Low risk (1)
Total quality score (0–26)	**High risk (7)**	**Low risk (17)**	**Low risk (18)**	**High risk (10)**	**Low risk (17)**	**Low risk (18)**	**Low risk (19)**	**Low risk (21)**
Blinding	High risk	High risk	Low risk	Low risk	High risk	High risk	High risk	High risk
Selective outcome reporting	High risk	High risk	Low risk	High risk	High risk	High risk	High risk	High risk
Other potential sources of bias	High risk	High risk	Low risk	Low risk	High risk	High risk	High risk	High risk

Table A7b. Quality assessment for which the Yates (2005) Quality of Study Design and Methods Scale was used – continued

Review: Pillai 2011	Trial		
Bias	**Hillgrove Stuart 2008**	**Ipp 2004**	**Kozub 2001**
Sample criteria (0–1)	Low risk (1)	Low risk (1)	Low risk (1)
Evidence criteria was met (0–1)	Low risk (1)	Low risk (1)	Low risk (1)
Attrition (0–2)	Low risk (1)	Low risk (1)	Low risk (2)
Rates of attrition (0–1)	Low risk (1)	Low risk (1)	Low risk (1)
Sample characteristics (0–1)	Low risk (1)	Low risk (1)	Low risk (1)
Group equivalence (0–1)	Low risk (1)	Low risk (1)	Low risk (1)
Randomization (0–2)	Low risk (2)	Low risk (1)	Low risk (2)
Allocation bias (0–1)	Low risk (1)	Low risk (1)	Low risk (1)
Measurement bias (0–1)	Low risk (1)	High risk (0)	Low risk (1)
Justification of outcomes (0–2)	Low risk (2)	Low risk (2)	Low risk (2)
Validity of outcomes for context (0–2)	Low risk (2)	Low risk (2)	Low risk (2)
Reliability and sensitivity (0–2)	Low risk (2)	Low risk (1)	Low risk (2)
Power calculation (0–1)	Low risk (1)	Low risk (1)	Low risk (1)
Sufficient sample (0–1)	Low risk (1)	Low risk (1)	High risk (0)
Planned analysis (0–1)	Low risk (1)	Low risk (1)	Low risk (1)
Statistics reporting (0–1)	High risk (0)	Low risk (1)	Low risk (1)
Intention-to-treat (0–1)	Low risk (1)	Low risk (1)	Low risk (1)
Adequate control group (0–1)	High risk (0)	Low risk (1)	Low risk (1)
Total quality score (0–26)	**Low risk (20)**	**Low risk (19)**	**Low risk (22)**
Blinding	High risk	High risk	High risk
Selective outcome reporting	High risk	High risk	High risk
Other potential sources of bias	High risk	High risk	High risk

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Appendix 3

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Balan 2009	**2**	**2.22**	**50**	**8**	**1.48**	**50**	**6.0%**	**-3.16 [-3.75, -2.56]**
Berberich 2009	**2**	**1.481**	**20**	**6.57**	**5.926**	**21**	**5.8%**	**-1.03 [-1.68, -0.37]**
Cassidy 2002	1.36	1.39	31	2.03	1.9	28	6.3%	-0.40 [-0.92, 0.12]
Cavender 2004	2.3	1.87	20	2.74	1.63	20	5.9%	-0.25 [-0.87, 0.38]
Fanurik 2000	22.6	24.03	53	27.29	29.27	56	6.8%	-0.17 [-0.55, 0.20]
Fowler-Kerry 1987	1.34	1.14	40	1.78	1.14	80	6.8%	-0.38 [-0.77, -0.00]
Gonzalez 1993	2.86	1.61	14	3.29	1.44	14	5.5%	-0.27 [-1.02, 0.47]
Kleiber 2001	3.24	1.95	22	2.7	1.4	22	6.0%	0.31 [-0.28, 0.91]
Kristjansdottir 2010	**1.01**	**1.48**	**38**	**1**	**0.95**	**39**	**6.6%**	**0.01 [-0.44, 0.45]**
Nguyen 2010	**2.35**	**1.9**	**20**	**5.65**	**2.5**	**20**	**5.6%**	**-1.46 [-2.16, -0.75]**
Noguchi 2006	**2.67**	**2.79**	**21**	**3.53**	**2.76**	**20**	**6.0%**	**-0.30 [-0.92, 0.31]**
Press 2003	2.8	2	48	3.8	2.9	46	6.7%	-0.40 [-0.81, 0.01]
Tak 2005	2.58	1.89	20	1.85	1.18	20	5.9%	0.45 [-0.17, 1.08]
Vessey 1994	2.18	1.61	50	3.23	1.78	50	6.7%	-0.61 [-1.02, -0.21]
Wang 2008	**4.55**	**2.262**	**100**	**5.22**	**2.529**	**100**	**7.1%**	**-0.28 [-0.56, 0.00]**
Windich-Biermeier 2007	**0.28**	**0.41**	**22**	**0.84**	**2.21**	**28**	**6.2%**	**-0.33 [-0.89, 0.23]**
Total (95% CI)			**569**			**614**	**100.0%**	**-0.51 [-0.84, -0.17]**

