MUSIC IN MEDICINE

The value of music interventions for hospitalised children

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Music in Medicine
The value of music interventions for hospitalised children

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De waarde van muziekinterventies voor kinderen in het ziekenhuis

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*“In Xhosa culture, Qongqothwane - the song of the beetle - points the way home;
it points the way to a better future in times of trouble”*

- Miriam Makeba -
Qongqothwane (The Click Song)

CONTENTS

CHAPTER 1

Introduction

"One good thing about music is when it hits, you feel no pain"

- Bob Marley -

Why music in medicine?

A hospital can be a frightening place, for children and their parents alike, filled with unfamiliar sounds, faces and eerie equipment. Furthermore, loss of control and self-sufficiency is lying in wait as they undergo medical procedures and have to await diagnosis and treatment plans.

On average a hospitalised child undergoes six painful procedures per day (1). Prematurely born babies admitted to the Neonatal Intensive Care Unit undergo an estimated number of 10-14 painful procedures per day (2-4). Children in intensive care, emergency care and surgical wards can experience high levels of background and acute pain related to their condition and medical procedures, as well as distress in anticipation of a medical procedure (5,6). Anticipatory distress, in turn, increases the likelihood of experiencing more pain and distress during the actual procedure (5). The higher the levels of distress, the more pain is remembered in hindsight, which memory can affect the pain experience of later painful procedures (7-9).

Preventing and reducing pain and distress, and improving relaxation and sleep are pivotal in the hospitalised child's recovery; and it is this knowledge that drives researchers and clinicians to search for new solutions and supportive therapies.
Music interventions are increasingly being considered as a means to improve the care for hospitalised children and their parents (10, 11). The scientific search engine PubMed shows an increase in 'music in medicine' research over the past decades. While until the 2000s yearly some 200 articles on music were published, this number had increased to almost 900 by 2010, and 1480 in 2017. However, much of this research was performed by scholars from the arts and music sciences who, understandably, did not follow the guidelines of evidence-based medicine. Therefore, the medical field is not yet convinced of the effects and the potential use of music in the care for hospitalised children.

The principles of music

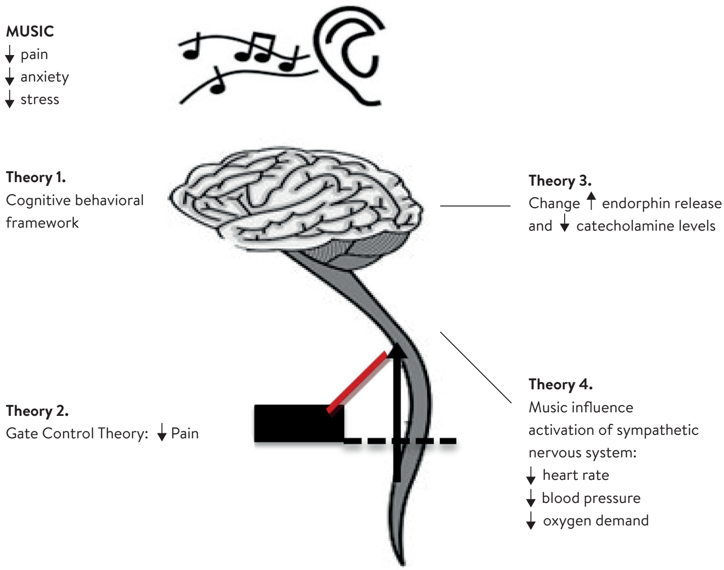
Music is defined as 'intentional sound described in terms of pleasing harmonies, dynamics, rhythm, tempo and volume' (12). But more than just pleasant sound, music has been celebrated for its ability to bring about emotional reactions, affect feelings and moods, inspire the imagination and facilitate human expression. Discussed throughout time by the greatest philosophers[1], music is often described as "the language of emotions" because "music can express that which words cannot" (13). Moreover, music can bring about physiological reactions such as change in skin temperature, heart rate and brain activation (6-8). Koelsch argues that music cannot be studied in terms of mechanisms that induce or produce emotions for this would imply a "one music fix for all" whereby a particular piece of music would presumably always have a specific emotional effect - which is not very likely. Instead Koelsch sees music as a process that can evoke or modulate emotions which have to be understood in the context of the patient's personal situation (14).

1. "Music is a moral law. It gives soul to the universe, wings to the mind, flight to the imagination and charm and gaiety to life and to everything" (Plato c.428 – 348 BC).
"The inexpressible depth of music, so easy to understand and yet so inexplicable, is due to the fact that it reproduces all the emotions of our innermost being, but entirely without reality and remote from its pain...music expresses only the quintessence of life and its events, never these themselves" (Arthur Schopenhauer 1788-1860).

Why does music have the ability to move us physically and emotionally? And how can we best make use of the unique principles of music? In their systematic review, van der Wal-Huisman et al. (15) reveal four theoretical models explaining how music might affect our brain and nervous and thereby our emotional reaction and pain perception (see Figure 1.1).

First, the cognitive behavioural framework takes into account that music serves as a distractor, diverting attention from painful stimuli and stressful events to something more pleasant and thereby supporting behavioural cognitive coping mechanisms (16, 17).
The second model is based on the Gate Control Theory, described in 1965 by Melzack et al. (18), which provides a neurobiological perspective on pain perception. According to this theory the synapses that receive the pain impulse from the nerve receptors are thought to act as gates that can either open or close and thus control whether the pain impulse reaches the brainstem. Pain impulses that are transmitted to the brain can be intercepted by other impulses such as shifting attention through distraction, in this case listening to music or making music.

Figure 1.1 - Theoretical principles of the effects of music



(Figure developed by van der Wal-Huisman et al. (2018) and printed with permission of the authors)

According to the third theory, music activates the limbic system - in particular the nucleus accumbens, amygdala and hippocampus, the pleasure and reward systems in the brain - thereby releasing dopamine and endorphins (19-22).
Lastly, the fourth model states that stress caused by pain may activate the sympathetic nervous system (23, 24). Furthermore, music is thought to reduce autonomic nervous system activity by inducing relaxation. This in turn results in lowering of the pulse and respiration rates and of the blood pressure (25-28). Music listening activates auditory, cognitive, motor and emotional functions across the brain (29, 30). In children, similar

parts of the brain are activated as in adults (31). Music has always been used to soothe infants and young children. Still, we are only now beginning to understand the biological processes of how children of different ages process and respond to music (31-34).

Different types of music interventions in medicine

Music can be used in different ways: from patient-initiated music listening, to pre-recorded music provided by hospital staff and to live music therapy offered by music therapists (25, 35, 36). Live music therapy is an individualised intervention in which the music therapist engages with the patient by making live music, playing an instrument together or improvising using voice and instruments (25). It is the therapeutic relationship that distinguishes music therapy from other forms of music listening (35). Music therapists are certified therapists who are at the same time musicians with an understanding of psychotherapy and who use music-making as part of the therapy. Music therapists can specialise in for example psychiatry, neurology, palliative care, paediatrics, intensive care (including neonatology), social work and community health care projects (for example in health awareness programmes).

An evidence base for music in medicine

A recently published meta-analysis from our research group that included 92 RCTs shows a significant reduction of anxiety and pain in adults following perioperative music interventions (37). Anxiety is related to the specific behaviours of fight-or-flight responses. It occurs in situations perceived as uncontrollable or unavoidable. In adult patients this is often operationalised with the use of the State-Trait Anxiety Inventory (STAI), and in adolescents with the State-Trait Anxiety Inventory for Children (STAIC) (38, 39). In young children, the unfamiliar and incomprehensible hospital setting may result to distress of a more general state (40). Therefore, in young children distress is operationalised with the COMFORT Behavioural scale (40, 41).

Notwithstanding evidence from the adult literature and despite their harmless character, music interventions have so far not been integrated in modern hospital care for children. Some departments or hospitals do offer music programmes, but these are often provided as an extra service funded privately or carried out by volunteers.

The studies in this thesis concern different paediatric patient groups and clinical settings. Below is summarised what is already known about music interventions in these groups and settings.

Music in the neonatal intensive care unit

Health professionals are increasingly aware that the acoustic environment in the NICU may affect neonates' well-being (42, 43). Although unpredictable noise adversely affects sleep and physiologic stability, meaningful auditory stimulation, such as music, might contribute to a premature infant's neurodevelopment. Up to August 2016, nine reviews on the effects of music interventions in premature infants have been published, not all of which included only RCTs (12, 44-50). Music interventions were found to have a potential beneficial effect on behavioural state, physiological measures and pain, but the heterogeneity in studies precluded definite conclusions on efficacy.

Music for perioperative care

Adults and children undergoing surgery may experience perioperative pain, anxiety and distress (51). Unfortunately it is not always possible to completely prevent perioperative pain, anxiety and distress with analgesics and anxiolytics (sedatives). In adults, music interventions have been shown effective in reducing pain and anxiety (28, 37, 52). However, few studies have been performed on the effects of music interventions in children, and music interventions are not included in guidelines for paediatric surgery and anaesthesiology.

Music in the emergency room

Undergoing a medical procedure in the emergency room can be very upsetting for children and their acute pain is often accompanied by distress (5). Listening to music or watching a cartoon might be beneficial distraction techniques, however the evidence is still inconclusive (53-59).

Music in burns wound care procedures

Burns are associated with painful and distressing experiences due to the trauma of the injury, hospitalisation and painful wound care procedures (WCP) (6, 60). Moreover, burn injuries have been linked to acute and post-traumatic stress disorders (61-63). The majority of children with burn wounds are under 5-year-olds. In a high-resource burns unit it was reported that 66% of the children expressed moderate and 25% severe procedural pain intensity during WCP (64). However, data is lacking on the level of pain during WCP in children from lower socio-economic circumstances with fewer resources, as is the case at Red Cross War Memorial Children's Hospital in Cape Town, South Africa.

In adults, music interventions seem to be beneficial in reducing WCP-related pain and anxiety (65-67). In children, only one small study with inconclusive results has been performed on the effects of music therapy during WCP (68).

This thesis addresses the question: 'music in medicine: does it work and should we use it in hospitalised children'? The overall aim was to find if live music therapy and recorded music interventions could reduce pain and distress evoked by medical procedures. The findings could help convince the medical field of the benefits of music interventions in hospitalised children.

The key objectives are:

1. To systematically review whether prematurely born infants in the Neonatal Intensive Care Unit can benefit from live and recorded music interventions (Chapter 2).
2. To perform a meta-analysis on the effects of perioperative music interventions in young children undergoing surgery (Chapter 3).
3. To compare a recorded music intervention to watching cartoons during painful procedures in the Emergency Room in children age 3-13 years (Chapter 4).
4. To evaluate the levels of pain and distress children experience during wound care procedures and to measure the effects of live music therapy on distress and pain after wound care procedures in a randomised controlled trial (Chapters 5 and 6).

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CHAPTER 2

Do hospitalised premature infants benefit from music interventions? A systematic review of randomised controlled trials

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ABSTRACT

Objective
Neonatal intensive care units (NICU) around the world increasingly use music interventions. The most recent systematic review of randomised controlled trials (RCT) dates from 2009. Since then, 15 new RCTs have been published. We provide an updated systematic review on the possible benefits of music interventions on premature infants' well-being.

Methods
We searched 13 electronic databases and 12 journals from their first available date until August 2016. Included were all RCTs published in English with at least 10 participants per group, including infants born prematurely and admitted to the NICU. Interventions were either recorded music interventions or live music therapy interventions. All control conditions were accepted as long as the effects of the music intervention could be analysed separately. A meta-analysis was not possible due to incompleteness and heterogeneity of the data.

Results
After removal of duplicates the searches retrieved 4893 citations, 20 of which fulfilled the inclusion/exclusion criteria. The 20 included studies encompassed 1128 participants receiving recorded or live music interventions in the NICU between 24 and 40 weeks gestational age. Twenty-six different outcomes were reported which we classified into three categories: physiological parameters; growth and feeding; behavioural state, relaxation outcomes and pain. Live music interventions were shown to improve sleep in three out of the four studies and heart rate in two out of the four studies. Recorded music improved heart rate in two out of six studies. Better feeding and sucking outcomes were reported in one study using live music and in two studies using recorded music.

Conclusions
Although music interventions show promising results in some studies, the variation in quality of the studies, age groups, outcome measures and timing of the interventions across the studies makes it difficult to draw strong conclusions on the effects of music in premature infants.

Abbreviations: AAP: American Academy of Pediatrics; dB: decibel; GA: gestational age; HR: heart rate; NICU: neonatal intensive care unit; NIDCAP: Newborn Individualized Development Care and Assessment Program; PAL: Pacifier Activated Lullaby; PIPP: Premature Infant Pain Profile; RCT: randomised controlled trial; REE: resting energy expenditure; RR: respiratory rate; SatO2: oxygen saturation

INTRODUCTION

Health professionals are increasingly aware that the acoustic environment in the neonatal intensive care unit (NICU) may affect infants' well-being. Where unpredictable noise adversely affects sleep and physiologic stability [1,2], meaningful auditory stimulation, such as music, might contribute to the neurodevelopment of premature infants.

Music is defined as intentional sound described in terms of pleasing harmonies, dynamics, rhythm, tempo and volume [3]. Music interventions can consist of a combination of instrumental music and song, performed live or pre-recorded. Music interventions for the NICU should be soothing and not use too many different elements in terms of instruments, rhythms, timbres, melodies and harmonies [4]. The preferred choice of music is a lullaby, softly sung or played on an instrument. Several observational studies suggest that music might have a positive effect on physiological parameters, feeding and development of premature infants [5-13].

Recorded music interventions in the NICU usually consist of music softly played through an audio player in or outside the incubator. This is recommended for infants from 28 weeks gestational age (GA) [14]. Another recorded music intervention is the pacifier activated lullaby (PAL), recommended for infants from 30 weeks GA [14], where the infants' sucking on a pacifier activates a lullaby played inside the incubator. In live music therapy interventions a certified music therapist softly sings lullabies, sometimes accompanied by guitar, harp, or drum playing. Other instruments used are the Gato Box, a 2- or 4-tone wooden box or drum that is played with the fingers, and the Ocean Disc, an instrument shaped as a round disc with metal beads inside that make a whooshing sound to the padded interior shell of the disc. Live music therapy in the NICU is recommended for infants from 32 weeks GA [14].

Up to August 2016, nine reviews on the effects of music interventions in premature infants have been published [3,14-21], not all of which included only RCTs. Standley et al. [14,21] published an updated meta-analysis in 2012 concluding that music interventions have a beneficial significant effect on heart rate, behavioural state, oxygen saturation, sucking/feeding ability and length of stay. Apart from RCTs, the meta-analysis also included non-randomised trials and studies with samples sizes <10 per group. Hartling et al. [16] published the most recent systematic review of only RCTs on the effects of music in neonates in 2009, including both preterm and term infants. The authors concluded that music may be beneficial on behavioural state, physiological measures and pain, but the heterogeneity in studies precluded a meta-analysis and definite conclusions on efficacy. Since 2009, fifteen new RCTs on this topic have been published, which justifies our update. This current systematic review of RCTs on the effectiveness of live and recorded music interventions in premature infants in the NICU was performed with no restrictions on type of outcome measures.

METHODS

This systematic review followed the recommendations of the Cochrane Collaboration and the PRISMA Guidelines for reporting a systematic review (see S1 Table for the PRISMA checklist). We made use of a pre-defined research protocol (see S2 File Review protocol).

Criteria for considering studies for this review

The following inclusion criteria were applied: papers published in English reporting RCTs including prematurely born infants 24-37 weeks GA with a parallel group, crossover or cluster design. Only studies in which the effects of music could be analysed separately from the control condition were included. Studies in which fewer than 10 patients received the intervention were considered pilot studies and were therefore excluded. Interventions were either recorded or live music interventions as defined above. Interventions that required participation of a parent were only accepted if it included musical expression such as singing. Excluded were studies using speech or the sounds of the womb, and studies with interventions that used non-human sounds, such as nature sounds.

Search methods for identification of studies

We searched 13 electronic databases and trial registers from their first available date until August 2016. Furthermore we hand-searched 12 journals from their first available date (see S3 File Full list of search terms, electronic databases and hand-searched journals). The reference lists of the articles were checked for other relevant articles not retrieved by the search strategies, and attempted to order full-text articles when necessary. Additionally, we defined key references (see S3 File Full list of search terms, electronic databases and hand-searched journals) and performed a forward citation search in Web of Science.

Data collection

Two authors (MvdH and SO) selected the potentially eligible articles by independently screening the titles and abstracts of the retrieved records for relevance. A study was rejected if the abstract made clear that the trial did not meet the inclusion criteria. If there was doubt about the inclusion the two independent reviewers would consult the final author (MvD). Two authors extracted data for all articles using the Cochrane Collaboration Data Collection Form for intervention reviews. The results of the data extraction were compared between the two authors to preclude any differences. Risk of bias was assessed using the Cochrane Risk of Bias tool. Items scored included: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data and selective reporting.

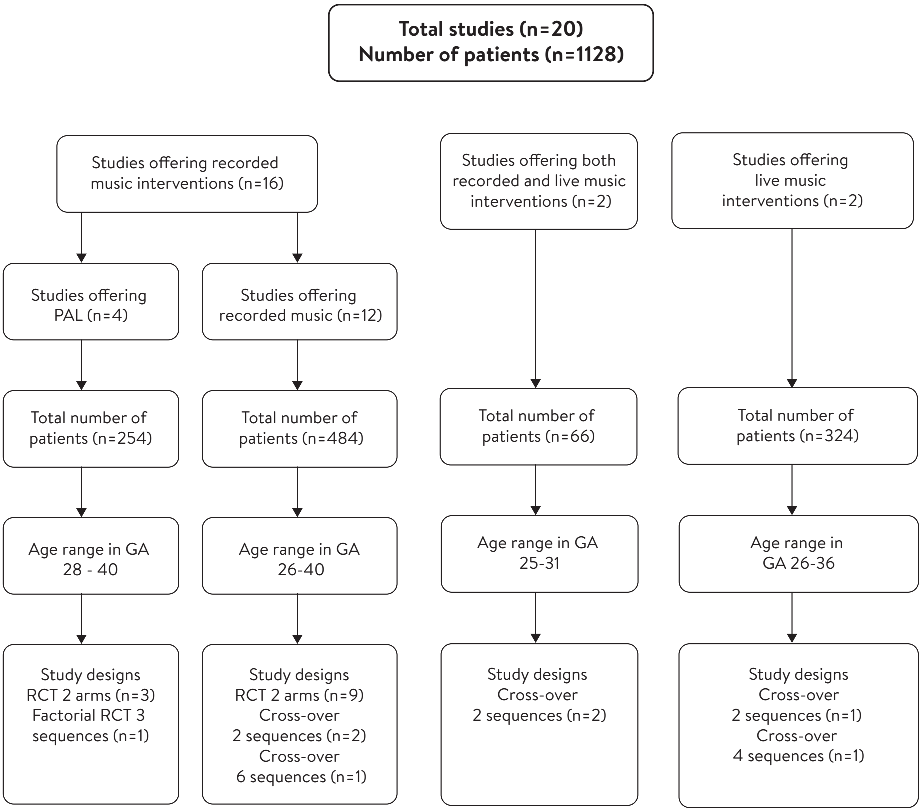
Data presentation and analysis

We classified the 26 different outcomes measured in the studies into three categories: physiological parameters; growth and feeding; behavioural state, relaxation outcomes and pain. A meta-analysis was not possible due to missing and heterogeneous data. For the purpose of this review we only present the results compared between the intervention and control groups. Figure 2.1 gives the characteristics of the included studies (see S4 Table for the extensive overview); Figure 2.2 depicts the number of records identified, included and excluded, and the reasons for exclusion in the PRISMA Flowchart. Table 2.1 shows the risk of bias for all studies (determined with the Cochrane Collaboration tool for assessing risk of bias in included studies [22]; and Table 2.2 the characteristics of the music interventions. Tables 2.3, 2.4, and 2.5 show the between group results for the respective outcome categories mentioned above.

RESULTS

The search strategy yielded 7744 citations; after duplicates were removed 4893 citations were left for screening. A total of 20 RCTs were included, of which 12 had a parallel group design, 7 a crossover design and 1 a factorial randomised trial design (see Fig 2.2 PRISMA flowchart).

Fig 2.1 - Characteristics of included studies

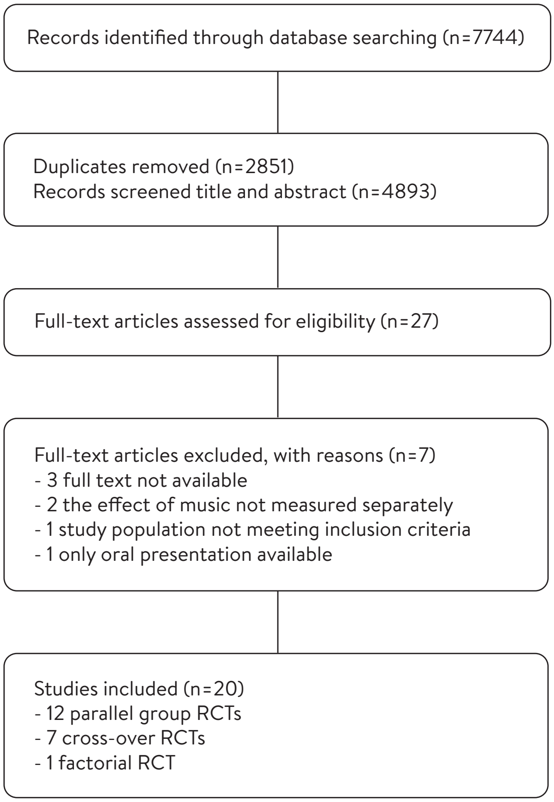


The total number of subjects was 1128, all born prematurely before 37 weeks, admitted to a NICU and receiving music interventions at ages ranging from 25 to 40 weeks GA. The studies dated from 2003 to 2016 and had been carried out in the USA [4,12,23-

26], Israel [27-29], Iran [30-33], Turkey [34], Australia [35,36], Lithuania [37], Germany [38,39] and Brazil [40]. Live music was offered in four studies; recorded music in eighteen studies. Two studies [29,37] offered both live and recorded music interventions.

Risk of bias

Fig 2.2 - PRISMA flowchart PRISMA flowchart



Thirteen out of 20 studies were rated to have an unclear risk of bias (see Table 2.1). Eight studies did not report the randomisation method. In two studies study personnel was not blinded; twelve other studies did not report on blinding. The outcome assessor was blinded to group allocation in ten studies [4,24-26,28,29,31,35-37]. Four studies published between 2012 and 2015 had a low overall risk of bias [4,26,31,36], which indicates an improvement of the quality of the recent studies.

Description of the interventions

Recorded music interventions: Eighteen studies [12,23-27,29-40] offered recorded music interventions consisting of recordings of lullabies with or without song and classical instrumental music. In nine studies the choice of the music intervention was based on the advice of a certified music therapist; the research team selected the music in the other nine studies. In two studies the music was delivered through headphones [31,40];

Table 2.1 - Risk of bias Cochrane Collaboration tool for assessing risk of bias

Author	Selection bias		Performance bias	Detection bias	Attrition bias	Reporting bias	Overall risk of bias
	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	
Cardoso (2014)	Low	Low	Unclear	Unclear	Unclear	Unclear	Unclear
Chorna (2014)	Low	Unclear	Low	Low	Low	Low	Low
Dorn (2014)	Low	Low	Unclear	Unclear	Low	Low	Unclear
Garunkstiene (2014)	Low	Unclear	Unclear	Low	Low	Low	Unclear
Amini (2013)	Low	Unclear	High	Unclear	Unclear	Unclear	High
Loewy (2013)	Low	Low	Low	Low	Low	Unclear	Low
Alipour (2012)	Low	Low	Unclear	Low	Low	Low	Low
Aydin (2012)	Unclear	Unclear	High	High	Low	Low	High
Olischar (2011)	Low	Low	Low	Low	Low	Low	Low
Shlez (2011)	Unclear	Unclear	Low	Low	Unclear	Low	Unclear
Farhat (2010)	Low	Unclear	Unclear	Unclear	Low	Unclear	Unclear
Lubetzky (2010)	Low	Unclear	Unclear	Unclear	Low	Low	Unclear
Standley (2010)	Low	Unclear	Unclear	Low	Low	Unclear	Unclear
Keith (2009)	Low	Unclear	Unclear	Unclear	Unclear	Unclear	High
Whipple (2008)	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Arnon (2006)	Low	High	Low	Low	Unclear	Unclear	Unclear
Calabro (2005)	Low	Low	Unclear	Low	Unclear	Low	Unclear
Standley(2003)	Unclear	Unclear	Unclear	Low	Low	Low	Unclear

Legend Table 2.1 - Low risk of bias – it is plausible that any bias present is unlikely to seriously alter the results. Unclear risk of bias – too few details known to classify. High risk of bias – it is plausible there is bias that seriously weakens the confidence in the results

four studies used the PAL [12,24-26]; the other twelve studies used speakers in or near the incubator. The decibel levels varied between 40 and 70 dB. The intervention was offered once or 3 times daily for 3 to 60 minutes during a period from 1 to 14 days. The intervention was performed after feeding [27,29-32,37,39]; before feeding [24,26]; in the afternoon [25,34]; between 8 and 9 PM [38]; between 10 AM and 7 PM[33]; during amplitude-integrated EEG recordings [36]; during heel stick procedure [12] and before arterial puncture [40]. Two studies did not report on the timing [23,35] (see Table 2.2).