Heterogeneity: $Tau^2 = 0.40$; $Chi^2 = 114.12$, df = 15 ($P < 0.00001$); $I^2 = 87\%$
Test for overall effect: Z = 2.92 (P = 0.003)

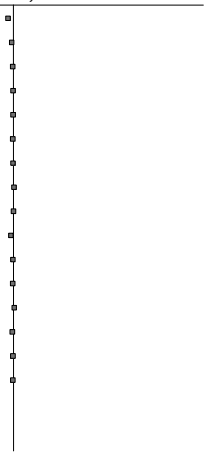

Figure A1. Distraction versus control/standard care – self-reported pain

Study or Subgroup	Treatment Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Cavender 2004	2.15	1.81	20	2.74	1.86	23	19.7%	-0.32 [-0.92, 0.29]
Fanurik 2000	35.5	30.1	56	35	29.8	59	23.9%	0.02 [-0.35, 0.38]
Nguyen 2010	**8.1**	**2.22**	**20**	**13**	**4.17**	**20**	**17.9%**	**-1.44 [-2.14, -0.73]**
Windich-Biermeier 2007	**0.36**	**0.9**	**22**	**0.54**	**1.04**	**28**	**20.5%**	**-0.18 [-0.74, 0.38]**
Zabin 1982	2	2.5	16	1.13	1.99	16	18.0%	0.38 [-0.32, 1.08]
Total (95% CI)			**134**			**146**	**100.0%**	**-0.29 [-0.79, 0.22]**

Heterogeneity: $Tau^2 = 0.24$; $Chi^2 = 16.00$, df = 4 ($P = 0.003$); $I^2 = 75\%$
Test for overall effect: Z = 1.10 (P = 0.27)

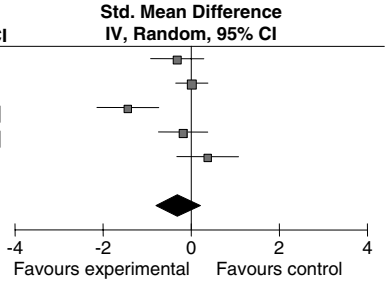

Figure A2. Distraction versus control/standard care – self-reported distress

Study or Subgroup	Treatment Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Berberich 2009	**1.65**	**2.037**	**20**	**5.71**	**2.963**	**21**	**30.5%**	**-1.56 [-2.27, -0.85]**
Cassidy 2002	5.16	2.67	27	4.69	2.96	25	33.5%	0.16 [-0.38, 0.71]
Vessey 1994	7.76	2.5	50	8.73	2.38	50	36.0%	-0.39 [-0.79, 0.00]
Total (95% CI)			**97**			**96**	**100.0%**	**-0.56 [-1.40, 0.27]**

Heterogeneity: $Tau^2 = 0.46$; $Chi^2 = 14.37$, df = 2 ($P = 0.0008$); $I^2 = 86\%$
Test for overall effect: Z = 1.32 (P = 0.19)

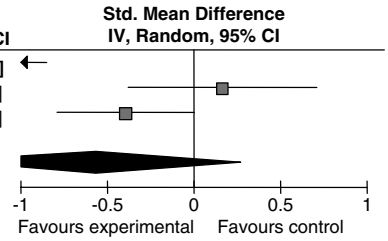

Figure A3. Distraction versus control/standard care – behavioural measures of pain