Live music interventions: Four studies [4,28,29,37] offered live music interventions in the form of lullabies selected and sung by a certified music therapist to the accompaniment of a harp, drum, the Ocean Disc , or the Gato Box. The decibel levels varied between 45 and 70 dB. The frequency varied between once daily and thrice weekly for 5 to 30 minutes. The intervention was performed after feeding and one study mentioned it was either in the morning or in the afternoon (see Table 2.2).

All recorded and live music interventions were in lullaby style and sung by a woman when the lullaby was a song. The music was culturally appropriate, for example studies carried out in Israel made use of both western and eastern musical elements. Five studies [27,30,34-36] used classical music.

Table 2.2 - Characteristics of music interventions per study

Author (year)	Music selection (selected by)	Type of delivery (location)	dB	Duration of study, length and frequency of intervention	Timing of intervention
Recorded music					
Cardoso (2015)	Lullaby (researcher)	Headphone with Mp4 player (in incubator)	NR	1 day, 10 minutes, 1x daily	10 minutes before arterial puncture
Chorna (2014)	Children's songs sung by mother (researcher)	Pacifier Activated Lullaby (PAL) (in incubator)	NR	5 days, NR, 15 minutes	30 – 45 minutes before feeding
Dorn (2014)	Collection of lullabies (researcher)	Audio player and loudspeaker (in incubator)	55-65 dB	14 days, 1x daily, 30 minutes	Between 20.00 and 21.00 every evening
Garunkstiene (2014)*	Selection of Lithuanian and traditional Western lullabies (same for live and recorded) sung by female (music therapist)	Speakers at 30 cm from infant's head (in incubator)	45 -50 dB	3 days, 1x daily, 20 minutes	30 minutes after feeding
Amini (2013)	Live: Iranian Lullaby Recorded: Mozart Sonata K.448, Baby Mozart CD (researcher)	Speakers at 30 cm from infant's head (in incubator)	45-50 dB	6 days, 1x daily for two days per intervention group, 20 minutes	1 hour after feeding
Alipour (2012)	Iranian Lullaby (researcher)	Headphone (in incubator)	50-60 dB	1 day, 1x daily, 20 minutes	30 minutes after the last feeding
Aydin (2012)	Classical music, not specified (researcher)	Two loudspeakers at the feet of the infant (in incubator)	40-65 dB	1 day till discharge (hospitalization 22-23 days), 1x daily, 1 hour	Afternoon
Olischar (2011)	Brahms Lullaby (researcher)	Speaker at 30 cm from infant's head (in incubator)	50-55 dB	1 day, 1x daily, 20 minutes	After one Sleep-Wake-Cycle on aEEG
Farhat (2010)	Iranian Lullaby (music therapist)	MP3 player and headphones (in incubator)	60-65 dB	8 days, 1x daily, 20 minutes	30 minutes after feeding
Lubetzky (2010)	Mozart (researcher)	Mini CD device and speakers at 30 cm distance from infants' ears (in incubator)	65-70 dB	2 days, 1x daily, 30 minutes	1 hour after the last feeding in the afternoon
Standley (2010)	Continuous selection of lullabies sung by female vocalist with minimal accompaniment (music therapist)	Pacifier Activated Lullaby (PAL) (in incubator)	65 dB	5 days, 1x or 3x daily, 15 or 45 minutes	From 16.00 to 17.00 o'clock in the afternoon

Keith (2009)	Lullaby: Female singing unaccompanied lullabies and songs for young children (music therapist)	CD player and speakers (in incubator)	<70 dB	4 days, 1x daily, 18 minutes	NR
Whipple (2008)	Traditional lullabies sung by female child accompanied by piano (music therapist)	Pacifier Activated Lullaby (PAL) (in incubator)	65 dB	1 day, 1x daily, 10 minutes	During heel stick procedure
Arnon (2006)*	Lullaby style with Eastern and Western musical elements accompanied by drum and harp (music therapist)	Tape recorded with two speakers 1 meter from infant's bed (outside incubator)	55-70 dB	3 days, 1x daily, 30 minutes	1 hour after feeding
Calabro (2005)	Lullaby "Brahms Lullaby" and "Sandman" from the CD Music for Dreaming (music therapist)	Cassette player (in incubator)	60-65 dB	4 days, 1x daily, 20 minutes	NR
Standley (2003)	Lullabies sung by female vocalist (music therapist)	Pacifier Activated Lullaby (PAL) (in incubator)	65 dB	1 day, 1x daily, 15-20 minutes	30-60 minutes before afternoon feeding
Live music					
Garunkstiene (2014)*	Selection of Lithuanian and traditional Western lullabies (same for live and recorded) (music therapist)	Music therapist 30 cm from infant's head (outside incubator)	45 -50 dB	3 days, 1x daily, 20 minutes	30 minutes after feeding
Loewy (2013)	1. Parent-preferred lullaby, 2. Ocean Disc, 3. Gato Box (music therapist)	1. Live lullaby, 2. Ocean Disc, 3. Gato Box (outside incubator)	55-65 dB	2 weeks, 3x per week, duration of 1 song (approximately 3 minutes)	Morning or afternoon
Schlez (2011)	Simple improvised melodies in lullaby style (music therapist)	Live harp music (outside incubator)	50-65 dB	3 to 5 days, 1x daily, 30 minutes	30 minutes after afternoon feeding
Arnon (2006)*	Lullaby style wordless blend of Eastern and Western musical elements (music therapist)	Live music with harp and drum, performed 1 or 2 meters from the infant's bed (outside incubator)	50-70 dB	3 days, 1x daily, 30 minutes	1 hour after feeding

Legend Table 2.2 - *Garunkstiene (2014) and Arnon (2006) measure both a recorded and live music intervention.

OUTCOMES

Physiological parameters

In fourteen studies the physiological parameters heart rate (HR), respiratory rate (RR), oxygen saturation (SatO2) and cortisol served as outcomes (see Table 2.3). These were measured before, during and after the intervention by either the investigators or a nurse. Seven of the twelve studies that used a recorded music intervention reported no statistically significant difference for any of the physiological parameters between the intervention and control group or condition [12,23,29,31,34,35,38]. Farhat et al. [32] found a significant difference for RR during the intervention ($p=0.017$) and for SatO2 during and after the intervention ($p=0.001$ and $p=0.019$ respectively). The authors did not report the direction of differences. Garunkstiene et al. [37] showed a significant decrease in HR after the intervention compared to the control condition ($p<0.001$). Jabraelili et al. [33] reported an statistically significant increase in SatO2 for the lullaby group compared to the control condition ($p=0.02$). Wirth et al. [39] showed a significant decrease in respectively HR and RR during and after the intervention compared to the control condition ($p<0.001$ for both HR and RR). Amini et al. [30] did not report the between group results.

Four studies measured the effect of a live music intervention on physiological parameters. Arnon et al. and Garunkstiene et al. showed a significant decrease in HR after the intervention (both $p<0.001$) [29,37]. In the two other studies no significant differences were found [4,28].

Growth and feeding outcomes

Seven studies [4,24-27,32,34] measured growth and feeding outcomes (see Table 2.4). Six studies measured the effect of a recorded music intervention. Lubetzky et al. reported a significant reduction in resting energy expenditure (REE) after the intervention ($p=0.03$) [27]. Chorna et al. reported a significant increase in feeding rate ($p<0.001$), oral volume intake ($p=0.001$), oral feeds per day ($p=0.001$) and fast time to full oral feedings ($p=0.04$) [26]. Three studies did not show a difference and one study [25] did not report intergroup results (see Table 2.4).

Loewy et al. measured the effect of live music interventions on growth and feeding [4]. Intergroup results for caloric intake were not reported. Sucking behaviour in the intervention group receiving the Gato Box intervention had significantly improved relative to the control group ($p=0.01$) (see Table 2.4).

Behavioural state, relaxation outcomes and pain

Thirteen studies [4,12,23,28,29,31,34-40] measured the effects of music on behavioural state, relaxation outcomes and pain. Outcome measurements included behavioural state, levels of activity and sleep, inconsolable crying, stress and pain (see Table 2.5). Eleven studies used a recorded music intervention; four studies a live music intervention (Garunkstiene et al. and Arnon et al. used both a recorded and live music intervention).

Behavioural state was measured with four different scales. Garunkstiene et al., Schlez et al. and Arnon et al. used a 7-point behavioural scale [41,42] distinguishing the following states: deep sleep; light sleep; drowsy; quiet awake or alert; actively awake and aroused; highly aroused; upset or crying; prolonged respiratory pause > 8 sec. Alipour et al. used a 6-point behavioural scale adapted from Als et al. [42] distinguishing six states: quiet sleep, active sleep, drowsy, quiet awake, active awake and crying. Calabro et al. assessed the infant's behavioural state from a Psychological and Behavioural Assessment Form (adapted from Als et al. [42]; Hiniker et al. [43]; Schoemark et al. [9]. Whipple et al. [12] measured behavioural state using the Continuous Response Digital Interface (CRDI) system, which distinguishes six behavioural states: deep sleep, light sleep, drowsy, alert, active, and crying. Whipple et al. used the CRDI also to measure stress on a nine-point continuum from minimum to maximum stress.

Four studies used recorded music interventions but none found a significant effect on behavioural state. Regarding live music interventions, Garunkstiene et al. ($p=0.003$) and Arnon et al. ($p<0.001$) reported a significant improvement in behavioural scores, reflecting a deeper state of sleep.

Wirth et al. used the GT3xt accelerometer, a device that tracks body movements, to measure activity during music stimulation. The lullaby group showed significantly less activity during the intervention [39]. Activity-rest behaviour was measured by Dorn et al. with an actigraph monitoring device (ActiSleep+, ActiGraph, Pensacola, FL) that monitors activity acceleration on vertical, horizontal and perpendicular axes. No significant difference was found between the recorded music and control conditions.

Olischar et al. used an amplitude-integrated EEG (aEEG) to monitor the sleep-wake cycles and quiet sleep in infants who received a recorded lullaby. Quiet sleep periods did not differ significantly between groups.

Infants in Loewy's study received a live lullaby, the Ocean Disc and Gato Box. The Ocean Disc intervention was associated with a significantly better quality of sleep ($p<0.001$).

Keith et al. measured the effects of a recorded intervention on the frequency and duration of inconsolable crying. For the purpose of that study, inconsolable crying was defined as 'intense and sustained cry vocalisations, accompanied by high motor activity for 5 minutes or more after interventions to comfort him'. There was a significant decrease in the frequency and duration of crying episodes (both $p<0.001$).

Stress outcomes were measured by Aydin et al. using a non-validated 4 point scale with score categories: no stress symptoms (0 points), mild stress symptoms (1 point), mid-level stress (2 points) and severe stress (3 points). A live music intervention was not associated with a significant reduction in stress scores.
Pain was measured by Cardoso et al. using the Premature Infant Pain Profile (PIPP), which has been validated to measure acute pain in premature infants. A recorded music intervention did not have a significant effect on these pain scores.

Table 2.3 - Results of the effects of music on physiological parameters.
Results of the effects of music on physiological parameters compared between the intervention and control groups. Tabulated results compare the experimental intervention in boldface to the control condition.

Author	Intervention(s) and comparator	(N); Age	Outcome measures	Results
Recorded Music Intervention				
Dorn (2014)	**1.Recorded lullaby** 2.Maternal voice reading 3. Control	(61); 30-37 weeks GA	Cortisol	NS
Garunkstiene (2014)	1.Live lullaby **2.Recorded lullaby** 3.Control	(35); 26-30 weeks GA	HR, SatO2	A statistically significant difference for HR ($p<0.001$).
Amini (2013)	**1.Lullaby** **2.Mozart** 3. Control	(25); 29.4 – 35 weeks GA	HR, RR, SatO2	Results between groups NR*
Alipour (2012)	**1. Lullaby music with headphone** 2. Silence with headphone 3. Control	(90); 28-36 weeks GA	HR; RR; $SatO_2$	NS
Aydin (2012)	**1. Classical music** 2. Control	(26); age NR	HR; RR; $SatO_2$	NS
Farhat (2010)	**1. Lullaby** 2. Control	(44); <34 weeks GA	HR; RR; $SatO_2$	Statistically significant difference between the groups during the intervention in RR ($p = 0.017$). NS between the groups after the intervention in RR ($p = 0.94$). Statistically significant difference between the groups during and after the intervention in SatO2 ($p = 0.001$ and $p = 0.019$ resp.)
Keith (2009)	**1.Lullaby** 2.Control	(24); 32-40 weeks GA	HR, RR, $SatO_2$	Results between groups NR
Whipple (2008)	**1.PAL** 2.Pacifier 3.Control	(60); 32-37 weeks GA	HR, RR, $SatO_2$	NS
Arnon (2006)	1. Live music lullaby 2. **Recorded music lullaby** 3. Control	(31); 25-34 weeks GA	HR; RR; $SatO_2$	NS
Calabro (2005)	**1. Lullaby** 2. Control	(22); 34 weeks GA	HR; RR; $SatO_2$	NS (HR: $p = 0.64$ RR $p=0.38$ $SatO_2$ $p=0.36$)

Live Music Intervention				
Garunkstiene (2014)	**1.Live lullaby** 2.Recorded lullaby 3.Control	(35); 26-30 weeks GA	HR, SatO2	A statistically significant difference for HR ($p<0.001$).
Loewy (2013)	**1.Lullaby** **2.Ocean Disc** **3.Gato Box** 4. Control	(272); 32-40 weeks GA	HR; RR; $SatO_2$	NS All 3 interventions have a significant effect over time but not control x condition
Schlez (2011)	**1. Harp music therapy with Kangaroo Care** 2. Control: Kangaroo Care	(52) 26-36 weeks GA	HR; RR; $SatO_2$	NS
Arnon (2006)	**1. Live music lullaby** 2. Recorded music lullaby 3. Control	(31); 25-34 weeks GA	HR; RR; $SatO_2$	Statistically significant difference for HR ($p < 0.01$).

Legend Table 2.3 - HR = heart rate; RR = respiratory rate; SatO2 = Oxygen saturation; NS = Not significant; NR = Not reported; * Results within groups: Statistically significant difference for RR for the lullaby group ($p=0.001$)

Table 2.4 - Results of the effects of music on growth and feeding outcomes.
Results of the effects of music on growth and feeding outcomes compared between the intervention and control groups. Tabulated results compare the experimental intervention in boldface to the control condition.

Author	Intervention(s) and comparator	(N); Age	Outcome measures	Results
Recorded music intervention				
Chorna (2014)	**1.PAL children's songs sung by mother** 2. Control	(94); 34-36 weeks GA	Feeding rate Length hospitalization Feeding volume and frequency No of days to full feed Balancing measurements (discharge weight, growth rate, change in salivary cortisol)	Statistically significant increase in feeding rate between the groups after the intervention ($p<0.001$); oral volume intake ($p= 0.001$); oral feeds per day ($p=0.001$) and faster time to full oral feedings ($p=0.04$)
Aydin (2012)	**1. Classical music** 2. Control	(26); NR	Growth (weight, height, head circumference)	NS (NS results in text, exact between group p-value not provided)
Farhat (2010)	**1. Lullaby** 2. Control	(44); <34 weeks GA	Weight Gain	NS ($p=0.093$)
Lubetzky (2010)	**1. Baby Mozart CD** 2. Control	(20); 30-34 weeks GA	REE	Statistically significant reduction in REE between the groups after the intervention ($p = 0.03$).
Standley (2010)	**1. PAL 1x** **2. PAL 3x** 3. Control	(68); 28-32 weeks GA	Days of nipple feeding prior to discharge Discharge weight Weight gain	Results between groups NR

Standley (2003)	**1. PAL** 2. Control	(32); 32 weeks GA	Feeding rate	NS (NS results in text, exact between group p-value not provided)
Live music intervention				
Loewy (2013)	**1. Lullaby** **2. Ocean Disc** **3. Gato Box** 4. Control	(272); 32-40 weeks GA	Caloric intake Sucks per minute and sucking pattern	Results between groups NR* Statistically significant difference between the Gato box intervention and control group in sucking behaviour (p = 0.01). Results for Lullaby and Ocean Disc NR.

Legend Table 2.4 - NR = Not reported; NS = Not significant, p-value not reported in the study; PAL = Pacifier Activated Lullaby; *Within group results only reported per age group, not per intervention group (32, 34 and 36 weeks GA).

Table 2.5 - Results of the effects of music on behavioural state, relaxation outcomes and pain. Results of the effects of music on behavioural state, relaxation outcomes and pain between the intervention and control groups. Tabulated results compare the experimental intervention in boldface to the control condition.

Author	Intervention(s) and comparator	(N); Age	Outcome measures	Results
Recorded music intervention				
Wirth (2016)	**1. Recorded lullaby** 2. Maternal voice 3. Control	(62); 30-37 weeks GA	Activity	Statistically significant less activity for the lullaby group ($p < 0.04$)
Cardoso (2014)	**1.Recorded lullaby** 2.Recorded lullaby with 25% glucose 3.Control	(80); 31-37 weeks GA	Pain (measured by PIPP)	NS (p=0.40)
Dorn (2014)	**1.Recorded lullaby** 2.Maternal voice reading 3.Control	(61); 30-37 weeks GA	Rest-activity behaviour	NS (NS results in text, exact between group p-value not provided)
Garunkstiene (2014)	1.Live lullaby **2.Recorded lullaby** 3.Control	(35); 26-30 weeks GA	Behavioural state (from deep sleep to prolonged respiratory pause >8sec)	NS (NS results in text, exact between group p-value not provided)
Alipour (2012)	**1.Lullaby music with headphone** 2.Silence with headphone 3.Control	(90); 28-36 weeks GA	Behavioural state (from quiet sleep to crying)	NS (NS results in text, exact between group p-value not provided)
Aydin (2012)	**1.Classical music** 2.Control	(26); NR	Stress (from no stress to severe stress)	NS (NS results in text, exact between group p-value not provided)
Olischar (2011)	**1.Lullaby** 2.Control	(20); >32 weeks GA	Sleep-Wake-Cycle and Quiet Sleep pattern on aEEG	NS (SWC p=0.90 QS p=0.08)

Keith (2009)	**1.Lullaby** 2.Control	(24); 32-40 weeks GA	Frequency of inconsolable crying (>5 minutes crying)	Statistically significant less crying episodes for the lullaby group ($p < 0.001$).
			Duration of inconsolable crying (in minutes)	Statistically significant difference between the groups for the duration of crying episodes ($p < 0.001$)
Whipple (2008)	**1.PAL** 2.Pacifier 3.Control	(60); 32-37 weeks GA	Behavioural state	NS (NS results in text, exact between group p-value not provided)
Arnon (2006)	1.Live music lullaby **2.Recorded music** lullaby 3.Control	(31); 25-34 weeks GA	Behavioural state (from quiet sleep to crying)	NS (NS results in text, exact between group p-value not provided)
Calabro (2005)	**1.Lullaby** 2.Control	(22); 34 weeks GA	Behavioural State	NS (NS results in text, exact between group p-value not provided)
Live music intervention				
Garunkstiene (2014)	**1.Live lullaby** 2.Recorded lullaby 3.Control	(35); 36-30 weeks GA	Behavioural state (from deep sleep to prolonged respiratory pause)	Statistically significant difference in the live lullaby ($p=0.003$) for behavioural state.
Loewy (2013)	**1.Lullaby** **2.Ocean Disc** **3.Gato Box** 4.Control	(272); >32 weeks GA	Activity level % of quiet-alert time	Results between groups NR*
			Sleeping level % time of active sleep	Increase in positive sleep patterns in Ocean Disc group ($p<0.001$)
Schlez (2011)	**1.Live harp music** 2.No music	(52) 26-36 weeks GA	Behavioural State (from deep sleep to prolonged respiratory pause)	NS (NS results in text, exact between group p-value not provided)
Arnon (2006)	**1. Live music lullaby** 2.Recorded music lullaby 3.Control	(31); 25-34 weeks GA	Behavioural State (from quiet sleep to crying)	Statistically significant difference for the live music therapy compared to recorded music therapy and no music therapy after the intervention ($p < 0.001$)

Legend Table 2.5 - NR = Not reported; NS = Not significant, p-value not reported in the study; PIPP = Premature Infant Pain Profile; * Within group results: activity level % of quiet-alert time for lullaby group ($p<0.05$). Increase in positive sleep patterns in Ocean Disc group: $p<0.001$).

DISCUSSION

This review shows that in three studies offering live music interventions an improvement in sleep quality was reported [4,29,37]. However, sample size varied greatly: Garunkstiene and Arnon used a sample size of respectively 35 and 31 patients, whereas Loewy's study included 272 patients. The smaller sample sizes could have influenced the positive outcome of the studies. In Loewy's study, only the patients receiving the Ocean Disc intervention showed an improvement in sleep. In a fourth study offering a live music intervention no behavioural state change was seen, perhaps because the infants simultaneously received kangaroo care, which in itself is an effective intervention. Four studies (Wirth; Garunkstiene both live and recorded; Arnon live) were associated with a significant decline in heart rate. However, seven studies did not show such an association. Better feeding and sucking outcomes were reported in one study using live music and two studies using recorded music [4,26,27]. The latest review on the effect of music interventions in premature infants was published in 2009. We included four [12,24,29,35] out of the nine studies in this review in our updated review; the other five [5,44-47] included too few patients or included term infants. Fifteen out of the twenty RCTs in this updated review were published after 2009, indicating a growing interest in this topic.

Limitations of the studies

It was not possible to perform a meta-analysis due to heterogeneity of type and duration of interventions, gestational age of the subjects, and outcome measures. In all included studies, 16 of the 26 outcome measures were addressed only once. Most studies reported their results only expressed as p-values and the authors did not respond to our requests for raw data. The studies included in this review vary in quality. The overall risk of bias was unclear in 13 out of the 20 studies and high in 3 studies. In 11 studies no more than 20 patients per treatment group were included.

Outcomes were measured with a wide range of methods and instruments. For instance, growth and feeding outcomes were measured with 8 different methods, ranging from Resting Energy Expenditure to weight gain and growth. Behavioural state was measured with four different, non-validated instruments. Duration of the intervention varied from 3 to 60 minutes; duration of the study period from 1 day to 3 weeks. In most studies, the intervention was offered after feeding and in all but two studies the intervention was offered once daily (28, 34). Either a music therapist or the research team selected the interventions. It is noteworthy that in the majority of the studies that showed a positive result a certified music therapist had selected the music. This suggests it is advisable for future studies to include the advice of a certified music therapist.

Furthermore, the studies included infants of a wide age range, i.e. although all children were born before 37 weeks GA, some studies provided the children with a music intervention for the duration of their stay in the NICU which resulted in an age range of 25 – 40 weeks GA. It is not unreasonable to assume that there is a relation between maturity and responses to music, but this was not discussed in these studies. Standley et al. [14] have suggested age guidelines for music interventions, but these recommendations were not adhered to in all studies [28,29,37].