Study or Subgroup	Treatment Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Caprilli 2007	**6.8**	**7.5**	**54**	**13.5**	**9.7**	**54**	**27.0%**	**-0.77 [-1.16, -0.38]**
Gonzalez 1993	4.84	1.46	14	5.81	1.2	14	17.6%	-0.70 [-1.47, 0.06]
Kleiber 2001	1.89	1.22	22	2.13	2.77	22	21.7%	-0.11 [-0.70, 0.48]
Kuttner 1987	13.8	4.4	8	9.1	5.5	8	12.6%	0.89 [-0.15, 1.93]
Noguchi 2006	**3.11**	**3.02**	**21**	**3.98**	**3.51**	**20**	**21.1%**	**-0.26 [-0.88, 0.35]**
Total (95% CI)			**119**			**118**	**100.0%**	**-0.30 [-0.77, 0.17]**

Heterogeneity: $Tau^2 = 0.17$; $Chi^2 = 10.93$, df = 4 ($P = 0.03$); $I^2 = 63\%$
Test for overall effect: Z = 1.24 (P = 0.21)

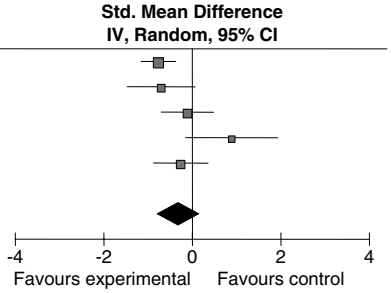

Figure A4. Distraction versus control/standard care – behavioural measures of distress

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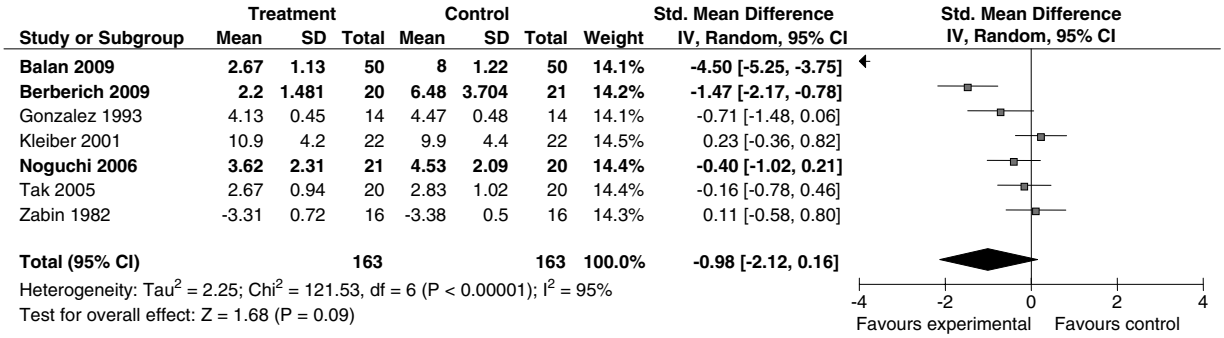

Figure A5. Distraction versus control/standard care – observer-reported distress

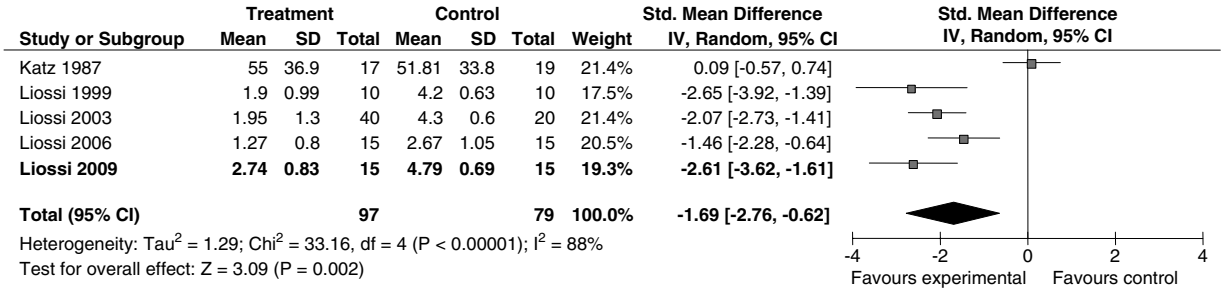

Figure A6. Hypnosis versus control/standard care – self-reported pain

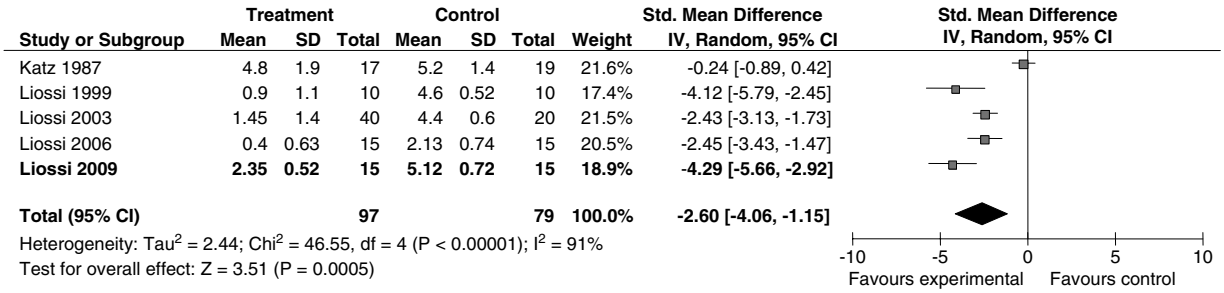

Figure A7. Hypnosis versus control/standard care – self-reported distress

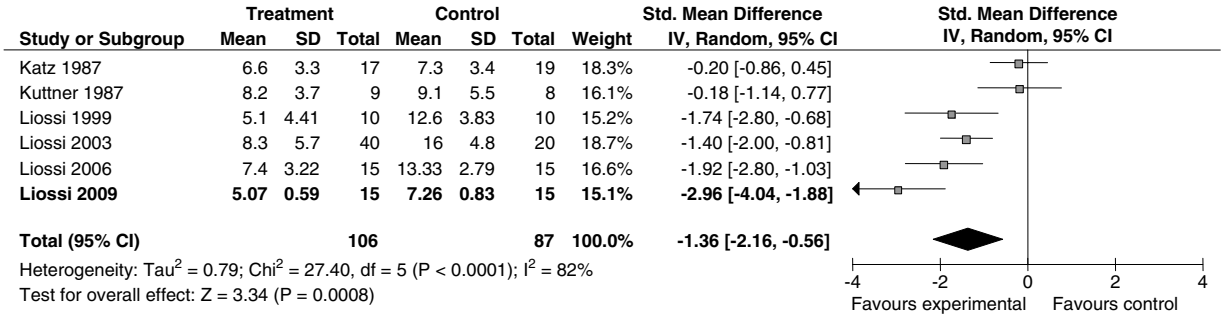

Figure A8. Hypnosis versus control/standard care – behavioural measures of distress

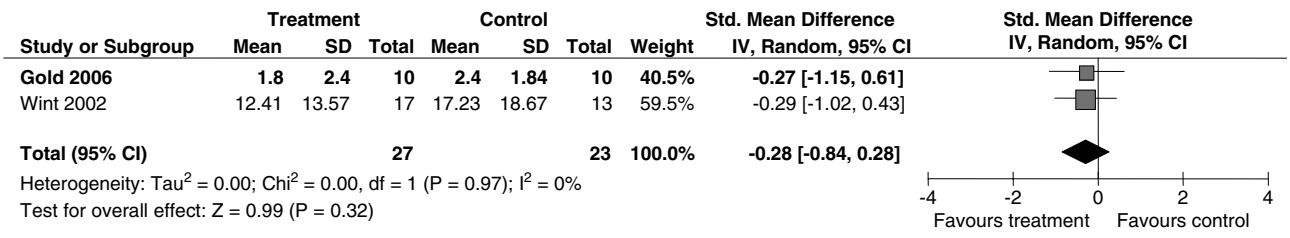

Figure A9. Virtual reality versus control/standard care – self-reported pain

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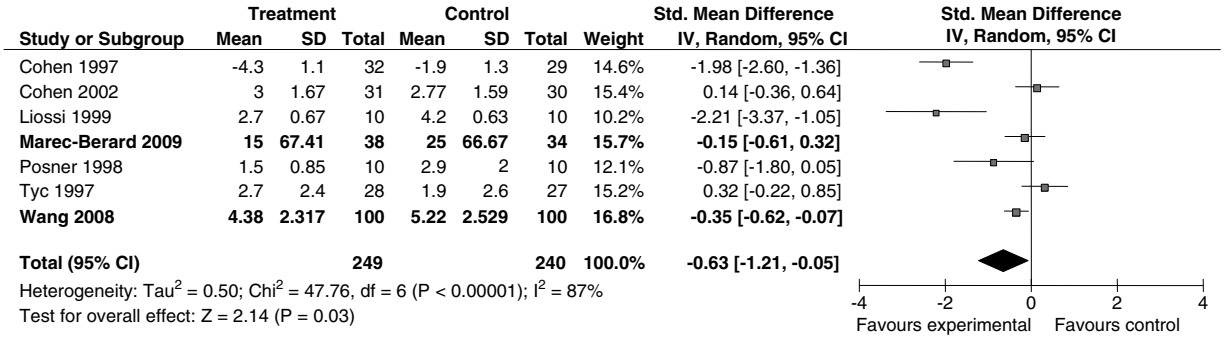