With regard to safety aspects, none of the studies addressed possible adverse effects of the noise levels or the use of headphones (risk of pressure sores) or disinfectants to clean the music equipment, or adherence to NICU hygiene standards. The American Academy of Pediatrics (AAP) has warned that high noise levels may adversely affect newborns' growth and development. Environmental noise levels should not exceed 40-45 dB and noise levels <35 dB are desired for sleep [48]. Yet, in no more than two studies the noise levels were kept lower than 45 dB [30,37]. Whipple et al. [12] did refer to guidelines for sound in the NICU but these were out-dated. Also, overstimulation can be harmful and therefore music interventions should not last 30 minutes or longer without a clear motivation for this duration.

Limitations of this review

A limitation to this review could be a possible language bias from the use of studies published in English only. Therefore we performed a post-hoc search and excluded the studies published in English (see S3 File). This search resulted in 113 articles, none of which matched with our inclusion criteria.

Implications for practice and research

First of all, for further studies to be useful, consensus must be reached on the most relevant outcomes, duration and timing of music interventions and how they should be measured. Sleep quality is an important outcome and it might be worthwhile to focus research efforts on measuring sleep-wake cycles through EEGs rather than only observing behavioural state.

Second, Shoemark et al. suggest that a music intervention should be selected on predictable patterns in rhythm, melody and phrasing, gradual changes in tempo in a lullaby, smooth melodic contours and an absence of harmonies [49]. They also suggest a vital role for music therapists in a family-centered approach with positive stimulation from music interventions and interventions including a parent's voice. Nine studies [12,23-25,32,37-39] in our review used music interventions accompanied by a female voice (Garunkstiene both for the recorded and live intervention) in one study [26] the infant's mother sung and one study [4] based the music intervention on the preference of both parents. Future studies should take into account the role of the father and place more emphasis on the possible effect of culturally specific music interventions.

In conclusion, taken together, the variation in quality of the studies, age groups, outcome measures and timing of the interventions across the studies makes it impossible to draw strong conclusions on the effects of music on premature infants' well-being. Still, music interventions might be promising in this respect, especially live music interventions administered by certified music therapists with timing and duration tailored to the infant's needs. Neonatology staff, music therapists and researchers need to systematically define clinically relevant outcome measures. Furthermore, safety measures for overstimulation should be developed. Future research should focus on performing well-powered RCTs and reporting the between group results.

ACKNOWLEDGEMENTS

We would like to thank Wichor Bramer, biomedical information specialist from the Medical Library of Erasmus University, Rotterdam for assisting in the searches. Furthermore we thank Ko Hagoort, editor at Erasmus Medical Center and dr. Sinno Simons, neonatologist at Sophia Children's Hospital / Erasmus Medical Center, Rotterdam, for reviewing this article. None of the authors has had a conflict of interest in performing this meta-analysis. The first and last authors have had full access to all the data in this study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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SUPPLEMENT S1: TABLE PRISMA CHECKLIST

Section/topic	#	Checklist item	Reported on page #
Title			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
Abstract			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
Methods			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g. web address), and, if available, provide registration information including registration number.	7
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g. years considered, language, publication status) used as criteria for eligibility, giving rationale.	7
Information sources	7	Describe all information sources (e.g. databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	7
Study selection	9	State the process for selecting studies (i.e. screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7
Data collection process	10	Describe method of data extraction from reports (e.g. piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8
Data items	11	List and define all variables for which data were sought (e.g. PICOS, funding sources) and any assumptions and simplifications made.	8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8
Summary measures	13	State the principal summary measures (e.g. risk ratio, difference in means).	8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g. I^2) for each meta-analysis.	8
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g. publication bias, selective reporting within studies).	8
Additional analyses	16	Describe methods of additional analyses (e.g. sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8

Results			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g. study size, PICOS, follow-up period) and provide the citations.	9
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	10-11
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	12 - 29
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	12 - 29
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	10
Additional analysis	23	Give results of additional analyses, if done (e.g. sensitivity or subgroup analyses, meta-regression [see Item 16]).	12 - 29
Discussion			
Summary of evidence	24	Summarise the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g. healthcare providers, users, and policy makers).	29 - 33
Limitations	25	Discuss limitations at study and outcome level (e.g. risk of bias), and at review-level (e.g. incomplete retrieval of identified research, reporting bias).	32
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	32
Funding			
Funding	27	Describe sources of funding for the systematic review and other support (e.g. supply of data); role of funders for the systematic review.	34

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

SUPPLEMENT S2: PROTOCOL SYSTEMATIC REVIEW PREMATURE INFANTS

Title

Do hospitalised premature infants benefit from music interventions? A systematic review of randomised controlled trials

Rationale

Neonatal intensive care units (NICU) around the world increasingly use music interventions. The most recent systematic review of randomised controlled trials (RCT) dates from 2009. Since then, new RCTs have been published. We provide an updated systematic review on the possible benefits of music interventions on premature infants' well-being.

Objective

To conduct a systematic review of randomised controls on the effects of music in preterm infants.

Methods

	Inclusion	Exclusion
Patients	Patients born between 24-37 weeks GA and admitted to the NICU* (patients receiving an intervention >37 weeks can be included if they were born <37 weeks)	
Interventions	Recorded or live music interventions, Interventions that required participation of a parent are only accepted if it includes a musical intervention such as singing. - Music selection: pre-selected by investigator or by therapist; - Modes of delivery: live music, recorded music, instrumental music, music with song and Pacifier Activated Lullaby (PAL)	Interventions using speech, sounds of the mother's womb, studies using non-human sounds such as nature sounds. Interventions using the mother or father's voice without music. Interventions comparing different music intervention to other music interventions, for example recorded vs. live music or PAL vs. live music.
Comparison	Any comparison, as long as the effect of music can be analyzed separately from the control condition.	
Outcomes	Unrestricted	
Study design	RCTs with a parallel group, cross-over or cluster design	Parallel or group design RCTs with fewer than 10 patients per group. Cross-over design fewer than 15 per group.
Setting	NICU*	
Type of publication	Scientifically peer-reviewed publications	Unpublished dissertations, conference papers
Year of publication	Unrestricted	
Language of publication	English	Non-English

*NICU: Neonatal Intensive Care Unit

Search strategy

- In collaboration with Wichor Bramer, information specialist, Erasmus Medical Center
- Information sources that will be used: Electronic databases; specialised journals; trial registers; contact with study authors; check the references in articles
- Data collection and selection MvdH and SO will both screen and read the articles. They will use the Cochrane Handbook for Systematic Reviews of Interventions.

Risk of bias in individual studies

Cochrane Risk of bias tool

Data synthesis

If data is appropriate for quantitative synthesis we will perform a meta-analysis, following the guidelines from the Cochrane Center

SUPPLEMENT S3: FILE FULL LIST OF SEARCH TERMS AND DATABASES

We searched 13 electronic databases and trial registers from their first available date:

1. Cochrane Central Register of Controlled Trials (CENTRAL)
2. MEDLINE (Ovid) (1950 to present)
3. EMBASE (1980 to present)
4. CINAHL (1982 to present)
5. PsycINFO (1967 to present)
6. AMED (The Allied and Complementary Medicine Database) (1985 to present)
7. Web of Science (1945 to present)
8. Scopus (1995 to present)
9. The specialist music therapy research database at www.musictherapyworld.net
10. CAIRSS for Music
11. ClinicalTrials.gov (http://www.clinicaltrials.gov/)
12. Current Controlled Trials (http://www.controlledtrials.com/)
13. National Research Register (http://www.updatesoftware.com/National/)

Furthermore we hand-searched 12 journals from their first available date:

1. Australian Journal of Music Therapy
2. Canadian Journal of Music Therapy
3. The International Journal of the Arts in Medicine
4. Journal of Music Therapy
5. Journal for Art Therapies in Education, Welfare and Health Care
6. Music Therapy
7. Music Therapy Perspectives
8. Nordic Journal of Music Therapy
9. Music Therapy Today (online journal of music therapy)
10. Voices (online international journal of music therapy)
11. New Zealand Journal of Music Therapy
12. British Journal of Music Therapy

Search terms

Embase

(music/de OR 'music therapy'/de OR (music OR musical OR musicotherap* OR ((mother* OR maternal) NEAR/3 (sang OR singing OR song OR songs OR lullab*))):ab,ti) AND (prematurity/de OR 'low birth weight'/de OR newborn/exp OR 'newborn care'/exp OR 'newborn monitoring'/de OR incubator/de OR 'neonatal incubator'/de OR 'newborn nursing'/exp OR 'neonatal stress'/de OR 'newborn period'/de OR 'premature labor'/de OR (prematur* OR preterm* OR (pre NEXT/1 (term* OR matur*)) OR (new* NEXT/1 born*) OR newborn* OR neonat* OR infan* OR baby* OR babies OR 'low birth weight' OR 'low birthweight' OR LBW OR VLBW OR ELBW OR ('small for' NEXT/2 (date OR age)) OR SGA OR incubator* OR NICU):ab,ti)

Medline OvidSP
(music/ OR “music therapy”/ OR (music OR musical OR musicotherap* OR ((mother* OR maternal) ADJ3 (sang OR singing OR song OR songs OR lullab*))).ab,ti.) AND (exp “Infant, Newborn”/ OR exp “Infant, Low Birth Weight”/ OR “Intensive Care, Neonatal”/ OR “Intensive Care Units, Neonatal”/ OR exp incubators/ OR “Premature Birth”/ OR (prematur* OR preterm* OR (pre ADJ (term* OR matur*)) OR (new* ADJ born*) OR newborn* OR neonat* OR infan* OR baby* OR babies OR “low birth weight” OR “low birthweight” OR LBW OR VLBW OR ELBW OR (“small for” ADJ2 (date OR age)) OR SGA OR incubator* OR NICU).ab,ti.)

Cochrane
((music OR musical OR musicotherap* OR ((mother* OR maternal) NEAR/3 (sang OR singing OR song OR songs OR lullab*))):ab,ti) AND ((prematur* OR preterm* OR (pre NEXT/1 (term* OR matur*)) OR (new* NEXT/1 born*) OR newborn* OR neonat* OR infan* OR baby* OR babies OR ‘low birth weight’ OR ‘low birthweight’ OR LBW OR VLBW OR ELBW OR (‘small for’ NEXT/2 (date OR age)) OR SGA OR incubator* OR NICU):ab,ti)

Web of science
TS=(((music OR musical OR musicotherap* OR ((mother* OR maternal) NEAR/3 (sang OR singing OR song OR songs OR lullab*)))) AND ((prematur* OR preterm* OR (pre NEAR/1 (term* OR matur*)) OR (new* NEAR/1 born*) OR newborn* OR neonat* OR infan* OR baby* OR babies OR “low birth weight” OR “low birthweight” OR LBW OR VLBW OR ELBW OR (“small for” NEAR/2 (date OR age)) OR SGA OR incubator* OR NICU)))

Scopus
TITLE-ABS-KEY(((music OR musical OR musicotherap* OR ((mother* OR maternal) W/3 (sang OR singing OR song OR songs OR lullab*)))) AND ((prematur* OR preterm* OR (pre W/1 (term* OR matur*)) OR (new* W/1 born*) OR newborn* OR neonat* OR infan* OR baby* OR babies OR “low birth weight” OR “low birthweight” OR LBW OR VLBW OR ELBW OR (“small for” W/2 (date OR age)) OR SGA OR incubator* OR NICU)))

CINAHL
(MH music OR MH “music therapy” OR AB (music OR musical OR musicotherap* OR ((mother* OR maternal) N3 (sang OR singing OR song OR songs OR lullab*))) OR TI (music OR musical OR musicotherap* OR ((mother* OR maternal) N3 (sang OR singing OR song OR songs OR lullab*)))) AND (MH “Infant, Newborn”+ OR MH “Intensive Care, Neonatal”+ OR MH “Intensive Care Units, Neonatal” OR MH “Infant Warmers” OR MH “Childbirth, Premature” OR AB (prematur* OR preterm* OR (pre N1 (term* OR matur*)) OR (new* N1 born*) OR newborn* OR neonat* OR infan* OR baby* OR babies OR “low birth weight” OR “low birthweight” OR LBW OR VLBW OR ELBW OR (“small for” N2 (date OR age)) OR SGA OR incubator* OR NICU) OR TI (prematur* OR preterm* OR (pre N1 (term* OR matur*)) OR (new* N1 born*) OR newborn* OR neonat* OR infan* OR baby* OR babies OR “low birth weight” OR “low birthweight” OR LBW OR VLBW OR ELBW OR (“small for” N2 (date OR age)) OR SGA OR incubator* OR NICU)) NOT (MH animals+ NOT MH humans+)

PsycINFO OvidSP

(music/ OR "music therapy"/ OR (music OR musical OR musicotherap* OR ((mother* OR maternal) ADJ3 (sang OR singing OR song OR songs OR lullab*))).ab,ti.) AND (120. ag. OR exp "Neonatal Development"/ OR "Neonatal Intensive Care"/ OR "Incubators (Apparatus)"/ OR "Premature Birth"/ OR (prematur* OR preterm* OR (pre ADJ (term* OR matur*)) OR (new* ADJ born*) OR newborn* OR neonat* OR infan* OR baby* OR babies OR "low birth weight" OR "low birthweight" OR LBW OR VLBW OR ELBW OR ("small for" ADJ2 (date OR age)) OR SGA OR incubator* OR NICU).ab,ti.)

PubMed publisher

(music[mh] OR "music therapy"[mh] OR (music OR musical OR musicotherap*[tiab] OR ((mother*[tiab] OR maternal) AND (sang OR singing OR song OR songs OR lullab*[-tiab])))) AND ("Infant, Newborn"[mh] OR "Infant, Low Birth Weight"[mh] OR "Intensive Care, Neonatal"[mh] OR "Intensive Care Units, Neonatal"[mh] OR incubators[mh] OR "Premature Birth"[mh] OR (prematur*[tiab] OR preterm*[tiab] OR pre term*[tiab] OR pre matur*[tiab] OR new born*[tiab] OR newborn*[tiab] OR neonat*[tiab] OR infan*[-tiab] OR baby*[tiab] OR babies OR "low birth weight" OR "low birthweight" OR LBW OR VLBW OR ELBW OR small for date*[tiab] OR small for age*[tiab] OR SGA OR incubator*[tiab] OR NICU)) AND (publisher[sb] OR inprocess [sb])

Google Scholar

Music|"mother|mothers|maternal singing|song" "premature infant|infants|babies"|"born prematurely"|prematures|preterm|preterms|"pre term|mature|terms|matures|maturely"|"new born"|newborn|newborns|neonate|neonates|neonatal|LBW|VLBW|ELBW|SGA|incubator|NICU

Search articles in non-English language

For the extra search on studies that were published in a language other than English we used the following search terms:

'music'/de OR 'music therapy'/de OR music:ab,ti OR musical:ab,ti OR musicotherap*:ab,ti OR ((mother* OR maternal) NEAR/3 (sang OR singing OR song OR songs OR lullab*)):ab,ti AND ('prematurity'/de OR 'low birth weight'/de OR 'newborn'/exp OR 'newborn care'/exp OR 'newborn monitoring'/de OR 'incubator'/de OR 'neonatal incubator'/de OR 'newborn nursing'/exp OR 'neonatal stress'/de OR 'newborn period'/de OR 'premature labor'/de OR prematur*:ab,ti OR preterm*:ab,ti OR (pre NEXT/1 (term* OR matur*)):ab,ti OR (new* NEXT/1 born*):ab,ti OR newborn*:ab,ti OR neonat*:ab,ti OR infan*:ab,ti OR baby*:ab,ti OR babies:ab,ti OR 'low birth weight':ab,ti OR 'low birthweight':ab,ti OR lbw:ab,ti OR vlbw:ab,ti OR elbw:ab,ti OR ('small for' NEXT/2 (date OR age)):ab,ti OR sga:ab,ti OR incubator*:ab,ti OR nicu:ab,ti) NOT [english]/lim

Forward citation search based on key references

- Garunkstiene, R.; Baunauskiene, J. et al. (2014) "Controlled trial of live versus recorded lullabies in preterm infants" Nordic Journal of Music Therapy 23 (1): 71-88
- Chorna, O.; Slaughter, J. et al. (2014) "A pacifier-activated music player with mother's voice improves oral feeding in preterm infants" Pediatrics 133 (3): 462-468
- Loewy, J.; Stewardt, K. et al. (2013) "The effects of music therapy on vital signs,

feeding and sleep in premature infants" Pediatrics 131 (5): 902 - 918

- Amini, E.; Rafiei, P. et al. (2013) "Effect of lullaby and classical music on physiologic stability of hospitalised preterm infants: a randomised trial" Journal of Neonatal Perinatology Medicine 6 (4): 295-301
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- Lubetzky, R.; Mimouni, F. et al. (2010) "Effect of music by Mozart on energy expenditure in growing preterm infants" Pediatrics 125 (1):e24-28
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SUPPLEMENT S4: TABLE BACKGROUND CHARACTERISTICS ALL STUDIES

	Intervention and Comparison					**Outcome measurements**	**Time of measurements**
Author, year, country	**Patient population in GA range (mean)**	**N**	**Study design**	**Intervention group**	**Control group or control condition**		
Wirth et al. (2016), Germany	30 – 37 GA	62	Parallel RCT with 3 arms	Recorded music: 1. Lullaby 2. Maternal voice	No music, standard care	Physiological parameters (HR, RR); activity	15 mins before, 30 mins during, 15 mins after intervention
Jabraeili et al. (2016), Iran	29 -34 GA	66	Parallel RCT with 3 arms	Recorded music: 1. Lullaby 2. Maternal voice	No music, standard care	Physiological parameters (SatO2)	10 mins before, 15 min during, 20 mins after intervention
Cardoso et al. (2014), Brazil	>31 - <37 GA	80	Parallel RCT with 3 arms	Recorded music: 1. Lullaby 2. Lullaby with 25% glucose	25% glucose, no music	1. Pain (PIPP)	Before arterial puncture During arterial puncture
Chorna et al. (2014), USA	34- 36 GA	94	Parallel RCT with 2 arms	PAL	No music intervention, standard care routine non nutritive sucking and maternal care	Feeding rate	Start and end of intervention
						Length hospitalization	Day 0 and day 5
						Feeding volume and frequency	Start and end of intervention
						No of days to full feed	Day 0 and day 5
						Balancing measurements (discharge weight, growth rate, change in salivary cortisol)	Day 0 and day 5
Dorn et al. (2014), Germany	30 – 37 GA	61	Parallel RCT with 3 arms	Recorded music: 1. Lullaby 2. Maternal voice reading	No acoustic stimulation, standard care	1. Physiological parameters (cortisol rhythm pattern)	Before intervention: 10 minutes After intervention: 10 minutes On the 1st, 7th and 14th day
						2. Rest-activity behaviour	

Garunkstiene et al. (2014), Lithuania	26-30 GA (28.6)	35	Cross-over RCT with 3 sequences	1. Live lullaby 2. Recorded lullaby	No music, standard care	Physiological parameters (HR, SatO2)	Before intervention: 30 minutes During intervention: 20 minutes After intervention: 30 minutes
						Behavioural State (7-point scale)	Before intervention: 30 minutes During intervention: 20 minutes After intervention: 30 minutes
Amini et al. (2013), Iran	29.4 – 35 GA (32.4)	25	Cross-over RCT with 6 sequences	Recorded music: 1. Lullaby 2. Mozart	No music, standard care	Physiological parameters (HR, RR, SatO2)	Before intervention: 10 minutes During intervention: 20 minutes After intervention: 10 minutes
Loewy et al. (2013), Israel	≥ 32 GA (32.9)	272	Cross-over RCT with 4 sequences	Live music: 1. Lullaby 2. Ocean disc 3. Gato Box	No intervention , standard care	Physiological parameters (HR, RR, SatO2)	Daily: before, during and after intervention
						Activity level: % of quiet -alert time	Daily: before, during and after intervention
						Feeding (sucks per minute and sucking pattern)	Daily: during feeding
						Sleeping (% time of active sleep)	Daily
						Caloric intake	Daily
Alipour et al. (2012), Iran	28-36 GA (33.6)	90	Parallel RCT with 3 arms	Recorded music: 1. Lullaby music with headphone 2. Silence with headphone	No music, standard care	Physiological parameters (HR, RR, $SatO_2$)	Before intervention: 5th and 10th minute after placing the earphones During intervention: 5th, 10th, 15th and 20th minutes After intervention: 5th and 10th minutes
						Behavioural state (6-point scale)	Before intervention: 5th and 10th minute after placing the earphones During intervention: 5th, 10th, 15th and 20th minutes After intervention: 5th and 10th minutes
Aydin et al. (2012), Turkey	(NR)	26	Parallel RCT with 2 arms	Recorded music: 1. Classical music	No music, standard care	Stress symptoms on a 4-point scale	Before intervention: 1 minute During intervention: 5th minute, 55th minute After intervention: NR
						Physiological parameters (HR, RR and $SatO_2$)	Before intervention: 1 minute During intervention: 5th minute, 55th minute After intervention: NR

						Growth parameters: weight, height and head circumference	At admission and discharge
Olischar et al. (2011), Australia	>32 GA (38)	20	Parallel RCT with 2 arms	Recorded music: 1. Brahms lullaby	No music, standard care	Sleep-wake-cycle and quiet sleep on a aEEG	aEEG during four sleep-wake-cycles: one before intervention, three after intervention
Shlez et al. (2011), Israel	26-36 GA (32)	52	Cross-over RCT with 2 sequences	Live music: 1. Harp music therapy with Kangaroo Care	Kangaroo Care without music	Physiological parameters (HR, RR and $SatO_2$)	During intervention: every 2 minutes
						Behavioural states (7-point scale)	During intervention
Farhat et al. (2010), Iran	≤ 34 GA (30.5)	44	Parallel RCT with 2 arms 1:1	Recorded music: 1. Lullaby	No music, standard care	Physiological parameters (HR, RR and $SatO_2$)	Before intervention: 10 minutes During intervention: 20 minutes After intervention: 10 minutes
						Weight gain	Daily
Lubetzky et al. (2010), Israel	30-34 GA (NR)	20	Cross-over RCT with 2 sequences	Recorded music: 1. Baby Mozart CD	No music, standard care	Resting Energy Expenditure (metabolic measurements)	Before intervention: Not measured During intervention: 3 times during 30 minutes intervention After intervention: Not measured
Standley et al. (2010), USA	28-32 GA (NR)	68	Factorial RCT with 3 sequences	Recorded music: 1. PAL 1x 2. PAL 3x	No PAL, standard care	Days prior to nipple feeding	Daily
						Days of nipple feeding prior to discharge	Daily
						Discharge weight	Discharge
						Weight gain	Birth and discharge
Keith et al. (2009), USA	32-40 GA (33)	24	Cross-over RCT with 2 sequences	Recorded music: 1. Lullaby with nursing intervention: gentle patting, swaddling, providing pacifier and shifting position	No music, standard nursing intervention	Frequency and duration of inconsolable crying	After nursing intervention when the infant continued to cry for 5 minutes
						Physiological parameters (HR, RR and $SatO_2$) and blood pressure	During crying

Whipple et al. (2008), USA	32- 37 GA (NR)	60	Parallel RCT with 3 arms	Recorded music: 1. PAL	1. Pacifier only 2. No intervention, standard care	Behavioural states	3 minutes before intervention During intervention 3 minutes after intervention
						Stress	3 minutes before intervention During intervention 3 minutes after intervention
						Physiological parameters (HR, RR, $SatO_2$)	3 minutes before intervention During intervention 3 minutes after intervention
Arnon et al. (2006), Israel	25-34 GA (29)	31	Cross-over RCT with 3 sequences	1. Live music: lullaby 2. Recorded music: lullaby	No music, standard care	Behavioural states (7-point scale)	Before intervention: every 5 minutes During intervention: every 5 minutes After intervention: every 5 minutes
						Physiological parameters (HR, RR and $SatO_2$)	30 minutes before, during and after intervention
Calabro et al. (2005), Australia	34 GA (NR)	22	Parallel RCT with 2 arms 1:1	Recorded music: 1. Lullaby	No music, standard care	Physiological parameters (HR, RR and $SatO_2$)	Before intervention: 10 minutes During intervention: 20 minutes After intervention: 15 minutes
						Behavioural states (22 positive and negative organised states)	Before intervention: 10 minutes During intervention: 20 minutes After intervention: 15 minutes
Standley et al. (2003), USA	32 GA (NR)	32	Parallel RCT with 2 arms 1:1	Recorded music: 1. PAL	No PAL, standard care	Feeding rate	Before intervention: morning After intervention: evening

S4 Legend - GA = gestational age; HR = heart rate; NR = not reported; RR = respiratory rate; SatO2 = saturated oxygen; PAL = pacifier activated lullaby

CHAPTER 3

The effects of perioperative music interventions in paediatric surgery: a systematic review and meta-analysis of randomised controlled trials

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ABSTRACT

Objective
Music interventions are widely used but have not yet gained a place in guidelines for paediatric surgery or paediatric anesthesia. In this systematic review and meta-analysis, we examined the effects of music interventions on pain, anxiety and distress in children undergoing invasive surgery.

Data sources
We searched 25 electronic databases from their first available date until October 2014.

Study selection
Included were all randomised controlled trials with a parallel group, crossover or cluster design that included paediatric patients from 1 month to 18 years old undergoing minimally invasive or invasive surgical procedures and receiving either live music therapy or recorded music.

Data extraction and synthesis
4846 records were retrieved from the searches; 26 full text reports were evaluated and data was extracted by two independent investigators.

Main outcome measures
Pain was measured with the Visual Analogue Scale, the Coloured Analogue Scale and the Facial Pain Scale. Anxiety and distress were measured with an emotional index scale (not validated), the Spielberger short State Trait Anxiety Inventory and a Facial Affective Scale.

Results
Three RCTs were eligible for inclusion encompassing 196 orthopedic, cardiac and day surgery patients (age of 1 day to 18 years) receiving either live music therapy or recorded music. Overall a statistically significant positive effect was demonstrated on postoperative pain (SMD -1.07; 95%CI-2.08; -0.07) and on anxiety and distress (SMD -0.34 95% CI -0.66; -0.01) and (SMD -0.50; 95% CI -0.84; - 0.16).

Conclusions and relevance
This systematic review and meta-analysis indicates that music interventions may have a statistically significant effect in reducing post-operative pain, anxiety and distress in children undergoing a surgical procedure. Evidence from this review and other reviews suggests music therapy may be considered for clinical use. MeSH keywords: music, music therapy, surgical anesthesiological procedures, preoperative, peroperative, postoperative
Abbreviations: CAS: coloured analogue scale; CI: confidence interval; FAS: facial pain scale; MD: mean difference; PACU: post anaesthesia care unit; RCT: randomised controlled trial; SMD: standardized mean difference; STAI: Spielberger short-State Trait Anxiety Inventory; VAS: visual analogue scale

INTRODUCTION

Adults and children undergoing surgery may experience perioperative pain, anxiety and distress [1]. Unfortunately, it is not always possible to completely prevent postoperative pain with analgesics. Therefore, there is an increasing interest in non-pharmacological interventions, among which music interventions [2-4].

Roughly two types of music interventions are distinguished: live music therapy and recorded music. In live music therapy a trained music therapist plays music and applies various therapeutic techniques to reach a therapeutic goal. One of these techniques is known as music entrainment [5], in which the music therapist first uses music to match the patient's physiological and emotional states and then gradually changes the music to modify the patient's state. Recorded music on the other hand, implies listening to pre-recorded music selected by a music therapist, or by patients themselves provided they are old enough to do so [3].

Few studies have been performed on the effects of music interventions in children, and music interventions are not included in guidelines for paediatric surgery and anaesthesiology. However, music is used in clinical settings around the world [6] and is perceived to be a non-invasive, inexpensive and useful complementary intervention to reduce pain, anxiety and distress and to improve relaxation.

Our aim is to examine the effectiveness of music interventions to reduce pain, anxiety and distress in paediatric patients undergoing minimally invasive or invasive surgery through a systematic review and meta-analysis of the literature.

METHODS

This systematic review and meta-analysis was performed according to the recommendations of the Cochrane Collaboration as documented in our review protocol (see supplement S1). For statistical analysis we used Review Manager (RevMan 5.2) (®The Nordic Cochrane Centre, Copenhagen, Denmark, 2012). For assessing risk of bias, we used the Cochrane Risk of Bias tool.

Criteria for considering studies for this review

Inclusion criteria were all randomised controlled trials (RCT) with a parallel group, crossover or cluster design that included paediatric patients from 1 month to 18 years old undergoing minimally invasive or invasive surgical procedures. Studies were only included if patients received the music intervention before, during or after the surgical procedure and if outcomes were measured during or after the surgical procedure. Studies were only included if the control group received standard care, no music or another intervention. Music interventions could be live music therapy offered by a music therapist or recorded music.

Exclusion criteria were studies on multimodal interventions, in which music is offered in combination with other therapies such as massage. Excluded were studies on non-invasive surgery, neonates, adults, dental and ophthalmological surgical patients, non-randomised trials, papers not written in English, and narrative reviews. Auditory stimuli produced by non-human agents such as nature sounds or sounds like fixated beeps were excluded. Studies that performed the intervention pre-operatively and only measured outcomes prior to surgery were also excluded.

Search methods for identification of studies

We searched 13 electronic databases and trial registers: 1. Cochrane Central Register of Controlled Trials (CENTRAL); 2. MEDLINE (Ovid) (1950 to present); 3. EMBASE (1980 to present); 4. CINAHL (1982 to present); 5. PsycINFO (1967 to present); 6. AMED (1985 to present); 7. Web of Science (1945 to present) 8. Scopus (1995 to present) 9. The specialist music therapy research database at www.musictherapyworld.net; 10. CAIRSS for Music; 11. ClinicalTrials.gov(http://www.clinicaltrials.gov/); 12. Current Controlled Trials (http://www.controlledtrials.com/); 13. National Research Register (http://www.updatesoftware.com/Nationa l/)

Furthermore we hand-searched 12 journals from their first available date until October 2014: 1. Australian Journal of Music Therapy; 2. Canadian Journal of Music Therapy; 3. The International Journal of the Arts in Medicine; 4. Journal of Music Therapy; 5. Journal for Art Therapies in Education, Welfare and Health Care; 6. Music Therapy; 7. Music Therapy Perspectives; 8. Nordic Journal of Music Therapy; 9. Music Therapy Today (online journal of music therapy); 10. Voices (online international journal of music therapy) 11. New Zealand Journal of Music Therapy; 12. British Journal of Music Therapy. We checked the reference lists of the most relevant articles (see supplement S2 for the full list of search terms and databases).

Data collection

Two authors (MvdH and SO) selected the studies by scanning the titles and abstracts of all 4846 records retrieved from the searches. The study was rejected if the title or abstract clearly indicated that the trial did not meet the inclusion criteria. Out of the 4846 records, 26 full text reports were evaluated and data was extracted following the Cochrane guidelines by two independent investigators (MvdH and SO). Any disagreements between the two data extractors were resolved by discussions with two other authors (MvD and JJ). Two authors (MvdH and SO) emailed researchers (Nilsson) to make further inquiries about their study.

Data analysis

All outcomes in this review are presented as continuous data. For all intervention and control groups we calculated intragroup mean differences (MD) with 95% confidence intervals (CI) comparing post versus pre-intervention outcomes. Furthermore, intergroup differences were analyzed comparing the intervention and control group outcomes. Effect size was defined by Cohen's rule-of-thumb: small effect is <0.2; moderate effect is 0.5 and large effect is >0.8. [7]

Comparable pain and distress outcome measures from the selected RCTs were used in a meta-analysis. For all outcome measures the intergroup standardized mean difference (SMD) with the corresponding 95% CI was calculated as effect size. Heterogeneity was determined by the I-squared (I2) statistic. Pooled estimates of the SMD were calculated using the random-effects model assuming that underlying heterogeneity exists, irrespective of whether the I2 statistic indicates heterogeneity, and to be conservative in our estimated 95% CI [8]. A forest plot analysis served to show the effects of music interventions on pain, anxiety and distress scores for the intervention and control groups.

Because the intervention used in one of the included studies consisted of a first and second live music intervention entrainment (one in the morning, one in the afternoon), these results were analyzed separately for the intergroup analysis [9]. However, in pooling the results, we could not use both entrainments because that would have duplicated the patients from this study. We decided to only use the results of the second music intervention entrainment because it was the most conservative estimate with the smallest reported effect.

RESULTS

An extensive search in 13 databases and 12 hand-searched journals resulted in 4846 records (See Supplement S3). Only 4 RCTs examining perioperative music interventions were identified. One was excluded because it did not match the inclusion criteria [10] (see supplement S4 for an overview of excluded articles). Table 3.1 gives an overview of the characteristics of the three included studies. These had a total of 196 participants, ranging in age from 1 day to 18 years old, were reported between 2006 and 2010 and carried out in the USA [9], Sweden[11] and Brazil[12]. Bradt et al. included orthopaedic in-patients, Nilsson et al. included patients undergoing minimally invasive day-surgery for miscellaneous conditions and Hatem et al. included in-patients undergoing cardiac surgery [9,11,12].

In all three studies the music interventions were performed post-operatively and all evaluated the effects of music on the patient after surgery comparing the outcome to the baseline measurement and to the control group. Medical conditions or the complexity of the surgery were not considered as possible confounding variables due to the paucity of data which precluded meaningful analysis of these variables. One study evaluated the effects of live music therapy (music entrainment) in a cross-over design [9]; two studies performed a parallel group RCT on the effects of a recorded music intervention (MusiCure® and Vivaldi's Four Seasons, respectively) [11,12] (see table 3.1).

Risk of bias

We have used the Cochrane Handbook for Systematic reviews of Interventions to assess the risk of bias of the included studies. The overall risk of bias was moderate (see supplement S5). Nilsson used an appropriate method of allocation by using opaque envelopes [11], Bradt et al. used the drawing of lots, and Hatem et al. assigned three consecutive participants to the intervention group and one to the control group [9,12]. Only Nilsson et al. and Hatem et al. reported their power and sample size calculations [11,12]. It was not clear if researchers were blinded for group allocation.

Table 3.1 - Characteristics of included studies

	Patient population					Intervention & Comparison			Outcome	
Author, year, country	**Patient population**	**Setting**	**N**	**Age mean (range)**	**Gender (%male)**	**Study design**	**Inter-vention (control)**	**Time of music intervention**	**Outcome measurements**	**Time of measure-ments**
Bradt (2010), USA	Orthopaedic pediatric patients [1]	Two pediatric hospitals in Pennsylvania	32	14.2 years (8-18 years)	56%	Cross-over RCT across 4 treatment sequences	Live music entrainment (No music, standard care)	Post-operative: 30-45 minutes	VAS (scale 0-10) |Pain| Self-reported Bipolar descriptor (scale 0-5) | Emotional State| Self-reported	Before, during, after intervention Before, during, after intervention
Nilsson (2009), Sweden	Pediatric day surgery patients [2]	Queen Silvia Children's Hospital, Gothenburg. Academic hospital.	80	NR (7-16 years)	50%	Parallel group RCT 1: 1	Recorded music MusiCure® (No music, standard care)	Post-operative: Started at admission to the PACU and continued for 45 minutes	CAS |Pain| (scale 0-10) Self-reported FAS |Distress| (scale 0-10) Self-reported STAI |Anxiety| (scale 6-24) Self-reported FLACC |Morphine administration| (scale 0 -10) Nurse	Pre-operative and 1h after PACU Pre-operative, in the PACU and 1h after PACU Pre-operative, in the PACU and 1h after PACU Every 15 minutes during stay in PACU and before the child left the PACU
Hatem (2006), Brazil	ICU pediatric cardiac patients [3]	Hospital do Coracao	84	NR (1 day – 16 year)	Not reported	Parallel group RCT 3.4 : 1	Recorded music Classical music: Vivaldi's Four Seasons (No music, standard care)	Post-operative: 30 minutes after the surgery during 30 minutes	FAS |Pain| (scale 0-10) Nurse Vital signs: BP, DBP, HR, IQ, MBP, RR, SBP, SatO2, T Nurse	First and last minutes of the intervention Before intervention and 30 minutes after intervention

Legend Table 3.1 - 1. spine fusion, centralization of wrist, scar revision, tibial rodding, osteotomy and placement of external fixator, osteotomy and leg lengthening, pectus repair, hardware removal 2. Arthroscopy, endoscopy, extraction of pain/nail/thread, hernia/hydrocele, superficial surgery 3. acyanotic congenital heart disease (ACHD) with left-right shunt; obstructive ACHD, cyanotic congenital heart disease (CCHD) with pulmonary hypoflow; CCHD with pulmonary hyperflow, complex congenital heart disease (CHD) and acquired heart diseases

Outcome measurements

Primary outcome: pain intensity

Across the studies pain intensity was measured with the Visual Analogue Scale (VAS), Coloured Analogue Scale (CAS) and the Facial Pain Scale (FPS) [9,11,12]. In Bradt et al. the patients self-reported pain intensity with the VAS [9] before, during and after the music intervention. Nilsson et al. assessed self-reported pain intensity by CAS preoperatively, at the arrival to the Post Anaesthesia Care Unit (PACU) and one hour after the PACU [11]. In the study of Hatem et al. the Facial Pain Scale was assessed by a nurse during the first and last minutes of the music intervention [12] (see table 3.1).

Secondary outcome: anxiety and distress descriptors

As a secondary outcome, two out of the three studies measured anxiety and distress descriptors [9,11]. Bradt et al. used a 5-point scale with 8 bipolar descriptor items to measure the participants' emotional state. Each of the items was given a numerical value from 1 'very negative' to 5 'very positive'. This emotional index scale was developed by Bradt et al. and was not validated.

To measure anxiety Nilsson et al. used the Spiegelberger short- State Trait Anxiety Inventory (STAI) on a scale of 6-24 points, which was not validated in children. The children filled in the short form of STAI preoperatively and 1 hour after the PACU. A Facial Affective Scale (FAS) was used to measure distress at the same time points as pain.

Outcomes

Table 3.2 provides the intragroup results of all the primary and secondary outcomes reported in the included studies. All three studies show statistically significant intragroup improvements for pain and anxiety and distress descriptors (Table 3.2). Table 3.3 and Figures 3.1-3.3 provide the comparison between the intervention and control groups for pain and anxiety and distress descriptors.

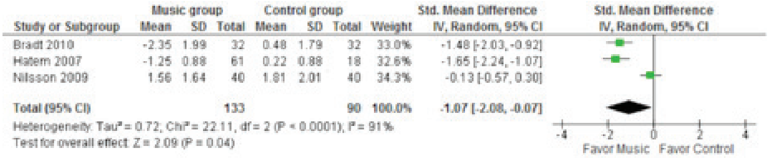
Table 3.2 - Intragroup comparisons of post music intervention versus baseline

	Scale (outcome)	N	MD	95% CI *	SE	SMD	95% CI **	P value
Bradt (2010)	VAS_{E2} (pain)	32	-2.83	[-3.76to -1.90]	0.47	-1.48	[-2.03; -0.92]	<0.001
	Emotional $State_{\_E2Afternoon}$ (anxiety)	32	-1.81	[-3.92to 0.30]	1.08	-0.41	[-0.91; 0.08]	0.10
Nilsson (2009)	CAS (pain)	80	-0.25	[-1.054; 2.45]	0.41	-0.13	[-0.57; 0.30]	0.54
	STAI (anxiety)	80	-0.88	[-2.28; 0.52]	0.72	-0.27	[-0.71; 0.17]	0.22
	FAS (anxiety)	80	-0.13	[-0.23; -0.03]	0.05	-0.58	[-1.06; -0.11]	0.02
Hatem (2006)	FAS (pain)	79	-1.47	[-1.93; -1.01]	0.24	-1.65	[-2.24; -1.07]	<0.001

Legend Table 3.2 - VAS = Visual Analogue Scale; CAS = Coloured Analogue Scale; STAI = Spielberger short-State Trait Anxiety Inventory; FAS = Facial Affective Scale; MD = mean difference; E1 = first entrainment; E2 = second entrainment; C = Control group; Negative MD = decreased mean difference; Positive MD = increased mean difference; 95% CI of the MD = Confidence Interval; SD = Standard deviation

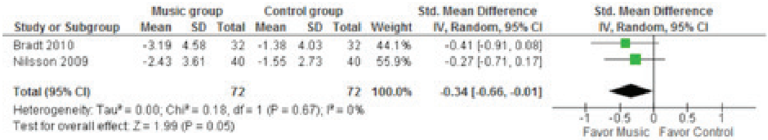
Pain scores (Figure 3.1) demonstrated significant heterogeneity (Chi2 22.11, I2= 91%, (P<0.0001)) across studies. The random effects pooled result showed a statistically significant standardized mean difference of -1.07 [95% CI -2.08 to -0.07] between the intervention and control group in favour of music.

Figure 3.1 - Pain change score (music vs. no music) before and after the intervention by CAS and FAS



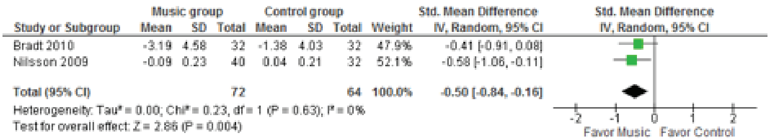
Anxiety scores (Figure 3.2) by Short-STAI and bipolar descriptors demonstrated no statistically significant heterogeneity (Chi2 0.18, I2= 0%, (P=0.67)). The standardized mean difference of anxiety and distress between the intervention and control group was -0.34 [95% CI -0.66 to -0.01] in favour of music.

Figure 3.2 - Anxiety/distress change score (music vs. no music) before and after the intervention measured by Short-STAI and bipolar descriptors



Anxiety and distress scores (Figure 3.3) by FAS and bipolar descriptors demonstrated no statistically significant heterogeneity (Chi2 0.23, I2= 0%, (P=0.63)). The standardized mean difference of anxiety between the intervention and control group was -0.50 [95% CI -0.84 to -0.16] in favour of music.

Figure 3.3 - Anxiety/distress change score (music vs. no music) before and after the intervention measured by FAS and bipolar descriptors.



DISCUSSION

The aim of this systematic review was to investigate the effect of perioperative music interventions in children undergoing surgical procedures.
Two studies reported a large significant pain-reducing effect and one study a small non-significant pain-reducing effect of music between the intervention and control group. Comparing before and after the intervention within the intervention groups, all studies showed a large and significant decline in pain, anxiety and distress descriptors.

The present review is the first on this topic that strictly adheres to the methods recommended in the Cochrane Guidelines for writing a Systematic Review [8]. The findings should be interpreted in the light of its limitations, most of which are related to the original studies. First, the overall risk of bias was moderate. Second, there was heterogeneity in the types of music interventions, the type of surgery across studies, patient populations and outcome measures.

Although the heterogeneity between the studies is a limitation, we were able to calculate the standardized mean difference per group and to pool the results for the pain and anxiety and distress descriptor outcomes. Ideally, we would have tried to adjust for the heterogeneity by performing a meta-regression analysis or subgroup analysis, but the number of studies was insufficient to perform such analyses. The variability in treatment effect across studies is likely to be due to the above-mentioned heterogeneity in the types of music interventions, the type of surgery across studies, patient populations and outcome measures.

Although only three studies could be included in this meta-analysis, the results show a significant reduction of pain, anxiety and distress descriptors in paediatric surgical patients. Similar results have been found in other patient populations. Thirteen Cochrane systematic reviews have been published on music interventions in adults for various indications [3,6,13-23]. All reported positive effects of music on anxiety and distress, pain and quality of life, although it was noted that the general methodological quality of reviewed studies was moderate to low. Furthermore, authors recommended exploring possibly differential effects of live music therapy versus recorded music interventions. Apart from the Cochrane reviews, thirty descriptive and systematic reviews on the effects of music interventions on perioperative pain and anxiety in adults were published [2,24-40]. Together the body of evidence suggests that music therapy in the perioperative setting has the potential to positively affect pain outcomes, anxiety and distress.

For future research we would like to stress the importance of rigorous study protocols, the use of larger sample sizes and validated outcome measures. For research in children, we would recommend to pay heed to the Consensus Statement of McGrath et al. regarding appropriate outcomes measurements in pain research [41].

Study populations should be more homogenous in terms of age and type of procedure. Observer bias could perhaps be prevented by recording the patient on video while receiving the intervention, blind the video images for the allocated intervention and have independent assessors score the outcome measures using validated measurements while watching the recordings [4].

Furthermore, we would like to suggest cost-effectiveness studies comparing live music therapy with recorded music. Apart from the possibly different effects of live music therapy versus recorded music, the timing of the intervention and the effect of self-selected versus therapist selected music deserve attention [3].

This review shows that few RCTs have been performed on effects of music in paediatric patients undergoing surgery, but that music interventions are worthwhile to further investigate for its clinical usefulness. State-of-the-art RCTs evaluating music interventions are difficult to perform in particular due to the inherent performance bias and detection bias. The only way to perform a double-blinded study is to offer recorded music through headphones to patients under general anesthesia which would preclude evaluation of the potential beneficial effect of music pre- and post-surgery [42]. Furthermore, it is impossible to blind patients for live music therapy by a music therapist.

In conclusion, this review shows that music as a non-pharmacological adjuvant intervention has potential in reducing pain, anxiety and distress in children undergoing surgery. Its non-invasive nature is an advantage.

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16. Bradt J, Magee WL, Dileo C, Wheeler BL, McGilloway E (2010) Music therapy for acquired brain injury. Cochrane Database Syst Rev: CD006787.
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32. Kemper KJ, Danhauer SC (2005) Music as therapy. South Med J 98: 282-288.
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34. Newman A, Boyd C, Meyers D, Bonanno L (2010) Implementation of music as an anesthetic adjunct during monitored anesthesia care. J Perianesth Nurs 25: 387-391.
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39. Tang HY, Vezeau T (2010) The use of music intervention in healthcare research: a narrative review of the literature. J Nurs Res 18: 174-190.
40. Wakim JH, Smith S, Guinn C (2010) The efficacy of music therapy. J Perianesth Nurs 25: 226-232.
41. McGrath PJ, Walco GA, Turk DC, Dworkin RH, Brown MT, et al. (2008) Core outcome domains and measures for pediatric acute and chronic/recurrent pain clinical trials: PedIMMPACT recommendations. J Pain 9: 771-783.
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SUPPLEMENT S1: REVIEW PROTOCOL

Title
The effects of perioperative music interventions in paediatric surgery: a systematic review and meta-analysis of randomised controlled trials. Review Protocol.

Objective
What is known about the effectiveness of music interventions to reduce pain, anxiety and distress in paediatric patients undergoing minimally invasive or invasive surgery.

Selection criteria: patients
Inclusion - All paediatric patients (<18 years old), inpatients and outpatients, emergency and non-emergency undergoing invasive and non-invasive surgical procedures.
Exclusion - Neonates (till 28 days), adults, ventilated, dental and ophthalmological surgical patients.

Selection criteria: Intervention
Inclusion - Music interventions delivered in a hospital setting. Live music therapy offered by a music therapist or recorded music, instrumental music, music with song. All type of interventionists. Individual delivery and group delivery (measured individually).
Exclusion - Multimodal interventions in which music is offered in combination with another therapy (example: massage). Auditory stimuli produced by non-human agents such as nature sounds or sounds like fixated beeps.

Selection criteria: Comparison
Inclusion - Standard care, no music or other interventions.

Selection criteria: Outcome
Inclusion - Interventions offered before during or after the surgical procedure, but only if the outcomes were measured during or after the surgical procedure. Pain, anxiety and distress outcomes.
Exclusion - Studies that offered the intervention pre-operatively but only measured the outcomes prior to surgery.

Selection criteria: Time frame
No restriction on date of publication, all sources searched from their first available date.

Selection criteria: Study design
Inclusion - All randomised controlled trials with a parallel group, cross-over or cluster design.
Exclusion - Non-randomised trials, papers not written in English, narrative reviews.

Search strategy
All medical journals and music therapy journals (electronic and print). All databases available.

Data extraction - Data will be extracted by two researchers: Marianne van der Heijden (MvdH) and Sadaf Oliai Araghi (S.O.). Any disagreements regarding the data extraction will be resolved by Monique van Dijk (MvD), Hans Jeekel (JJ) and Myriam Hunink (MH). The Cochrane guidelines for Systematic Review will be followed.