Figure A10. Cognitive–behavioural therapy combined versus control/standard care – self-reported pain

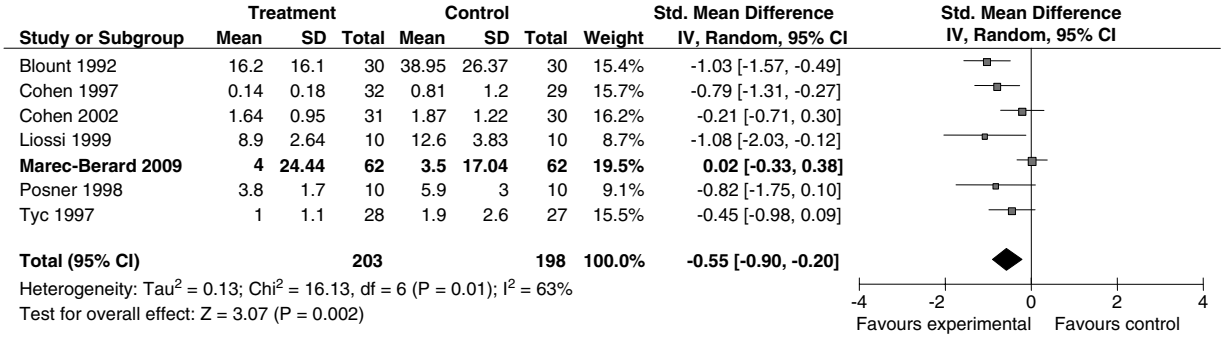

Figure Ax211. Cognitive–behavioural therapy combined versus control/standard care – behavioural measures of distress

Appendix 4

Table A8. Pain scales

Abbreviation	Scale
BAADS	Behavioral Approach-Avoidance and Distress Scale
CAMPIS	Child-Adult Medical Procedure-Interaction Scale
CAMPIS-R	Child-Adult Medical Procedure-Interaction Scale—Revised
CAMPIS-SF	Child-Adult Medical Procedure-Interaction Scale—Short Form
CAS	Colour Analogue Scale
CFCS	Child Facial Coding System Child Medical Distress Scale
CHEOPS	Children's Hospital of Eastern Ontario Pain Scale*
FLACC	Face Legs Arms Cry Consolability Scale*
FPS	Faces Pain Scale*
FPS-R	Faces Pain Scale—Revised* Fear Self-Report Glasses Fear Scale
GDS	Groningen Distress Scale LeBaron Scale Loebach & Schroeder 1979 tool (adapted) MRI Behavior Checklist MRI Distress Rating
MAISD	Measure of Adult and Infant Soothing and Distress
MBPS	Modified Behavioral Pain Scale Modified Frankl Behaviour Rating Scale
NFCS	Neonatal Facial Coding System
NRS	Numeric Rating Scale
OSBD	Observation Scale of Behavioral Distress

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Table A8. (*Continued*)

Abbreviation	Scale
OSBD-A	Observation Scale of Behavioural Distress—Amended
OSBD-R	Observation Scale of Behavioural Distress—Revised
	Oucher Pain Scale*
	Pain Self-Report
PCT	Poker Chip Tool*
PIPP	Premature Infant Pain Profile
PBCL	Procedural Behaviour Checklist*
PBRS-R	Procedural Behaviour Rating Scale—Revised*
PPQ-R	Perception of Procedures Questionnaire—Revised
STAI	State-Trait Anxiety Inventory
STAI-C	State-Trait Anxiety Inventory for Children
VAS	Visual Analogue Scale*
	Wong-Baker FACES Scale/FACES Scale*

* PedIMMPACT recommended pain scale.

If you would like to make a comment on the above article, you are invited to submit a letter to the Editor by email (child@ualberta.ca). Selected letters may be edited and published in future issues of the journal.

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