SUPPLEMENT S2: FULL LIST OF SEARCH TERMS AND DATABASES

Embase
(music/de OR 'music therapy'/de OR (music OR musical OR musicotherap*):ab,ti) AND (surgery/exp OR 'obstetric operation'/exp OR 'postoperative complication'/exp OR 'anesthesiological procedure'/exp OR 'perioperative nursing'/de OR 'postanesthesia nursing'/de OR 'operating room'/de OR 'recovery room'/de OR 'operating room personnel'/de OR (surger* OR surgic* OR peroperat* OR perioperat* OR preoperat* OR postoperat* OR operati* OR interoperat* OR intraoperat* OR anesthe* OR anaesthe* OR perianesthe* OR peranesthe* OR perianaesthe* OR peranaesthe* OR preanasthe* OR preanaesthe* OR postanasthe* OR postanaesthe*):ab,ti OR surgery:lnk)

Medline OvidSP
(music/ OR "music therapy"/ OR (music OR musical OR musicotherap*).ab,ti.) AND (exp "Surgical Procedures, Operative"/ OR exp "postoperative complications"/ OR "Anesthesiology"/ OR "perioperative nursing"/ OR "Operating Rooms"/ OR "recovery room"/ OR (surger* OR surgic* OR peroperat* OR perioperat* OR preoperat* OR postoperat* OR operati* OR interoperat* OR intraoperat* OR anesthe* OR anaesthe* OR perianesthe* OR peranesthe* OR perianaesthe* OR peranaesthe* OR preanasthe* OR preanaesthe* OR postanasthe* OR postanaesthe*).ab,ti. OR surgery.xs.)

Cochrane central
((music OR musical OR musicotherap*):ab,ti) AND ((surger* OR surgic* OR peroperat* OR perioperat* OR preoperat* OR postoperat* OR operati* OR interoperat* OR intraoperat* OR anesthe* OR anaesthe* OR perianesthe* OR peranesthe* OR perianaesthe* OR peranaesthe* OR preanasthe* OR preanaesthe* OR postanasthe* OR postanaesthe*):ab,ti)

Web-of-science
TS=(((music OR musical OR musicotherap*)) AND ((surger* OR surgic* OR peroperat* OR perioperat* OR preoperat* OR postoperat* OR operati* OR interoperat* OR intraoperat* OR anesthe* OR anaesthe* OR perianesthe* OR peranesthe* OR perianaesthe* OR peranaesthe* OR preanasthe* OR preanaesthe* OR postanasthe* OR postanaesthe*)))

Scopus
TITLE-ABS-KEY((music OR musical OR musicotherap*) AND (surger* OR surgic* OR peroperat* OR perioperat* OR preoperat* OR postoperat* OR operati* OR interoperat* OR intraoperat* OR anesthe* OR anaesthe* OR perianesthe* OR peranesthe* OR

perianaesthe* OR peranaesthe* OR preanasthe* OR preanaesthe* OR postanasthe* OR postanaesthe*))

PsycINFO OvidSP
(music/ OR “music therapy”/ OR (music OR musical OR musicotherap*).ab,ti.) AND (exp “Surgery”/ OR “Surgical Patients”/ OR exp “Postsurgical Complications”/OR exp “Surgical Complications”/ OR “Anesthesiology”/ OR (surger* OR surgic* OR peroperat* OR perioperat* OR preoperat* OR postoperat* OR operati* OR interoperat* OR intraoperat* OR anesthe* OR anaesthe* OR perianesthe* OR peranesthe* OR perianaesthe* OR peranaesthe* OR preanasthe* OR preanaesthe* OR postanasthe* OR postanaesthe*).ab,ti.)

PubMed publisher
(music[tiab] OR musical[tiab] OR musicotherap*[tiab]) AND (surger*[tiab] OR surgic*[-tiab] OR peroperat*[tiab] OR perioperat*[tiab] OR preoperat*[tiab] OR postoperat*[-tiab] OR operati*[tiab] OR interoperat*[tiab] OR intraoperat*[tiab] OR anesthe*[tiab] OR anaesthe*[tiab] OR perianesthe*[tiab] OR peranesthe*[tiab] OR perianaesthe*[tiab] OR peranaesthe*[tiab] OR preanasthe*[tiab] OR preanaesthe*[tiab] OR postanasthe*[-tiab] OR postanaesthe*[tiab]) AND publisher[sb]

CINAHL
(MH music+ OR MH “music therapy”+ OR TX (music OR musical OR musicotherap*)) AND (MH “Surgery, Operative”+ OR MH “postoperative complications”+ OR MH “Anesthesiology”+ OR MH “perioperative nursing”+ OR MH “Operating Rooms”+ OR MH “Post Anesthesia Care Units”+ OR TX (surger* OR surgic* OR peroperat* OR perioperat* OR preoperat* OR postoperat* OR operati* OR interoperat* OR intraoperat* OR anesthe* OR anaesthe* OR perianesthe* OR peranesthe* OR perianaesthe* OR peranaesthe* OR preanasthe* OR preanaesthe* OR postanasthe* OR postanaesthe*))

Amed OvidSP
(music OR musical OR musicotherap*) AND (surger* OR surgic* OR peroperat* OR perioperat* OR preoperat* OR postoperat* OR operati* OR interoperat* OR intraoperat* OR anesthe* OR anaesthe* OR perianesthe* OR peranesthe* OR perianaesthe* OR peranaesthe* OR preanasthe* OR preanaesthe* OR postanasthe* OR postanaesthe*)

Handsearch
(surger* OR surgic* OR peroperat* OR perioperat* OR preoperat* OR postoperat* OR operati* OR interoperat* OR intraoperat* OR anesthe* OR anaesthe* OR perianesthe* OR peranesthe* OR perianaesthe* OR peranaesthe* OR preanasthe* OR preanaesthe* OR postanasthe* OR postanaesthe*)

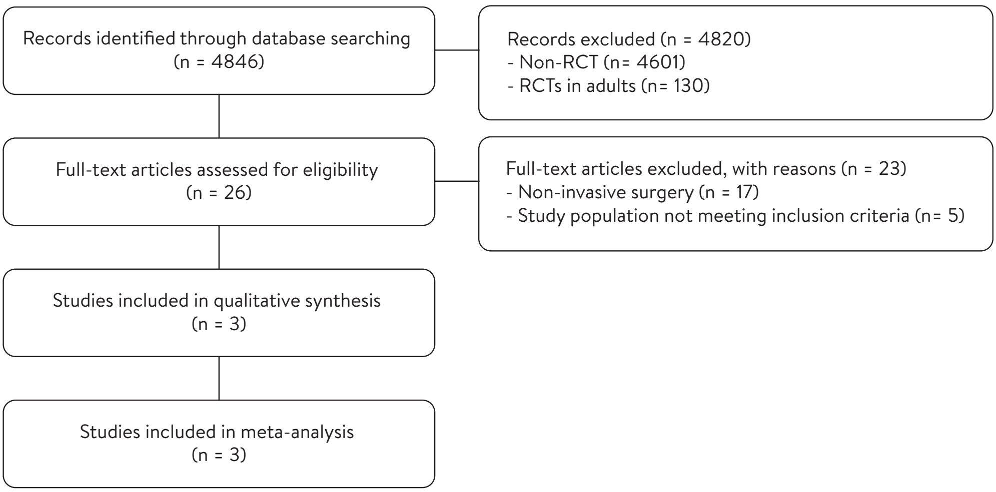
Databases: 1. Cochrane Central Register of Controlled Trials (CENTRAL); 2. MEDLINE (Ovid) (1950 to present); 3. EMBASE (1980 to present); 4. CINAHL (1982 to present); 5. PsycINFO (1967 to present); 6. AMED (1985 to present); 7. Web of Science (1945 to present) 8.Scopus (1995 to present) 9. The specialist music therapy research database at www.musictherapyworld.net; 10. CAIRSS for Music; 11. ClinicalTrials.gov(http://www.

clinicaltrials.gov/); 12. Current Controlled Trials (http://www.controlledtrials.com/); 13. National Research Register (http://www.updatesoftware.com/Nationa l/)

Furthermore we hand-searched 12 journals from their first available date: 1. Australian Journal of Music Therapy; 2. Canadian Journal of Music Therapy; 3. The International Journal of the Arts in Medicine; 4. Journal of Music Therapy; 5. Journal for Art Therapies in Education, Welfare and Health Care; 6. Music Therapy; 7. Music Therapy Perspectives; 8. Nordic Journal of Music Therapy; 9. Music Therapy Today (online journal of music therapy); 10. Voices (online international journal of music therapy) 11. New Zealand Journal of Music Therapy; 12. British Journal of Music Therapy. See appendix 1 for the search terms. A recent search update was performed in October 2014.

SUPPLEMENT S3: PRISMA CHECKLIST AND FLOWCHART

Flowchart



PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
Title			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
Abstract			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2

Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
Methods			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6
Results			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7

Discussion			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	9
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	10
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	11
Funding			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	

SUPPLEMENT S4: EXCLUDED ARTICLES

One study was excluded because the interventions and measurements only took place before surgery (1). Seventeen studies were excluded because they included non-invasive (surgical) procedures (2-18). Five studies were excluded because the study population did not meet the inclusion criteria (19-23).

1. Kain ZN, Caldwell-Andrews AA, Krivutza DM, et al. Interactive music therapy as a treatment for preoperative anxiety in children: a randomised controlled trial. Anesth Analg. May 2004;98(5):1260-1266, table of contents.
2. Nguyen TN, Nilsson S, Hellstrom AL, Bengtson A. Music therapy to reduce pain and anxiety in children with cancer undergoing lumbar puncture: a randomised clinical trial. J Pediatr Oncol Nurs. May-Jun 2010;27(3):146-155.
3. Balan R, Bavdekar SB, Jadhav S. Can Indian classical instrumental music reduce pain felt during venepuncture? Indian J Pediatr. May 2009;76(5):469-473.
4. Windich-Biermeier A, Sjoberg I, Dale JC, Eshelman D, Guzzetta CE. Effects of distraction on pain, fear, and distress during venous port access and venipuncture in children and adolescents with cancer. J Pediatr Oncol Nurs. Jan-Feb 2007;24(1):8-19.
5. Caprilli S, Anastasi F, Grotto RP, Scollo Abeti M, Messeri A. Interactive music as a treatment for pain and stress in children during venipuncture: a randomised prospective study. J Dev Behav Pediatr. Oct 2007;28(5):399-403.
6. Liu RW, Mehta P, Fortuna S, et al. A randomised prospective study of music therapy for reducing anxiety during cast room procedures. J Pediatr Orthop. Oct-Nov 2007;27(7):831-833.
7. Kain ZN, Wang SM, Mayes LC, Krivutza DM, Teague BA. Sensory stimuli and anxiety in children undergoing surgery: a randomised, controlled trial. Anesth Analg. Apr 2001;92(4):897-903.
8. Fratianne RB, Prensner JD, Huston MJ, Super DM, Yowler CJ, Standley JM. The effect of music-based imagery and musical alternate engagement on the burn de-

bridement process. J Burn Care Rehabil. Jan-Feb 2001;22(1):47-53.
9. Loewy J, Hallan C, Friedman E, Martinez C. Sleep/sedation in children undergoing EEG testing: a comparison of chloral hydrate and music therapy. J Perianesth Nurs. Oct 2005;20(5):323-332.
10. Noguchi LK. The effect of music versus nonmusic on behavioral signs of distress and self-report of pain in pediatric injection patients. J Music Ther. Spring 2006;43(1):16-38.
11. Kim SJ, Oh YJ, Kim KJ, Kwak YL, Na S. The effect of recorded maternal voice on perioperative anxiety and emergence in children. Anaesth Intensive Care. Nov 2010;38(6):1064-1069.
12. Padmanabhan R, Hildreth AJ, Laws D. A prospective, randomised, controlled study examining binaural beat audio and pre-operative anxiety in patients undergoing general anaesthesia for day case surgery. Anaesthesia. Sep 2005;60(9):874-877.
13. Huth MM, Broome ME, Good M. Imagery reduces children's post-operative pain. Pain. Jul 2004;110(1-2):439-448.
14. Hartling L, Newton AS, Liang Y, et al. Music to reduce pain and distress in the pediatric emergency department: a randomised clinical trial. JAMA Pediatr. Sep 2013;167(9):826-835.
15. Fanurik D, Koh JL, Schmitz ML. Distraction techniques combined with EMLA: Effects on IV insertion pain and distress in children. Children's Health Care. 2000;29(2):87 - 101.
16. Press J, Y. G, Maimon M, Gonen A, Goldman V, Buskila D. Effects of active distraction on pain of children undergoing venipuncture. The Pain Clinic. 2003;15(3):261.
17. Bufalini A. [Role of interactive music in oncological pediatric patients undergoing painful procedures]. Minerva Pediatr. Aug 2009;61(4):379-389.
18. Shahabi M, Kalani-Tehrani D, Eghbal M, Alavi-Majd H, Abed Saidi J. Comparing the effects of EMLA ointment with a diversionary activity (music) on vein puncture pain in school-age children. Journal of Shahid Beheshti School of Nursing and Midwifery. 2007;17(56).
19. Bansal P, Kharod U, Patel P, Sanwatsarkar S, Patel H, Kamar H. The effect of music therapy on sedative requirements and haemodynamic parameters under spiral anaesthesia: a prospective study. Journal of Clinical and Diagnostic Research. 2010;4(August):2782 - 2789.
20. Whitehead-Pleaux AM, Baryza MJ, Sheridan RL. The effects of music therapy on pediatric patients' pain and anxiety during donor site dressing change. J Music Ther. Summer 2006;43(2):136-153.
21. Burns DS, Robb SL, Haase JE. Exploring the feasibility of a therapeutic music video intervention in adolescents and young adults during stem-cell transplantation. Cancer Nurs. Sep-Oct 2009;32(5):E8-E16.
22. Lee DW, Chan AC, Wong SK, et al. Can visual distraction decrease the dose of patient-controlled sedation required during colonoscopy? A prospective randomised controlled trial. Endoscopy. Mar 2004;36(3):197-201.
23. Bradt J. The effects of music entrainment on postoperative pain perception in pediatric patients. Music and Medicine. 2010;2(3):150-157.

SUPPLEMENT S5: RISK OF BIAS. QUALITY ASSESSMENT OF STUDIES

	Selection bias		Performance bias	Detection bias	Attrition bias	Reporting bias	Overall risk of bias
	Random sequence generation	**Allocation concealment**	**Blinding participants and personnel**	**Blinding of outcome assessment**	**Incomplete outcome data**	**Selective reporting**	
Bradt (2010)	Low	Unclear	Unclear	High	Unclear	Low	Moderate
Nilsson (2009)	Low	Low	Low	Low	Low	Low	Low
Hatem (2006)	High	Unclear	Low	Low	Unclear	Low	Moderate

CHAPTER 4

Assessing and addressing the problem of pain and distress during wound care procedures in South African paediatric patients with burns

Burns 2018, 44 (1)

Marianne J.E. van der Heijden • Alette de Jong • Heinz Rode • Roux Martinez • Monique van Dijk

ABSTRACT

Objective

While the prevalence of burn injuries in children is highest in low and middle-income countries, most research on burn-related pain intensity and distress is carried out in high-income countries. In this study we assessed pain intensity and distress in paediatric patients with burns undergoing wound care procedures without distraction and parental presence in a South–African children's hospital and sought to identify predictors for the outcomes.

Methods

This observational study, carried out as part of a randomised controlled trial, took place at a burns unit in Cape Town, South Africa and included patients between the ages of 0 and 13 years undergoing their first or second wound care procedure. We measured pain intensity and distress using the COMFORT Behavioural scale (COMFORT-B) across four distinct phases of wound care procedures: removal of bandage; washing the wound; administering wound care; putting on new dressings. COMFORT-B scores ≥ 21 indicate severe pain intensity and distress.

Results

124 patients were included, median age 21.2 months (IQR 14.9 to 39.5 months), 90% suffered scalds, and median total body surface 8% (IQR 5 to 14%) Assessment scores for the majority of patients were indicative of severe pain intensity and distress during wound care procedures. Median COMFORT-B scores across the four phases were 24, 25, 25 and 22 respectively. Across the four phases respectively 76%; 89%; 81% and 62% of the patients were indicated with severe pain intensity and distress. Age was a predictor for pain intensity and distress as younger children were assigned higher scores than older children (Unstandardized B -.052; 95% CI -.071 to -.032 $p<0.001$).

Conclusions

In this study children received wound care procedures without distraction or parental presence and were assessed to have high pain intensity and distress. There is a correlation between age and COMFORT-B scores: younger children show higher distress, indicating a great need for better pain and distress control during wound care procedures. It is difficult to identify whether pain or distress is the specific primary cause for the high COMFORT-B scores.

Abbreviations: WCP: wound care procedures; RCWMCH: Red Cross War Memorial Children's Hospital; COMFORT-B: COMFORT Behavioural scale.

INTRODUCTION

Burns are associated with painful and distressing experiences due to the trauma of the injury, hospitalization and medical procedures. Pain experiences are shaped by a constant background pain caused by the inflammatory response in and around the burn site; and by acute intense procedural pain caused by manipulation of the burned area (1, 2). Moreover, burn injuries have been linked to acute and posttraumatic stress disorder (3-6). Distress has been defined as 'behaviours of negative affect associated by pain, anxiety and fear' (7). In children with burns, pain intensity and pain-related distress are intrinsically connected (1, 8). Inadequate pain management might evoke a distress response, arousal for subsequent procedures, and can influence the child's pain perception and processing in later life (9-11).

Treatment of burn injury involves repeated wound care procedures (WCP), which are painful and frightening (12). Four phases of WCP can be distinguished: removal of the bandage, cleaning the wound (including wiping away loose skin with gauze swabs), administering new wound care products and putting on new dressings. When children have negative emotions such as distress or anger they may perceive the pain as more intense (13, 14). Therefore it is important to support the child in coping with pain and distress of the recurring WCP.

When children cannot self-report pain intensity and distress the use of behavioural observation scales is indicated, such as the COMFORT-behaviour scale (COMFORT-B) (1). A study by de Jong et al. using the COMFORT-B to determine the extent and course of background and procedural pain in children in a high-resource burns unit showed that 66% of the children expressed moderate and 25% severe procedural pain intensity (8).

To our knowledge there is no baseline measurement of pain and distress during WCP in children from resource-limited settings. Therefore the aim of this observational study was to assess the extent of pain intensity and distress in children in South Africa during a standard WCP, without distraction interventions or parental presence. Furthermore we studied whether patient characteristics, pharmacological treatment and type of wound care product predicted the level of pain intensity and distress.

MATERIAL AND METHODS

Design

This observational study measured the levels of pain intensity and distress in children with burns during WCP. This study was carried out as part of a randomised controlled trial (RCT) that measured the effects of live music therapy on pain and distress after WCP, comparing pain and distress scores before the WCP and music intervention to after the music intervention.

Setting and inclusion criteria

This study took place at the paediatric burn unit of the Red Cross War Memorial Children's Hospital (RCWMCH) in Cape Town, South Africa from October 2014 to November 2015 (RCT registered at the Pan African Clinical Trials Registry number PACTR201505000906290). The medical ethical committee of Cape Town University and the medical ethical committee of theRCWMCH approved the study.

The RCWMCH is a state hospital and most of its patients come from poor backgrounds. The burn unit has 17 beds, including 6 high care beds, and has access to intensive care facilities. Annually, around 1300 patients are admitted to the ward and approximately 5000 patients visit the outpatient burn clinic. Children from age 0 – 13 are admitted; 70% are younger than 6 years old (RCWMCH Information Management Department). Criteria for admission are a full thickness burn greater than 5% of the total body surface area (%TBSA), partial thickness burns >10% TBSA and/or burns involving inhalation, electrical injuries, face, hands, perineum, genitalia, or body circumference, associated trauma or suspected child abuse.

Eligible subjects included newly admitted inpatients of all ages receiving their first or second WCP after admission. For practical reasons we could only include children who received WCP in the morning. Excluded were children newly admitted but receiving WCP in the afternoon of the day of admission. Furthermore, children with a hearing impairment or altered level of consciousness were excluded.

Outcome measurements

Outcome variables were pain intensity and distress during WCP, measured with the COMFORT-B scale. This scale has been found a reliable, valid and practical tool to measure background and procedural pain and distress behaviour in children with burns aged 0-5 years (1, 15). It has been validated for the use in various paediatric patient groups such as critically ill, mechanically ventilated and mentally impaired children. Although officially validated for children up to 7 years old, the COMFORT-B is used for children up to 18 years old (16). The COMFORT-B has been validated cross-culturally in European countries, the USA and in Chinese and Portuguese speaking populations (17-19). It asks observers to consider intensity of six behavioural manifestations: alertness, calmness, crying, body movement, facial tension and muscle tone. For each of these items 5 descriptions rated from 1 to 5 are provided reflecting increasing intensity of the behaviour in question. Summing the ratings of the separate manifestations leads to a score ranging from 6 to 30. De Jong et al. determined cut-off points for the COMFORT-B scores during WCP, and defined 6-13 as mild pain and distress, 14-20 as moderate pain and distress; and 21-30 as severe pain and distress (8). Observers without any specific background who have completed the COMFORT-B training can use the scale, and thus it is an easily accessible tool for both clinical research and practice.

Furthermore, data on the following candidate predictors for the COMFORT-B scores were collected: age, sex, first assessment of TBSA (%), time since last medication, time since burn incident, type of burn, type of wound care product.

We collected information on the most recent analgesics and sedatives administered before WCP. The burns units' pain medication protocol prescribes the following orally administered medication at set times: paracetamol 15 mg/kg 6 hourly; gabapentin 2-5 mg/kg 8 hourly; and oral clonidine 2-3 microgram/kg 6 hourly.

Procedure

The primary investigator (PI) attended a 2-hour training session during which the COMFORT-B scale was explained, and applied to video footage of children in possibly painful situations. Next, the PI applied the scale to videos that had been scored by the trainer as well. A comparison of the scores resulted in an excellent interrater reliability between the PI and the trainer (intraclass correlation coefficient 0.922).

Prior to WCP the parent, and the child as well when older than 7 years, were asked for informed consent/assent to participate in the study. Parents are not present during WCP because it is considered too stressful for the parent, the child and the nurses. Apart from a radio occasionally playing in the background, distraction was not standardly provided. The PI stood in the back of the room, observed the child during WCP and took note of any possible influential distractions such as giving a pacifier to the child. The PI applied the COMFORT-B scale during four time slots in order to observe the behaviour of the patient over the four phases of WCP: removal of the bandage; washing the child; administering wound care product; putting on new dressings.

Data analysis

Data was analysed with the statistical programme SPSS 23.0 (SPSS Inc., Chicago USA). Descriptive statistics are used to describe background characteristics of patients. Normally distributed data are presented as mean (standard deviation); non-normally distributed data are presented as median (interquartile range). The mean COMFORT-B score was calculated across the four COMFORT-B scores assigned during the different phases of the WCP. Pearson product moment correlation coefficient was used to determine the linear association between the mean COMFORT-B score during WCP and TBSA%, age, time since burn, and time since last medication in hours. Mann-Whitney test was used to compare mean COMFORT-B score between children with and without scald burns and between boys and girls. The mean COMFORT-B score served as outcome variable in a multivariable regression analysis. The following predictor variables were entered: age, sex, TBSA (%), , time since last medication till the start of WCP (in minutes), time since burn incident (less or more than two days), type of burn. The variance inflation factors (VIF) were calculated to check for multicollinearity between the predictor variables (VIF> 5).

RESULTS

A total of 124 patients were included in this study, 64 boys (52%) and 60 girls (48%). The median age was 21.2 months (IQR 14.9 to 39.5). The majority of the burns were scalds (90%) and the median TBSA was 8% (IQR 5 to 14). Most of the patients received WCP within two days post burn (85%) (see also Table 4.1). The mean COMFORT-B score before WCP was M=11 (IQR 10 to 13).

Table 4.1 - Background characteristics of included patients (n=124)

Variables	Total (%)
Sex in n (%)	
Boy	64 (51.6)
Girl	60 (48.4)
Age in months, median (IQR)	21.2 (14.9 to 39.5)
Language	
Xhosa	57 (46)
Afrikaans	51 (41)
English	11 (9)
Other	5 (4)
Type of burn	
Scald	112 (90)
Flame	7 (6)
Electric	4 (3)
Oil	1 (1)
TBSA (%)	8 (5 to 14)
TBSA Min- Max	1 to 32
Body parts burned[1]	
Head	67 (54)
Arms	107 (86)
Thorax/ abdomen	63 (51)
Back	36 (29)
Legs	53 (43)
Genitalia	4 (2)
Change of dressing	
First change of dressing	102 (82)
Second change of dressing	22 (18)
WCP days postburn	
< 2 days postburn	(85%)
> 2 days postburn	19 (15%)
Depth of burn[2]	
Partial thickness	102 (82)
Indeterminate depth	21 (17)
Full thickness	1 (1)

Legend Table 4.1 - IQR= interquartile range; TBSA=% Total Body Surface Affected; WCP = wound care procedure. Numbers are N (%) or median (IQR). 1 More than one burned body part possible 2 In young children the distinction between partial and full thickness is not always evident during the first two days post burn. Therefore the depth given here is indeterminate.

Type of medication

Six types of analgesics and sedative were administered: paracetamol, clonidine, gabapentin, tilidine, ibuprofen and chloralhydrate. All medication was administered orally and at set times according to the burns unit pain medication protocol. Table 4.2 presents the time elapsed between the WCP and medication administration.

Table 4.2 - Analgesics and sedatives prescribed to patient population (n=124)

Type of medication in mg/kg	Median dose mg/kg (IQR)	Minutes between bolus and WCP
Analgesics		
Paracetamol (n=119)	15 (14 to 18)	230 (215 to 255)
Clonidine (n=81)	2.3 (1.9 to 2.8)	225 (150 to 250)
Gabapentin (n=79)	4 (4 to 5)	115 (100 to 140)
Tilidine (n=20)	0.9 (0.8 to 1)	135 (105 to 249)
Ibuprofen (n=8)	7 (4 to 8)	100 (86 to 185)
Sedatives		
Chloralhydrate (n=1)	1	225

Legend Table 4.2 - IQR = interquartile range; WCP = wound care procedure 1Number of medication given per person: median 3 (IQR 2 to 3)

COMFORT-B scores

The median COMFORT-B scores for the four time slots varied from 24 (IQR 21 to 26) during removal of the bandages to 25 (IQR 23 to 27) during washing and 25 (IQR 22 to 29) during administering new dressings). The median score declined to 22 (IQR 18 to 24) when new bandages were put on (see Figure 4.1). Washing the wound and administering new dressings inflicted severe pain and distress in respectively 89% and 81% of the patients. Severe pain and distress was found in 76% and 62% of the patients during removal and applying of bandage (see Table 4.3 for cut-off points COMFORT-B scores).

Figure 4.1 - Boxplot representing COMFORT-B scores across time slots

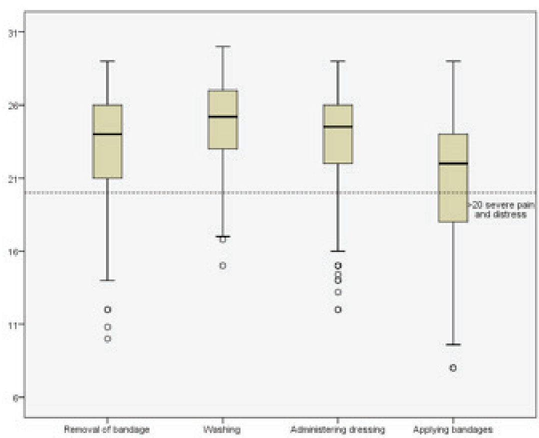


Table 4.3 Classification of COMFORT-B scores across time slots

COMFORT-B scale Classification, N (%)	Removal of bandage n (%)	Washing n (%)	Administering new dressing n (%)	Applying bandage n (%)
N of included COMFORT-B scores	124	123*	123*	121*
Mild pain and distress (score 6 to 13)	4 (3.2)	-	2 (1.6)	8 (6.6)
Moderate pain and distress (score 14 to 20)	26 (21.0)	14 (11.4)	21 (17.1)	38 (31.4)
Severe pain and distress (score 21 to 30)	94 (75.8)	109 (88.6)	100 (81.3)	75 (62.0)

Legend Table 4.3 - 1. Missing values due to not being able to take full COMFORT-B scores

Mean COMFORT-B score during WCP was not significantly associated with time since last medication. Table 4.4 gives the results of the multivariable regression analysis with mean COMFORT-B during WCP as outcome variable. All VIF scores remained <2, indicating a reliable estimate of the regression coefficients.

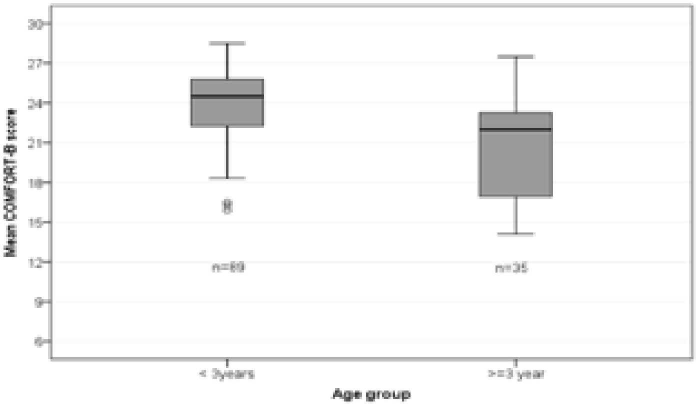
Table 4.4: Multivariable regression analysis with mean COMFORT-B scale scores as outcome variable

Predictor	Unstandardized B	95% CI for B	p-value
Age in months	-.052	-.071 to -.032	<0.001
Sex (0 = boy; 1=girl)	.80	-.33 to 1.93	.17
TBSA	-.06	-.015 to .003	.19
Time since burn	-.36	-1.96 to 1.23	.59
Time since last medication	-.005	-.013 to .003	.21

Legend Table 4.4 - IQR = interquartile range; TBSA = % Total Body Surface Affected

Age proved a significant predictor for the COMFORT-B score, in that younger children experience more pain and distress during WCP (Unstandardized B -.052; 95% CI -.071 to -.032 p<0.001) (see Figure 4.2), after controlling for the other predictor variables in the analysis. Sex, TBSA, time since burn, type of wound, type of wound care product and time since last medication were not significantly associated with the COMFORT-B score (Table 4.4). Furthermore, the mean COMFORT-B score during WCP was not associated with administration of particular sedatives or analgesics; nor with the total number of sedative or analgesics given; nor with the time between drug administration and WCP.

Figure 4.2 Age & COMFORT-B scale scores



DISCUSSION

In this study we determined pain intensity and distress in children with burns undergoing WCP without distraction or parental presence, and sought to identify predictors for the outcomes. Across the four phases of WCP, from 62% to 89% of the children presented severe pain and distress, and 11% to 31% of the children experienced moderate pain and distress. Most severe pain was measured in 89% of the children during phase 2 of the WCP in which the wound was washed. These findings are irrespective of type of burn, type of wound care product, time of medication, TBSA % burned and sex. Only younger age predicted higher COMFORT-B scores.

A similar study by de Jong et al. in a comparable patient population severe pain and distress in 25% of the children, and moderate pain and distress in 66% (8). In contrast to our findings, age was not statistically significantly related to differences in baseline pain or pain course over time in that study. Moreover, in that study parents and child life specialists were present during WCP, which was not the case in our study. At RCWMCH, parents are not routinely allowed in during WCP because it is considered too stressful for the parent, child and the nurses, and resources are lacking for extra staff to support the parent and the child during or afterwards the procedure. Time of medication was not a predictor for the extent of pain and distress in both studies. The patients in our study received orally administered analgesics and sedatives by set times of the protocol. However, our data showed a considerable amount of time between WCP and the medication. It is difficult to interpret these findings because the effectiveness of medication depends on factors such as age, weight and severity of illness. Ideally, the WCP schedule would have to be synchronized to the medication schedule.

Possible solutions to make medical procedures less distressing and painful could include parental support and distraction interventions before, during or after the procedure. Few RCTs have been performed on peri-procedural distraction in children with burns.

One study on the use of a handheld device on which the child watches videos in preparation for the procedure and for distraction during the procedure resulted in a significant reduction in treatment time for children aged 3 to 10 years (38). Distraction techniques have been suggested to reduce pain and distress during WCP in children between the ages of 4 and 12. These include virtual reality and augmented reality games; multimodal devices such as the Ditto (a handheld device showing interactive videos for procedural preparation and distraction); and watching cartoons (36-40).
Most studies on peri-procedural distraction have been performed during emergency care, needle-related procedures and in a perioperative setting (20-24). Nonetheless, burn care research might benefit from these studies on interactive distraction such as guided imagery; passive distraction such as listening to music or watching a video; physical contact and parental involvement (23, 24, 32, 34, 35). However, not all interventions will be feasible during WCP, such as reading books or touch therapy.

In addition, attention should be paid to what language is used during WCP. Language that distracts, praises, encourages, is informative or coaches to cope can be more effective than language that is reassuring, vague, has a negative focus, apologizes or gives too much control (30). Verbal reasoning as a way to control distress is often not effective in young children, likely as a consequence of their immature neurodevelopment (23). Furthermore, young children do not relate a past experience to a present one, so they will not understand phrases such as “almost done” (23, 41).

Age is an important factor for deciding what kind of peri-procedural support should be offered (22, 23, 30). Young infants are thought to respond better to caregiver soothing than to distraction, verbal reassurance and pacifying; which is supported by attachment theory and the idea that a distressed infant seeks proximity to the parent (25-28). However, parents of patients with burns can suffer from acute stress reaction, anxiety, depression and guilt as a result of the traumatic nature of a burn wound (29). It has also been shown that parental distress is a predictor for the child’s level of distress in. Therefore, using parental support needs to be approached carefully. Giving the parent a sense of competence and empowerment in the care for their child might reduce distress (6, 29-31). This can be accomplished by explaining the details of WCP, giving the parent hands-on tasks such as helping monitor pain and vital signs and through distraction and soothing interventions after the painful procedure.

Limitations of this study

Due to the many preverbal patients admitted to the burns unit we were restricted in using a behavioural assessment scale instead of a self-report scale. Furthermore, it was not possible to measure physiological outcomes during WCP.
Assessment took place only once and in most cases soon after the burn event because we included the first or second WCP. Therefore we were not able to determine the course of pain and distress over time. For practical reasons we only included patients who received WCP in the morning, however we don’t know whether this has somehow biased the study

Recommendations

Severe and moderate pain and distress during WCP is a problem that needs to be addressed. Future studies should aim to include two or more WCPs to determine whether stress increases over time.

We recommend clinicians to measure pain and distress during WCP in children using the COMFORT-B scale to better evaluate pain and distress.

We would like to suggest future research to focus on pre-procedural support for caregivers and children older than four years; interventions during and after WCP; and interventions tailored per age group. Future research could focus on ways to include the parent before, during or after WCP without obstructing the WCP.

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CHAPTER 5

Can live music therapy reduce distress and pain in children with burns after wound care procedures? A randomised controlled trial

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ABSTRACT

Objective

Burn wound care procedures are very painful and lead to distress. Live music therapy has shown beneficial effects on distress and pain in specific paediatric patient populations. In this study we measured whether live music therapy has beneficial effects in terms of less distress and pain in children with burns after wound care procedures.

Methods

This randomised assessor-blinded controlled trial (RCT) took place at the burns unit of the Red Cross War Memorial Children's Hospital, Cape Town, South Africa. It included newly admitted inpatients between the ages of 0 and 13 years undergoing their first or second wound care procedures. Excluded were children with a hearing impairment or low level of consciousness. The intervention group received one live music therapy session directly after wound care in addition to standard care. The control group received standard care only. The primary outcome was distress measured with the Observational Scale of Behavioral Distress-revised (OSBD-r). The secondary outcome was pain measured with the COMFORT-behavioral scale (COMFORT-B). In addition, in children older than 5 years self-reported distress with the validated Wong-Baker scale (FACES) and pain with the Faces Pain Scale-Revised (FPS-R) were measured. Patients in both groups were videotaped for three minutes before wound care; during the music therapy or the control condition; and for two minutes thereafter. Two researchers, blinded to the study condition, independently scored the OSBD-r and the COMFORT-B from the video footage before and after music therapy.

Results

We included 135 patients, median age 22.6 months (IQR 15.4 to 40.7 months). Change scores did not significantly differ between the intervention and the control groups for either distress ($p=0.53$; $d=0.11$; 95% CI -0.23 to 0.45) or pain ($p=0.99$; $d=0.04$; 95% CI -0.30 to 0.38). Self-reported distress in a small group of children ($n=18$) older than 5 years indicated a significant reduction in distress after live music therapy ($p=0.05$).

Conclusions

Live music therapy was not found effective in reducing distress and pain in young children after burn wound care. Older children might be more responsive to this intervention.

INTRODUCTION

Hospitalised children with burns may experience severe pain, distress, acute stress, and posttraumatic stress disorder as a result of painful medical procedures such as surgery, wound care procedures (WCP) and rehabilitation therapy (1-3). Distress has been defined as behaviors of negative affect associated with pain, anxiety and fear (4). Distress is intrinsically linked with pain intensity and should be limited as best as possible as it can affect a child's pain perception and pain processing later in life (4-8). Burns pain is experienced differently per person, irrespective of the nature and size of the burn. Furthermore, the pain experience changes over time as the damaged tissue regenerates. Apart from physiological changes, psychological and environmental factors such as context (expectations and past experiences), cognition (distraction and self-belief) and mood (depression and anxiety) also determine the pain perception (3). Therefore it is important to provide both pharmacological and psychological support around painful procedures. In particular WCPs are painful and distressing as they involve removal of bandage; cleaning the wound; administering new wound care products; and putting on new dressings (9-11).

Several studies on pain and distress in hospitalised children suggest the benefits of offering psychological interventions before, during and after painful procedures (12, 13). In burns, some of the current coping strategies to tolerate WCPs include preparing the patient before the procedure and applying distraction and relaxation techniques such as music listening (14-18).

Music interventions can consist of listening to pre-recorded music or live music therapy from a trained music therapist. Live music therapy aims, amongst other things, to help children distract and cope with being in an unfamiliar environment; provide a space for emotional expression; allowing them to have a sense of control by being able to choose an instrument to play with; and assist in inducing a state of relaxation (19). A music therapist engages with the patient by making live music, playing an instrument together or improvising using the voice and instruments (20). Live music therapy focuses on the creation of the music experience and the emotional impact music can have such as changing or releasing emotions, bringing comfort, inducing relaxation and providing distraction (21, 22). Furthermore, music stimuli are thought to influence the limbic system: the part of the brain that controls the areas of memory, emotions, and the release of neuropeptides such as dopamine, which in turn influences pain and distress experiences (23-26).

In the burns unit of the Red Cross War Memorial Children's Hospital in Cape Town, South Africa, a music therapist routinely provides live music therapy during the day in order to distract and bring comfort to the children. In this setting it is not possible to perform music therapy during the WCP. Therefore we performed a study to determine whether live music therapy directly after WCP could be beneficial in reducing children's distress and pain. To our knowledge no studies have assessed the effects of live music therapy after WCP in children.

MATERIAL AND METHODS

Design

In this randomised assessor-blind controlled trial (RCT) children with burns were randomly assigned to either of two study arms: a single live music therapy session offered after wound care or standard care as control condition.

Setting and participants

This study took place at the paediatric burns unit of the Red Cross War Memorial Children's Hospital (RCWMCH) in Cape Town, South Africa from October 2014 to November 2015. The RCWMCH is a state hospital that admits children aged from 0 to 13 years. The families speak either isiXhosa, Afrikaans or English.

Eligible patients were inpatients receiving their first or second WCP, which is usually on post-burn day 1 or 2, because most children would receive their third WCP in a different ward in the hospital. Children with a hearing impairment or low levels of consciousness (children who were unable to communicate because of the sedatives they had received or children who were asleep) were excluded. The medical ethical committee of the University of Cape Town and the medical ethical committee of the RCWMCH approved the study. This RCT was registered at the Pan African Clinical Trials Registry number PACTR201505000906290. The measurements of distress and pain during WCP were published elsewhere (27).

Interventions

Live music therapy was given directly after the WCP at the bedside by one of three certified music therapists (members of the South African Music Therapy Association). The choice of providing music therapy after WCP, instead of prior to or during, was a practical consideration. This specific burns unit has a high admission rate of 1300 patients per year and is regularly crowded with patients and their families (27). A high workload of the nurses responsible for WCP makes it difficult to accommodate live music therapy during WCP. Also, the room in which the WCP takes place is small and there is not enough space for a music therapist. There is no standard sequence in which the nurses take the children into the dressing room. It often depends on the availability of the doctor. Therefore, it is difficult in this setting to plan the MT prior to WCP. Furthermore, out of fear for infections this burns unit only allows staff directly involved with the WCP into the dressing room. Family members have to wait outside the dressing room and the children are reunited with their caretakers directly after WCP.

All therapists had experience working with young hospitalised children. We standardized the intervention as follows: the therapist first introduced him or herself, assessed the child's behavior, mood and level of engagement and matched the music accordingly. The music therapists were asked to standardize the duration of the session to 3 -5 minutes to ensure internal validity and to minimize confounders in order to make the intervention as replicable as possible. At the end of the sessions the therapist said goodbye to the child to make clear the session was over, and left. We did not expect the music therapy to be harmful to the children, but made sure the parents understood they were always allowed to interrupt and stop the intervention if they felt necessary. Furthermore, hygienic precautions were taken: the music therapists always wore scrubs and made sure the

instruments were cleaned with a disinfectant.
In both the control and music group children received standard care after WCP, which meant that the mother would take the child back to the bed and try to calm the child down. In the music group the mother was also allowed to feed and hold the child or change their clothes. All patients received pain medication before the WCP according to the burns unit protocol. Six types of analgesics and sedatives might be administered orally: paracetamol, clonidine, gabapentin, tilidine, ibuprofen and chloralhydrate.

Outcome measurements

The primary outcome was level of distress, assessed from video footage with the Observational Scale of Behavioral Distress-revised (OSBD-r). The OSBD-r has been validated for the use in children and consists of 8 behavioral categories (information seeking, cry, scream, restraint, verbal resistance, emotional support, verbal pain and flail) that are all scored per 15-second intervals for the duration of the video footage (see Supplement S1) (28, 29). Each behavioral category is weighted, varying from 1.5 for information seeking to 4.0 for screaming. An OSBD-r score of 0 implies no distress; the maximum score of 23.5 implies maximum distress. The OSBD-r has been validated as a reliable distress assessment tool in hospitalised children and has been used to evaluate distress responses in children undergoing burns WCP (8, 30).

The secondary outcome was level of pain, assessed from video footage with the COMFORT-behavioral scale (COMFORT-B). Researchers reported convergent and construct validity, reliability and clinical usefulness of the COMFORT-B in children with burns aged from 0 to 5 years (11, 31). It asks observers to consider intensity of six behavioral manifestations: alertness, calmness, crying, body movement, facial tension and muscle tone. For each of these items five response categories are provided, rated from 1 to 5, reflecting increasing intensity of the behavior in question. Summing the ratings of the six behavioral manifestations leads to a score ranging from 6 to 30. A COMFORT-B score of 6-13 represents mild pain; 14-20 moderate pain; and 21-30 severe pain (32).
For children in both groups, two blinded investigators scored the video footage covering the three-minute period prior to the WCP; i.e. the child in bed or in the room (phase I), walking through the hallway (phase II), and going into the procedure room (phase III). Both outcome measurements were scored over these three phases and a weighted total score was calculated. The OSBD-r and COMFORT-B were again scored for the two-minute period after the music therapy.
In addition, before and after WCP children older than 5 years self-reported distress and pain on the FACES scale and the FPS-R respectively. Both scales require selecting a picture of a face that represents respectively one's emotional state and pain intensity on a 0-to-10 rating scale (33-35). For both scales the instruction is standardized. The FACES scale is predominantly used to self-report pain, but has also been modified to measure distress (36, 37). Assuming a state of relaxation, children who were asleep (n=3) were scored 0 on both the FACES and the FPS-R.

Sample size and power

We hypothesized that 75% of the children in the intervention group would show less distress and pain after WCP compared to children in the control group. Based on an expected 20% difference in OSBD-r scores with a power of 0.80 and alpha 0.05 (two-tailed) we would require a sample of 128 subjects. Taking into account a 15% dropout rate we aimed to include 150 subjects.

Randomisation sequence and allocation concealment

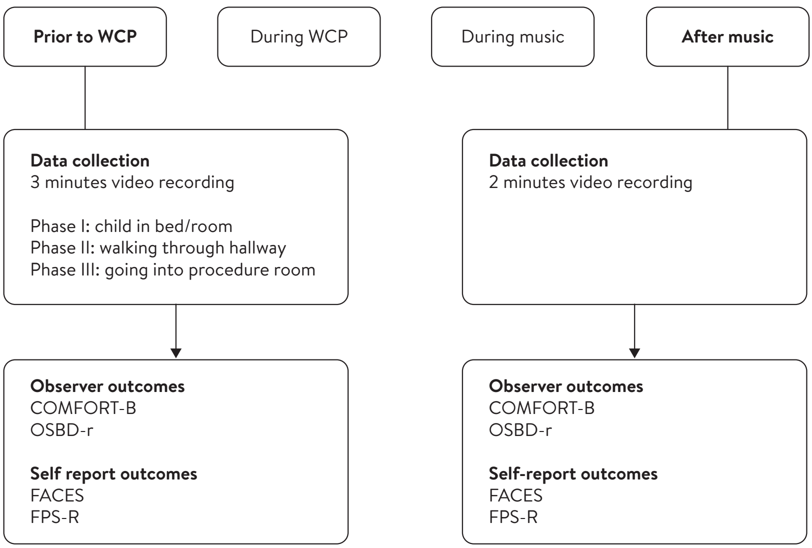
After a child's admission to the burns unit the researcher would explain the study to the accompanying parent or caregiver and seek informed consent. Children aged 7 years or older needed to provide assent. The primary researcher explained the study in English or Afrikaans as appropriate. An interpreter was available if a parent or child could only speak isiXhosa. An independent statistician used a random number generation table for simple randomisation. Consecutively numbered sealed opaque envelopes prepared by an independent researcher were used for randomisation. The envelopes were kept in a secure place, only available for the primary researcher who obtained informed consent, enrolled the patients and subsequently opened the envelope to assign the child to one of the study arms. The music therapists could not be randomised because not all therapists were present all the time.

Data collection

The primary researcher used an iPad to videotape patients 3 minutes before going into WCP; during the music therapy or control condition; and 2 minutes after music therapy (see Figure 5.1).

The primary researcher trained two independent researchers (JvdP and CvW) in scoring the OSBD-r and the COMFORT-B from video footage.
These researchers assessed the video footage before and after the study condition (and not during the active intervention or control condition), while blinded to the study condition. Intraclass correlation coefficients between the primary researcher and each

Figure 5.1 - Flowchart data collection



independent assessor were calculated with a two-way mixed model, based on absolute agreement with single measures to determine interrater reliability. The training consisted of a workshop in which the outcome measurements were explained; twenty training videos were watched and scored and then discussed amongst the assessors.

Statistical methods

All data was analyzed according to the intention-to-treat principle. Descriptive statistics are presented as mean (standard deviation) for normally distributed variables; non-normally distributed variables as median (interquartile range) and range. For the primary and secondary outcomes, change scores (before – after) were compared between the intervention and control arms with the Mann-Whitney U test. Multiple linear regression analyses were performed with the change scores of OSBD-r and COMFORT-B as outcome variables and study group, age and %TBSA as predictor variables. Age was taken categorically with categories 0 to 36 months, 37 to 60 months and older than 60 months. In contrast to what was specified in the protocol, we did not include first language as a predictor variable in the linear regressions, as the group of children who spoke English as a first language was small (n=10). Plots of the model residuals of the linear regressions were checked for normality.

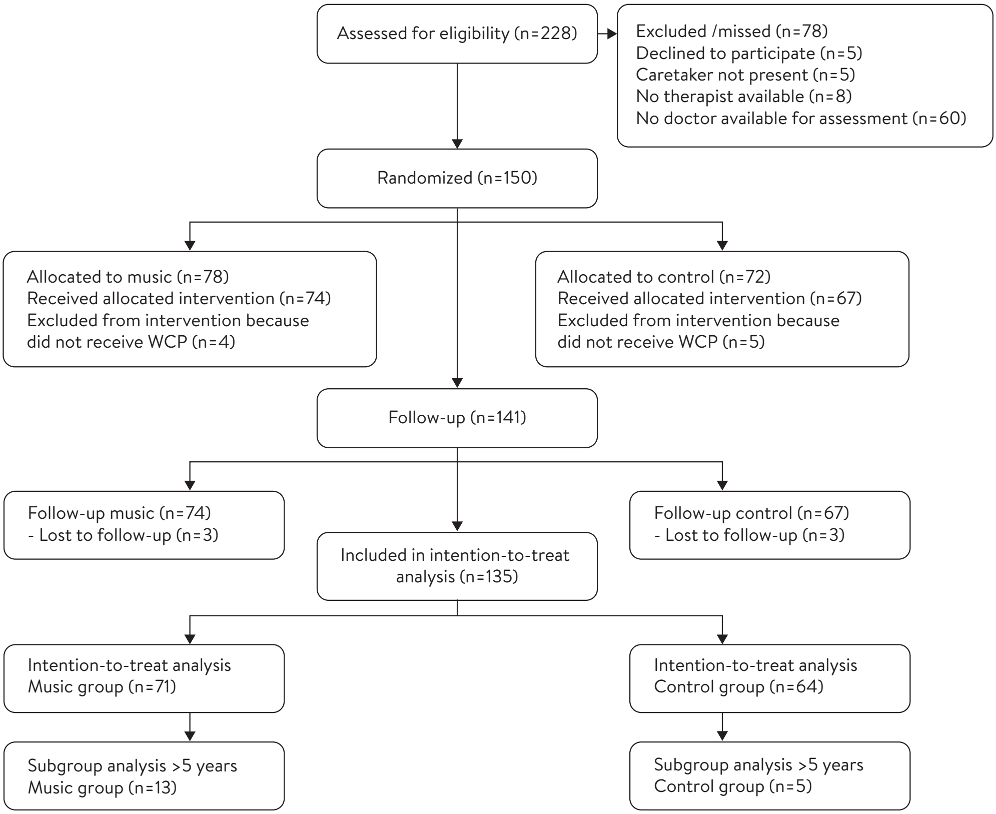
Children older than 5 years also self-reported distress and pain levels. The change scores (before-after) of self-reported distress and pain levels were compared between the intervention and control arms with the Mann-Whitney U test. Correlation between the self-report outcome measurements was calculated using Spearman's rank correlation coefficient.

Data was reported based on the Consolidated Standards of Reporting Trials (CONSORT) statement, including the extension for non-pharmacological treatments. All statistical tests used a two-sided significance level of 0.05.

RESULTS

Between October 2014 and November 2015 we enrolled 150 children. Data of 15 children were not included in the final analysis due to interruption and discontinuation of the WCP (see Figure 5.2). Of the remaining 135 children, 71 received the music intervention, and 64 were controls. The overall median age was 22.6 months (IQR 15.4 – 40.7). There were no significant differences between the groups in patient demographic and clinical characteristics. Twenty-three patients (17%) were older than 5 years and eligible to self-report distress and pain. Most of the burns were scalds (98%) and the median total body surface area (%TBSA) was 8% (IQR 5-14) (see Table 5.1). Therapist A provided music therapy in nearly half (49%) of the cases; therapist B in 39% and therapist C in 11%.

Figure 5.2 - CONSORT flowchart



Distress and pain outcomes

Two researchers separately assessed the primary and secondary outcomes from videotape, blinded to the study group allocation. The intraclass correlation coefficient between the trainer and OSBD-r assessor CvW was 0.997; between the trainer and COMFORT-B assessor JvdP 0.922. Table 5.2 shows the OSBD-r and COMFORT-B scores per group, per phase scored before and after the intervention. Median OSBD-r scores before WCP were low and in both groups 35% of the children did not show distress in the three phases before WCP. The distress scores were low also after WCP and subsequent intervention time. In both groups the median OSBD-r-after was zero, with IQR 0 to 0.70 in the control group and IQR 0 to 0.26 in the music group. COMFORT-B scores indicated mild background pain on average in both groups, both before and after WCP.

Data analysis with the Mann-Whitney U test did not reveal a statistically significant difference in change scores between the intervention and control group in OSBD-r (p = 0.53; SMD=0.11; 95% CI -0.23 to 0.45) and COMFORT-B (p= 0.99; SMD=0.04; 95% CI -0.30 to 0.38) before and after the intervention.

Table 5.1 - Patient demographic and clinical characteristics (n=135)

	Music (n=71) n (%)	Control (n=64) n (%)	Total (n=135) n (%)
Sex			
Boy	37 (52)	32 (50)	69 (51)
Girl	34 (48)	32 (50)	66 (49)
Age in months			
Median (IQR[1])	24.3 (15.7 to 49.1)	20.8 (15.3 to 35.9)	22.6 (15.4 to 40.7)
Language			
Xhosa	32 (45)	30 (47)	62 (46)
Afrikaans	33 (47)	25 (39)	58 (43)
English	5 (7)	5 (8)	10 (7)
Other	1 (1)	4 (6)	5 (4)
Type of burn			
Scald[2]	70 (99)	62 (97)	132 (98)
Electric	1 (1)	2 (3)	3 (2)
TBSA[3] (%)			
Median (IQR)	7 (4 to 13)	10 (5 to 15)	8 (5 to 14)
Depth of burn			
Superficial	58 (82)	54 (84)	112 (83)
Partly superficial and deep	2 (3)	5 (8)	7 (5)
Deep	10 (14)	5 (8)	15 (11)
Full thickness	1 (1)	0 (0)	1 (1)
Body parts burned[4]			
Head	24 (34)	32 (50)	56 (41)
Arms	48 (68)	45 (70)	93 (69)
Chest/abdomen	28 (39)	31 (48)	59 (44)
Back	23 (32)	13 (20)	36 (27)
Legs	29 (41)	28 (44)	57 (42)
Genitalia	6 (8)	1 (2)	7 ((5)
Wound care procedure (WCP)			
First WCP[5]	55 (78)	51 (80)	106 (79)
Second WCP	16 (22)	13 (20)	29 (21)
Days post-burn included in study			
Day of the burn	2 (3)	6 (9)	8 (6)
1 day post-burn	49 (69)	44 (69)	93 (69)
2 days post-burn	3 (4)	3 (5)	6 (4)
3 or more days post-burn	17 (24)	11 (19)	28 (21)

Days after admission included in study			
Day of admission	10 (14)	19 (30)	29 (22)
1 day after admission	44 (62)	35 (55)	79 (59)
2 days after admission	4 (6)	3 (5)	7 (5)
3 or more days after admission	13 (18)	7 (10)	20 (14)
Duration of WCP in minutes			
Median (IQR)	25 (20 to 30)	25 (20 to 30)	25 (20 to 30)

Legend Table 5.1 - 1. Interquartile range; 2. Hot water burn, steam, food; 3. Total body surface area affected by a burn; 4. More than one body part burned possible; 5. Wound care procedure

Table 5.2 OSBD-r and COMFORT-B scores by group

	Control (n=64)	Music (n=71)	Total (n=135)	P-value[1]
OSBD-r before				
Total weighted OSBD-r				**0.92**
N	64	71	135	
Mean (SD[2])	2.08 (2.30)	2.12 (2.43)	2.10 (2.36)	
Median (IQR[3])	1.42 (0 to 3.04)	1.88 (0 to 3.5)	1.68 (0 to 3.16)	
Range	0 to 9	0 to 10.96	0 to 10.96	
Weighted phase 1 (bed)				**0.12**
N	62	68	130	
Mean (SD)	0.41 (0.82)	0.24 (0.69)	0.32 (0.76)	
Median (IQR)	0 (0 to 0.42)	0 (0 to 0)	0 (0 to 0)	
Range	0 to 3.0	0 to 3.0	0 to 3.0	
Weighted phase 2 (hallway)				**0.88**
N	64	69	133	
Mean (SD)	0.31 (0.84)	0.32 (0.91)	0.31 (0.88)	
Median (IQR)	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	
Range	0 to 4.25	0 to 5.49	0 to 5.49	
Weighted phase 3 (dressing room)				**0.50**
N	64	69	133	
Mean (SD)	1.37 (1.43)	1.62 (1.64)	1.50 (1.54)	
Median (IQR)	1.17 (0 to 2.5)	1.68 (0 to 2.64)	1.25 (0 to 2.5)	
Range	0 to 4.75	0 to 5.50	0 to 5.50	
COMFORT-B before				
Total weighted mean COMFORT-B				**1**
N	64	71	135	
Mean (SD)	13.6 (2.9)	13.6 (2.9)	13.6 (2.9)	
Median (IQR)	13.2 (11.4 to 15.3)	13.3 (11.3 to 15.7)	13.33 (11.3 to 15.7)	
Range	8 to 23	8 to 21.3	8 to 23	

Weighted phase 1 (bed)				**0.78**
N	57	55	112	
Mean (SD)	11.3 (3.6)	11.4 (4.1)	11.3 (3.9)	
Median (IQR)	11 (9 to 13)	11 (8 to 13)	11 (9 to 13)	
Range	6 to 19	5 to 22	5 to 22	
Weighted phase 2 (hallway)				**0.25**
N	61	67	128	
Mean (SD)	11.5 (2.7)	12 (2.8)	11.8 (2.8)	
Median (IQR)	11 (10 to 13)	12 (10 to 13)	11 (10 to 13)	
Range	6 to 22	7 to 23	6 to 23)	
Weighted phase 3 (dressing room)				**0.73**
N	63	69	132	
Mean (SD)	17 (3.9)	16.7 (3.9)	16.9 (3.9)	
Median (IQR)	18 (13 to 20)	18 (13 to 20)	18 (13 to 20)	
Range	10 to 24	10 to 25	10 to 25	
OSBD-r after				
N	64	71	135	**0.22**
Mean (SD)	0.56 (1.0)	0.31 (0.67)	0.43 (0.85)	
Median (IQR)	0 (0 to 0.70)	0 (0 to 0.26)	0 (0 to 0.33)	
Range	0 to 4	0 to 2.85	0 to 4	
COMFORT-B after				
N	64	71	135	**0.83**
Mean (SD)	13.88 (5.25)	13.66 (4.19)	13.76 (4.71)	
Median (IQR)	12 (10 to 18)	13 (11 to 16)	12 (11 to 17)	
Range	5 to 25	6 to 24	5 to 25	

Legend Table 5.2 - 1. Mann-Whitney U test. Scores are presented as measured before going into WCP and after the study condition; 2. Standard deviation; 3. Interquartile range

Linear regression analysis revealed that study group, age and %TBSA did not significantly affect the change in OSBD-r and COMFORT-B scores (calculated as the score before WCP minus the score after WCP) (see Table 5.3).

Twenty-three children were older than 5 years and eligible to self-report distress and pain. Self-reported scores before and after were missing for five patients because they refused to answer or did not understand the question. For the FPS-R one out of the 18 children did not provide self-reported data after the procedure. Baseline characteristics were not statistically significantly different in the group of patients older than 5 years between the music and control group (see Table 5.4). The distress outcomes measured by OSBD-r and Wong Baker FACES and between the pain outcomes measured by COMFORT-B and FPS-R were significantly related (respectively $p=0.012$ and $p=0.013$). Self-reported data of 18 children older than 5 years (78.3%) (music group n=13, control group n=5) were analyzed and the results were compared with the OSBD-r and COMFORT-B scores for the group of children older than 5 years. Overall, those in the music group reported statistically significant less distress on the self-reported FACES scale ($p=0.05$) than those in the control group (Table 5.5).

Table 5.3 - Linear regression analyses with OSBD-r change scores (before – after) as outcome variable

	B	95% CI	P-value
Study group			
Music	.36	-0.53 to 1.26	0.43
Control	Reference	-	-
Age group			0.94
0-36 months	-0.02	-1.22 to 1.19	0.98
37- 60 months	-0.23	-1.81 to 1.36	0.78
>60 months	Reference	-	-
Sex			
Boy	0.44	-0.46 to 1.33	0.34
Girl	Reference	-	-
TBSA%[1]	0.05	-0.02 to 0.11	0.15

Legend Table 5.3 - 1. Total Body Surface Area %

Table 5.4 - Baseline characteristics for over 5-year-olds

	Music n=13 n(%)	Control n=5 n(%)	p-value*
Sex			
Boy	10 (76.9)	3 (60)	0.49
Girl	3 (23.1)	2 (40)	
Age in months			
Median (IQR[1])	88.1 (77.3 to 116.6)	71.7 (61.7 to 122.7)	0.26
Language			
Xhosa	5 (39)	1 (20)	0.52
Afrikaans	6 (46)	3 (60)	
English	2 (15)	1 (20)	
Other	0 (0)	0 (0)	
TBSA%[2]			
Median (IQR)	5 (2 to 13.5)	10 (5 to 12.5)	0.46

Legend Table 5.4- *Mann-Whitney U test 1. Interquartile range 2. Total Body Surface Area %

Table 5.5 - Results of observational and self-reported distress and pain scores

	Control (n)	Change scores median (IQR)	Music (n)	Change scores median (IQR)	P-value
FACES²	5	-1 (-3.5 to 1.5)	13	0 (0 to 2.5)	**0.05**
OSBD-r³	5	0 (-2.48 to 0)	13	0 (0 to 4.9)	**0.05**
FPS-R⁴	4	0 (-6 to 4.5)	13	2 (0 to 6)	0.20
COMFORT-B⁵	5	-0.33 (-8.17 to 5)	13	1.5 (-0.5 to 6.17)	0.34

Legend Table 5.5 - 1. Mann-Whitney U test; 2. Wong Baker FACES; 3. Observational Scale Behavioral Distress-revised; 4. Faces Pain Scale Revised; 5. COMFORT Behavior Scale

DISCUSSION

This study was aimed at answering the question: can live music therapy reduce distress and pain in children with burns after wound care procedures? The distress and pain scores assigned by observers were not significantly different between the music and control groups, irrespective of sex, age or %TBSA. In a small group of over 5-year olds, both self-reported distress and observational distress change scores were lower for those in the music group. There was a strong correlation between observed and self-reported distress and pain.

To our knowledge this is the first assessor-blinded RCT on the effects of live music therapy in a large sample of children with burns. One experimental study during donor site dressing change in 14 children with burns was inconclusive regarding the effects of live music therapy on pain and anxiety (38). Our results do not concur with those of studies in hospitalised children undergoing surgery, and for children undergoing needle-related procedures. In those studies, live music therapy and recorded music interventions offered prior to, during or after painful procedures were found beneficial in reducing distress and pain (13, 39-41). A possible explanation for the discrepancy could be that WCPs are more painful and last longer than needle-related procedures. Furthermore, in our study, the OSBD-r distress scores were assigned before WCP, and these were low.

It is difficult to reliably observe pain and anxiety in young children; the gold standard has not yet been found. However, the COMFORT-B score has sound clinimetric properties. To measure the effects of live music therapy through observation is also challenging. The majority of the children in this study were of preverbal age and unable to provide self-report. Those old enough to provide self-report seemed to have benefitted from the live music therapy offered. This is in agreement with the literature on music interventions aimed to reduce pain and anxiety in older children and adults with burns (42-45) and adults undergoing surgery (46). Live and recorded music and other types of non-pharmacological interventions in children with burns are worth further study. Augmented virtual reality, cartoons, imagery and massage might also be beneficial in reducing distress and pain (15, 16, 47-52). However, studying the effectiveness of these strategies in preverbal infants will be also challenging.

Strengths and limitations

The duration of the live music therapy was standardized to 3-5 minutes to ensure internal validity and to minimize confounders. Also, all children received live music therapy directly after WCP. Independent researchers who were blinded to the study condition assessed the video footage, thereby minimizing bias. A possible limitation to this method of data collection is that the child, parent and medical staff were aware of the camera, which may have influenced their behavior.

Although it is a strength that the behavioral scales we used have been validated cross-culturally and for this specific patient group, we were limited in our choice of outcome measures and there remains a level of subjectivity (53-55). Unlike in intensive care environments, where physiological measurements are standardly taken throughout the day, measuring these would imply an extra intervention, which can be distressing especially for young children.

Instead, pain assessment in burns care relies strongly on self-reported assessments and structured assessments, even in young children. Furthermore, physiological parameters are considered inappropriate in children with burns (3). Another limitation is that only a small group of children were old enough to self-report distress and pain. Furthermore, because simple randomisation was applied instead of age-stratified randomisation, a disproportionate number of children older than 5 years received live music therapy (13 versus 5 controls). Therefore the results of the older children should be interpreted conservatively.

Considerations

This study is one of the first with a large population of pre-verbal children. More research on non-pharmacological coping strategies for distress and pain in children with burns is warranted. In the burns unit the parent is the primary support giver. Studies on immunization in young children have shown that their expression, reactivity and regulation of pain and distress are directly related to the caregiver's behavior and level of attachment to the child (56, 57). Furthermore, distressed infants tend to seek proximity to the caregiver, and will be more contained in their emotions when feeling safe (57-59). Therefore, future research on young children with burns should include interventions aiming at the parent-child dyad. Live music therapy could encourage a positive engagement between child and parent, and could make the hospital a less frightening place.

Another consideration is the shape of future research. The RCT is seen as the gold standard in evidence-based medicine research but may not be ideal to study non-pharmacological interventions in young children. For the sake of rigor, in the present study we standardized the timing and the duration of the intervention, which would otherwise have been adjusted to the child's needs. Proposed alternatives to the RCT include powered observational studies, mixed methods research and comparative effectiveness research (60-63). The choice in research design depends not only on the research question and intervention but also on the outcome measurements. Non-pharmacological interventions such as live music therapy aim, among other things, to induce a state of relaxation. Because validated outcome measurements to show an improvement in relaxation are lacking, we measured – by proxy – reduction in distress and pain. However, if baseline levels of distress or pain are already low, it is difficult to show a significant reduction (41). Future discussions on the use of live music interventions should include the question of whether the therapist deems music therapy necessary for the individual child and whether the timing of the intervention is right for the child and the parent.

Complementary therapies, such as music therapy, aim to be supportive of clinical practice and take place at the convenience of the staff and clinical care of the patient. Although distraction interventions during procedures might be considered a logical choice, it is not feasible in every clinical setting and it might be more practical to provide post-procedural support.

Overall conclusions

Effectiveness of live music therapy to reduce distress and pain associated with painful burn wound care was not shown in young children. Still, a small group of children old enough to self-report distress seemed to have benefitted from this intervention.

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CHAPTER 6

Children listening to music during ER procedures had lower pain scores than children watching cartoons or without distraction: a randomised controlled trial

Submitted

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ABSTRACT

Objectives
Listening to music and watching cartoons might reduce distress and pain in children during medical procedures. This study aims to determine if these interventions would be effective to reduce pain and distress in a South African paediatric emergency room (ER).

Methods
This single–centre, superiority randomised controlled trial compares listening to music or watching cartoons to standard care during medical procedures in the ER. We included children aged 3-13 years. The primary outcome was pain measured with the Alder Hey Triage Pain Score (AHTPS). Children older than four years self-reported pain with the Faces Pain Scale-Revised (FPS-R). The secondary outcome was distress measured with the Observational Scale of Behavioural-Distress-Revised (OSBD-r). Furthermore, heart rate was measured as indicator of distress.

Results
191 participants were included. In the music group pain was significantly lower (B= -1.173, 95%CI -1.953 to -0.394, p=0.003) than in the cartoon and the control groups. Children across the three groups self-reported pain with the FPS-R after the procedure, the scores were lowest in the music group, but the differences between groups were not significant (p=0.077).

OSBD-r distress scores assigned during the medical procedures were not significantly different between the groups (p=0.55). Heart rate directly after the medical procedure was not statistically significantly different between the three groups (p=0.83).

Discussion
Listening to recorded music is a beneficial distraction for children experiencing pain during ER procedures. Watching cartoons did not seem to reduce distress. Future studies should investigate if using self-selected music might increase the effectiveness.

Abbreviations: AHTPS: Alder Hey Triage Pain Score; ER: emergency room; FPS-R: faces pain scale revised; HR: heart rate; OBSD-r: observational scale of behavioural distress revised; POP: Plaster of Paris; RCT: randomised controlled trial; RCWMCH: Red Cross War Memorial Children's Hospital

INTRODUCTION

Having to undergo a medical procedure in the emergency room (ER) can be very upsetting for children (1). The resulting pain and distress should be minimized to avoid development of fear for medical procedures (2-5). Current pain management for children in the ER includes, in addition to medication, non-pharmacological approaches such as touch, positioning, application of heat or cold compresses and distraction methods (6). Distraction techniques differ in the level of interaction required by the patient (7). Generally a distinction is made between active distraction such blowing bubbles and balloon inflation (8, 9), hypnosis (10), vibration (11), playing with toys (7, 12) and music therapy (13-16), and passive distraction, such as music listening or watching a movie (7, 17). There is conflicting evidence about whether active or passive distraction is more effective during painful ER procedures (17, 18). During needle-related procedures, both passive and active distraction methods seem effective, however these studies were not performed in a busy ER setting (10, 19).

Not all interventions, especially active distraction, are easy to implement and some require extra staff. Also, costly distraction interventions may not always be feasible in resource-limited settings. From an implementation point of view, passive distraction methods might be favourable over active distraction. Interventions such as listening to music and watching cartoons do not require many extra (financial) resources and are relatively easy to implement.

The question which distraction intervention is best to alleviate children's pain and distress during the wide range of procedures in the ER remains unsolved. Although both music and cartoon interventions seem beneficial in reducing children's distress and pain in during ER procedures, the evidence is not conclusive and more research has been recommended (14, 15, 20-22).

The objective of this randomised controlled trial (RCT) was to explore if listening to recorded music or watching cartoons can reduce pain and distress in children aged 3 – 13 years during medical procedures performed in the ER in a South African setting.

MATERIAL AND METHODS

Study design

This single–centre, three-armed, superiority randomised controlled trial was conducted from March 2014 through September 2014 at the surgical trauma unit and medical emergency room of the Red Cross War Memorial Children's Hospital (RCWMCH), Cape Town, South Africa.

Setting and participants

All children aged 3 to 13 years attending the surgical trauma unit and medical emergency room were eligible if they were undergoing: venepuncture; IV placement; application of a temporary splint or plaster cast; injection of local anaesthetics; wound dressing and suturing of open wounds. If more than one procedure was performed, only the first procedure was included. The exclusion criteria were the following: hearing impairment, developmental disability, or altered level of consciousness. In addition, children were excluded for whom the attending staff felt that the study would interfere with the treatment or if seeking consent would be too delicate, for example in case of suspected intentional trauma. After written informed consent was obtained from parents and in addition assent was obtained from the child if older than 7 years, the child was allocated to one of the three trial arms: music intervention; cartoon intervention or the control group. If the child did not want to continue with the intervention the music or cartoon would be turned off, but the child would still be included in an intention-to-treat analysis. Blinding of the observers to the nature of the intervention was not possible. To minimize detection bias, one researcher (MvdH) assessed all relevant video recordings, while two other researchers each assessed footage of patients from only one of the study arms.

Interventions

The music intervention consisted of listening to recorded music of a repetitive and relaxing quality. To avoid possible negative connotation with familiar music we asked a female music therapist to compose music with a variety of rhythms, instruments, and lyrics sung in English. The music was played through ambient speakers, set at a fixed volume, connected to an iPod dock on repeat for the duration of the procedure.

The cartoon intervention consisted of watching three 10-minute Disney's "Chip and Dale" cartoon animations, selected by a paediatric psychologist. "Chip and Dale" cartoons are simple, funny stories about the adventures of two chipmunks and are currently no showing on mainstream television in South Africa. The cartoon animations were shown on a laptop connected to speaker boxes, set at a fixed volume, for the duration of the procedure. The laptop was placed on a table or held by the researcher such that the child could comfortably watch the movie. The control group received standard care, which could include comforting words from attending family or medical staff as is normal in ER practice.
The whole procedure was videotaped using a video camera on a tripod aiming to focus on the child's face and body.

The music and cartoon interventions were administered from the start of the procedure. Start of the Plaster of Paris (POP) back-slab procedure was defined as the placement of the first cotton padding; the end of the procedure was defined as placing tape on the cast. Start of the other procedures was defined as cleaning the injection or wound site and the end as placing tape or after the last injection.

Outcome measures

The primary outcome was pain as assessed with the Alder Hey Triage Pain Score (AHTPS), which was specifically designed to measure pain during painful procedures. This scale has been validated for all age groups in the ER setting in England (23) and in the ER of the RCWMCH (24). The scale assesses five behaviours: cry, facial expression, posture, movement and pallor. All items are scored from 0 to 2 with a total score between 0 and 10.

Children older than 4 years self-reported pain with the Faces Pain Scale - Revised (FPS-R), which has been validated for children from 4 to 16 years old (25, 26). It comprises a horizontal series of six line drawings of faces representing increasing levels of pain, from 'no hurt' to 'very much hurt', scored 0-2-4-6-8-10, respectively.

The secondary outcome, distress, was measured with the Observational Scale of Behavioural Distress-revised (OBSD-r) (27), which includes 8 behaviours: information seeking, cry, scream, restraint, verbal resistance, seeking emotional support, verbal pain and flail. A score of 0 indicates 'no distress behaviour' up to a maximum of 23.5. The OSBD-r has been validated for the assessment of procedural distress in the paediatric ER (14, 16, 28). The OSBD-scores were obtained from video recordings for the following phases: (1) two minutes immediately before the procedure, (2) during the whole procedure and (3) two minutes immediately after the procedure. Heart rate (HR) was measured before and after the procedure as a second indicator of distress, using a transcutaneous oximeter placed on the child's finger.

Furthermore, we took clinical notes on whether a caretaker was present and whether the attending nurse restrained the child during the procedure.

Ethical approval

The medical ethical committee of the University of Cape Town and the medical ethical committee of the RCWMCH approved the study in March 2014. Due to a low number of enrolment or recruitment an additional site was added. We obtained the required ethical approval for this amendment on July 27, 2014. Changes to the protocol were made without breaking the blind on the accumulating data on participants' outcomes. The trial was registered in the Pan African Clinical Trials Registry (PACTR) under number PACTR201408000830410.

Sample size and power

Sample size calculations were based on the primary outcome pain, scored with the AHTPS (23, 29). A 30% reduction in pain score is considered clinically meaningful, which corresponds with a standardized mean difference at 0.54 (30). Setting the power at 0.80 and significance level at 0.05 (two-tailed) would yield a sample size of 55 for each arm. To allow for a 10% dropout, the study was designed for 60 patients per arm, thus a total of 180 patients.

Randomisation and allocation concealment

Patients were randomised using consecutively numbered sealed opaque envelopes prepared by an independent researcher, who used a random number generation table for simple randomisation. The envelopes were kept in a secure place, only accessible to the researchers (NvH and HM) who enrolled the patients.

Statistical methods

All data was analysed according to the intention-to-treat principle. Descriptive statistics are presented as mean (standard deviation) for normally distributed variables and as median (interquartile range) or non-normally distributed variables. The intraclass correlation with a 95% confidence interval (two-way mixed effect model with an absolute agreement definition, reporting single measures) was calculated between the observers who assessed all video footage for the AHTPS and the OSBD-r.

The AHTPS scores during, OSBD-r scores during and FPS-R and HR after the procedure were compared between study arms using Kruskal-Wallis tests. Because relatively many children were restrained during the procedure, the ages of the restrained and non-restrained children were compared using the Mann-Whitney U test. Four multivariable linear regression analyses were performed with the outcome variables AHTPS during the procedure, OSBD-r during the procedure, FPS-R after the procedure and HR after the procedure. Predictor variables were study arm, type of procedure (IV placement; venepuncture; injection of local anaesthetics pop back-slab; and wound dressing/suturing open wound), age, sex and, depending on the outcome variable, OSBD-r before, FPS-R before or HR before. Plots of the model residuals of the linear regressions were checked for normality. A p-value of <0.05 (two-tailed) was considered statistically significant, but we applied a Bonferroni correction to the significance level (adjusted significance level: $0.05/2=0.025$) for analyses with multiple comparisons of the two intervention groups to the control group. All data was analysed in SPSS 23.0.

RESULTS

Between April and September 2014, we included 197 children, 191 of whom data were included in the analysis (see flowchart in Figure 6.1). The major reason for having missed eligible patients (n=491) was admission during the weekends or nights, when the researchers were not present.

The median age of the included 191 patients was 7.3 years (4.9 to 9.7); 68% were boys (see Table 6.1). Of the five selected procedures the POP back-slab was most often performed (44%) and venepuncture the least often (10%). In 23.8% of patients, AHTPS pain scores were 0, indicating no pain during the procedure. Distress, as measured with the OSBD-r, was scored 0 (no distress) in 78% before the procedure, in 39% during and in 75% of the patients after the procedure. Children older than 4 years self-reported FPS-R scores before (n=117) and after the procedure (n=108). In 39.3% of the patients before and in 43.5% after the procedure the FPS-R was scored 0. There was no significant difference in duration of the procedures between the three groups (p=0.082) (see Table 6.1).

Figure 6.1 - Flowchart

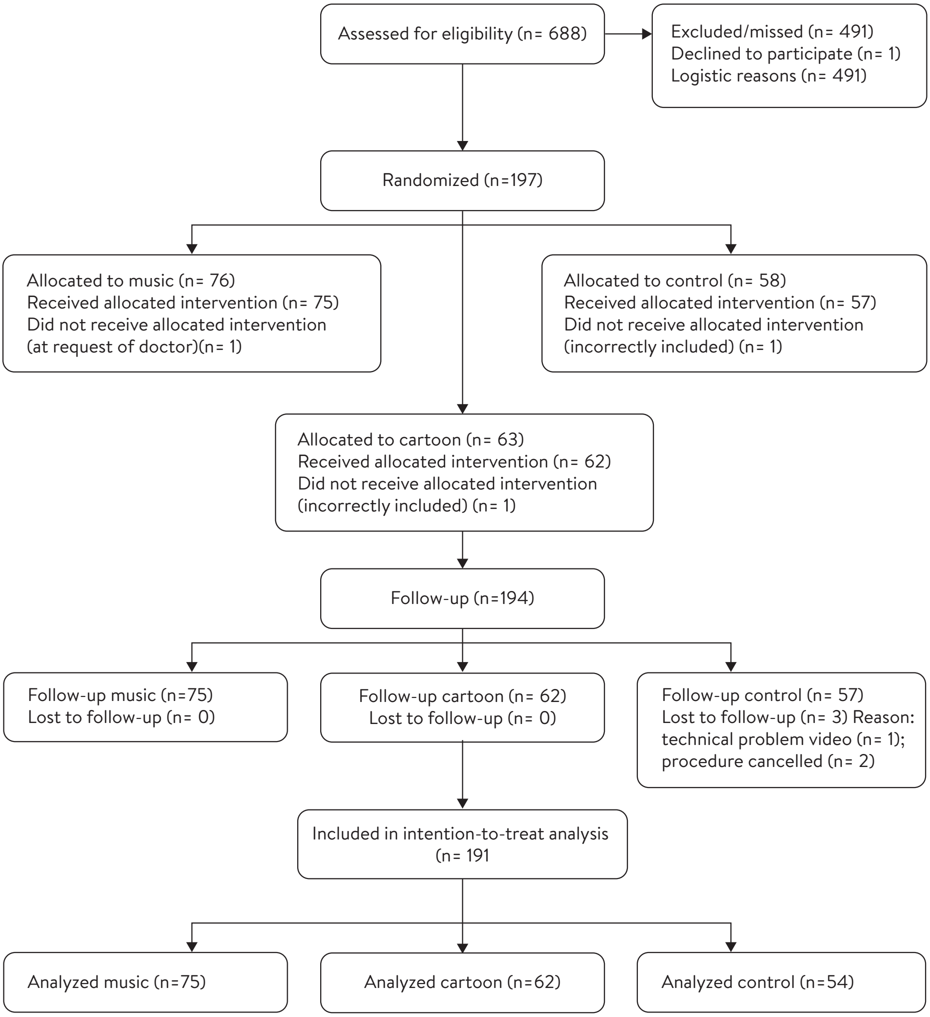


Table 6.1 - Patient characteristics and clinical characteristics

	Control (n= 54)	Cartoon (n=62)	Music (n=75)	Total (n=191)
Sex				
Boy (%)	40 (74)	42 (68)	48 (64)	130 (68)
Age in years, median (IQR)	7.7 (5.1 to 9.8)	6.6 (4.8 to 8.6)	7.5 (5.0 to 10.1)	7.3 (4.9 to 9.7)
First language n (%)	n=51	n=59	n=71	n=181
English	17 (33)	26 (44)	26 (37)	69 (38)
Xhosa	15 (29)	18 (31)	28 (39)	61 (34)
Afrikaans	18 (35)	15 (25)	16 (23)	49 (27)
Other	1 (2)	-	1 (1)	2 (1)
Type of procedure, n (%)				
Pop back-slab	27 (50)	28 (45)	29 (39)	84 (44)
IV placement	6 (11)	10 (16)	21 (28)	37 (19)
Wound dressing, suturing open wounds	11 (21)	12 (20)	7 (9)	30 (16)
Injection of local anaesthetics	5 (9)	5 (8)	11 (15)	21 (11)
Venipuncture	5 (9)	7 (11)	7 (9)	19 (10)
Reason for admission, n (%)				
Arm fracture	24 (44)	25 (40)	29 (39)	78 (41)
MVA	7 (13)	10 (16)	5 (7)	22 (12)
Leg fracture	4 (7)	5 (8)	7 (9)	16 (8)
Laceration	2 (4)	2 (3)	6 (8)	10 (5)
Burn	4 (7)	3 (5)	2 (3)	9 (5)
Head injury	1 (2)	4 (7)	4 (5)	9 (5)
NAI	2 (4)	2 (3)	4 (5)	8 (4)
Dog bite	2 (4)	1 (2)	3 (4)	6 (3)
Other	8 (15)	10 (16)	15 (20)	33 (17)
Parental presence, n (%)	44 (82)	59 (95)	67 (89)	170 (89)
Restraint, n (%)	8 (15)	10 (16)	15 (20)	33 (17)
Duration of procedure (minutes), median (IQR)	05:12 (02:58 to 08:23)	05:27 (02:52 to 09:01)	03:43 (01:43 to 07:11)	04:22 (02:08 to 07:51)

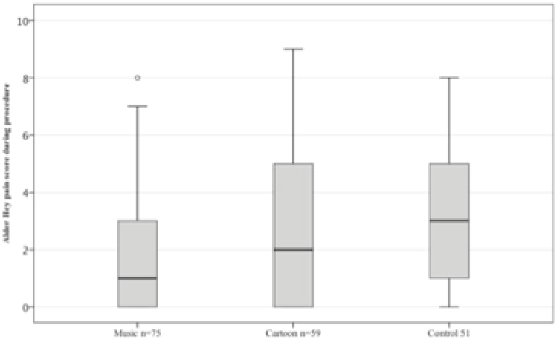
Legend Table 6.1 - IQR: Interquartile range; MVA: motor vehicle accident; NAI: non-accidental injury

Distress and pain outcomes

Three observers separately assessed the AHTPS and OSBD-r outcomes from video footage. The interrater reliability was good with intraclass correlations of 0.94 (AHTPS), 0.76 (OSBD-r before), 0.90 (OSBR-r during) and 0.89 (OSBD-r after). Data for six patients were missing for the primary outcome AHTPS.
The AHTPS scores during the procedure were significantly different between the groups; patients in the music group expressed significantly less pain during the procedure (Kruskal Wallis p=0.017) than the other two groups (see Figure 6.2).

FPS-R scores, OSBD-r, and HR before, during and after the procedure did not significantly differ between the three study groups (see Table 6.2).

Figure 6.2 - Boxplot showing the AHTPS scores during the procedures



Legend Figure 6.2 - The music group shows a significant reduction in pain scores

Multivariable linear regression analysis with AHTPS as outcome also revealed a statistically significant reduction in pain (B=-1.173, 95%CI -1.953 to -0.394, p=0.003) for the music group as compared to the control group after adjusting for type of procedure, age and sex (Table 6.3). Multivariable linear regression analysis with OSBD-r as outcome revealed no significant difference in distress scores between the three trial arms when correcting for OSBD-r before, age, sex and type of medical procedure (Table 6.3). Higher OSBD-r scores before the procedure were significantly and positively associated with higher scores during the procedure (p<0.001). Younger children had significantly higher scores than had older children (p<0.001). Type of procedure had a significant effect on AHTPS scores and OSBD-r scores in that putting on a cast was significantly less painful (p=0.004) and less distressing (p=0.01) than was wound dressing/suturing. Pain scores were not significantly different for boys and girls.

Regression analysis with FSP-R scores after as outcome variable did not show an overall statistically significant difference between treatment arms (p= 0.064). The comparison of music versus the control condition did show a trend favouring music (p= 0.025), but this was not statistically significant after adjustment for multiple testing. The difference in FPS-R scores between cartoon and control groups was not significant (p=0.51).

For the regression analysis with HR after the procedure as outcome variable we did not find statistically significant differences between the study arms before and after procedures.

One of the items of the OSBD-r concerns physical restraint (e.g. child being held down by parent or nurse). Thirty-three children (17%) were restrained during the procedure. These children were significantly younger (p<0.001) than the children who were not restrained, median age 5.3 years (IQR 4.2 to 7.0) and 7.7 years (IQR 5.4 to 9.9), respectively.

Table 6.2 - Outcomes per treatment arm

Outcome	Control (n=54)	Cartoon (n=62)	Music (n=75)	Total (n=191)*	p-value+
AHTPS during (n)	51	59	75	185	
Median (IQR)	3 (1 to 5)	2 (0 to 5)	1 (0 to 3)	2 (1 to 4)	0.017
Range	3.10 (0 to 8)	2.86 (0 to 9)	2 (0 to 8)	2.58 (0 to 9)	
OSBD-r before (n)	49	56	74	179	
Median (IQR)	0 (0 to 0)	0 (0 to 0)	0 (0 to 0.3)	0 (0 to 0)	0.985
Range	0 to 2.70	0 to 5.00	0 to 4.94	0 to 5	
OSBD-r during (n)	51	57	74	182	
Median (IQR)	0.37 (0 to 2.63)	0.33 (0 to 2.54)	0.49 (0 to 2.51)	0.38 (0 to 2.54)	0.550
Range	0 to 7.33	0 to 10.50	0 to 9.12	0 to 10.50	
OSBD-r after (n)	48	56	74	178	
Median (IQR)	0 (0 to 0)	0 (0 to 0.74)	0 (0 to 0.05)	0 (0 to 0.05)	0.749
Range	0 to 3.00	0 to 8.75	0 to 7.40	0 to 8.75	
FPS-r before (n)	33	39	45	117	
Median (IQR)	2 (0 to 4)	2 (0 to 8)	2 (0 to 4)	2 (0 to 5)	0.462
Range	0 to 10	0 to 10	0 to 10	0 to 10	
FPS-r after (n)	30	35	43	108	
Median (IQR)	3 (0 to 6)	2 (0 to 6)	0 (0 to 2)	2 (0 to 6)	0.077
Range	0 to 10	0 to 10	0 to 10	0 to 10	
HR before (n)	53	57	70	180	
Median (IQR)	100 (84 to 115)	106 (93 to 118)	103 (93 to 118)	102 (91 to 116)	0.450
Range	66 to 158	62 to 161	66 to 164	62 to 164	
HR after (n)	53	56	69	178	
Median (IQR)	112 (94 to 129)	109 (94 to 137)	111 (94 to 125)	111 (94 to 130)	0.825
Range	66 to 172	65 to 169	62 to 164	62 to 172	

Legend Table 6.2 - *AHTPS scores were missing for 6 patients in the intention-to-treat analysis; + Kruskal Wallis; Abbreviations: AHTPS = Alder Hey Triage Pain Scale; IQR = interquartile range; OSBD-r = Observational Scale of Behavioural Distress-revised; FPS-r = Faces Pain Scale-revised; HR = heart rate

Table 6.3 - Results of multiple linear regression analyses with pain and distress measurements as outcome variables

	B	95% CI	P-value
Outcome AHTPS during procedure			
Study arm			
Music	-1.173	-1.953 to -0.394	0.003
Cartoon watching	-0.377	-1.177 to 0.422	0.353
Control	Reference	-	-
Type of procedure			
IV placement	0.076	-.991 to 1.143	0.888
Venepuncture	-0.877	-2.141 to 0.387	0.173
Injection local anaesthetics	0.101	-1.136 to 1.337	0.872
POP back-slab	-1.337	-2.251 to -0.422	0.004
Wound dressing/suturing	Reference	-	-
Age in years	-0.253	-0.365 to -0.141	0
Sex			
Boys	0.107	-0.564 to 0.777	0.754
Girls	Reference	-	-
Outcome FPS-R after procedure			
Study arm			
Music	-1.96	-3.67 to -0.25	**0.025**
Cartoon watching	-0.58	-2.31 to 1.15	0.51
Control	Reference	-	-
Type of procedure			
IV placement	1.94	-0.46 to 4.33	0.12
Venepuncture	1.27	-2.10 to 4.64	0.46
Injection local anaesthetics	2.27	-0.64 to 5.17	0.13
POP back-slab	0.98	-1.10 to 3.06	0.35
Wound dressing/suturing	Reference	-	-
FPS-R before	0.32	0.12 to 0.51	**0.002**
Age in years	0.01	-0.30 to 0.32	0.96
Sex			
Boys	-0.33	-1.75 to 1.09	0.65
Girls	Reference	-	-
Outcome OSBD-r after procedure			
Study arm			
Music	-0.23	-0.84 to 0.38	0.45
Cartoon watching	0.031	-0.60 to 0.66	0.93
Control	Reference	-	-

Type of procedure			
IV placement	0.19	-0.63 to 1.01	0.65
Venepuncture	-0.16	-1.22 to 0.89	0.76
Injection local anaesthetics	0.68	-0.29 to 1.64	0.17
POP back-slab	-0.92	-1.63 to -0.22	**0.01**
Wound dressing/suturing	Reference	-	-
OSBD-r before procedure	0.82	0.54 to 1.11	**<0.001**
Age in years	-0.16	-0.25 to -0.073	**<0.001**
Sex			
Boys	-0.08	-0.60 to 0.45	0.77
Girls	Reference	-	-
Outcome HR after procedure			
Study arm			
Music	-5.54	-11.89 to 0.82	0.09
Cartoon watching	-3.47	-10.0 to 3.08	0.30
Control	Reference	-	-
Type of procedure			
IV placement	3.89	-4.69 to 12.47	0.37
Venepuncture	-5.47	-16.31 to 5.38	0.32
Injection local anaesthetics	3.18	-7.33 to 13.69	0.55
POP back-slab	-7.01	-14.24 to 0.22	0.06
Wound dressing/suturing	Reference	-	-
HR Before procedure	0.66	-0.52 to 0.80	**<0.001**
Age in years	-1.76	-2.74 to -0.78	**0.001**
Sex			
Boys	-1.72	-7.48 to 4.04	0.56
Girls	Reference	-	-

Legend Table 6.3 - AHTPS = Alder Hey Triage Pain Scale; FPS-r = Faces Pain Scale-revised; OSBD-r = Observational Scale of Behavioural Distress-revised

DISCUSSION

In this RCT we found that children receiving a music intervention during a procedure in the ER showed significantly lower pain than children watching cartoons or receiving only standard care. Distress scores did not significantly differ between these groups. Almost three-quarters of the children showed no signs of distress before and after the procedure, so that there was little room for improvement in these cases. Also, the types of procedures were not equally distressing. Although there was a significant reduction in pain, we did not find one in distress. A possible explanation for this could be that although there is overlap in the indicators assessed on the AHTPS and OSBD-r, the scoring procedure is different. Firstly, the AHTPS scores five items over the entire duration of the procedure regardless of the length of duration. In contrast, the OSBD-r scores eight items per every 15 seconds of the entire procedure, taking into account the duration of the behaviour. Furthermore, the OSBD-r items are weighted according to intensity.

The results of our study contrast the findings of some other studies. Downey et al. found that cartoon watching had a significant pain-reducing effect in young children in the ER, and Cohen et al. found this to be a beneficial distraction during immunizations (20, 21). Hartling et al. found music interventions to have a significant distress-reducing effect during IV placement in children aged 3 – 11 years in the ER, but only after patients with low OSBD-r scores had been excluded from the analysis (14). We refrained from this type of analysis because this would substantially reduce the numbers of patients and consequently result in a lack of power. In our study the control group had lower median OSBD-r scores during the procedure; 0.37 (IQR 0 to 2.63) compared to Hartling's median of 2.21 (IQR 0.18 to 3.83). This is probably due to inclusion of less distressing procedures such as putting on an orthopaedic cast in our study. We chose not to limit the interventions to IV placement because we wanted to be able to generalize our findings.

A substantial number of children (17%), equally divided across the groups, were restrained for fear of movement during procedures. Although this does not directly affect the outcomes of our study, it is not a desirable approach because it is a source of distress.

Limitations

This study was bound by some limitations. Firstly, it was not possible to blind the patients, their parents and the medical staff to the interventions, nor could the observers who assessed the videos be blinded. Secondly, filming in itself may have influenced the behaviour of patients, parents and medical staff. One might be more conscious of how one is perceived knowing your behaviour is filmed, albeit for research purposes

Conclusions and recommendations

Listening to recorded music is a beneficial distraction for children experiencing pain during ER procedures. However, it did not have an effect on the distress scores. Future studies should investigate if using self-selected music or parent-selected music might increase the effectiveness.

We found that some children were too old to appreciate the cartoons or that it might have been better to use self-selected music and perhaps headphones as well. Recorded music is non-invasive, can be administered at low costs and can be implemented independently by nurses, which is particularly useful in resource-limited settings.

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CHAPTER 7

Discussion

"It always seems impossible until it's done"

- Nelson Mandela -

An evidence base for music in medicine

This thesis addressed the questions: 'music in medicine: does it work and should we use it in hospitalised children'? Music is part of everyday life; throughout history it has been used to bring joy, to motivate, to relax, to distract and to bring people together. Moreover, there are indications that music can help reduce pain, anxiety and distress. The hospital is a scary and unsettling place for children due to the trauma of their injury, hospitalization and medical procedures. Music could bring a sense of normality and a promise of control and distraction from pain, distress and psychological trauma. So why not bring music to the children's hospital? There is no simple answer to the question 'does it work', because a simple yes evokes other questions such as "should we use live or recorded music, and for who"?

This thesis aims to contribute to the evidence on music interventions for hospitalised children and consists of 5 articles published between 2015 and 2018. The main findings are summarized below:

- In our systematic review, premature infants receiving live music therapy showed a significant improvement in sleep, although this conclusion was based on no more than three studies.
- Our meta-analysis of three studies showed that children undergoing surgery had significant less postoperative pain, anxiety and distress when receiving music interventions before or after the procedure.
- Older children with burns receiving music therapy after wound care procedures, and children in the emergency room listening to music during procedures self-reported a significant reduction in pain and/or distress.
- In children under the age of 3 years admitted to the burns unit and ER we could not show a significant improvement in pain and distress outcomes, which is partly due to study limitations.

The overall conclusion of this thesis is that music can be beneficial for hospitalised children around operations and during painful procedures. However, a strong and widely supported one-on-one relation between music and pain and distress reduction was not clearly discovered. For example, we measured both observed and self-reported pain and distress but found reductions only in observed pain and in self-reported distress. We have not been able to explain why these were not found for observed distress and self-reported pain.

Based on our research and what is otherwise known on the effects of music, I propose that music is harmless and beneficial for the majority of hospitalised children. This final chapter discusses considerations for further research on music interventions in hospitalised children and provides recommendations for the future of music in medicine.

Over the past years the research on 'music in medicine' has soared. What new studies have emerged that are relevant for the patient populations discussed in this thesis?

Music in the neonatal intensive care unit

Since our systematic review from 2016 on music in the NICU (1), two systematic reviews and three RCTs on this subject have been published (2-6). The two systematic reviews included the same articles as our review, plus one RCT published in 2017, which showed a decrease in pain response as measured by ß-endorphin concentration (4). One study in 35 patients aimed to explore via MRI how music exposure modulates the brain processing of music in preterm infants compared to cortico-subcortical music processing in term newborns (5). The results of this exploratory study suggest that music can induce brain functional connectivity changes that are associated with music processing. Lastly, one RCT in 17 patients with a gestational age of 32 to 36 weeks, showed a reduction of heart rate and respiratory rate (6). Both our systematic review and the two published later address the problem of the variety in outcome measurements, which complicates generating an evidence-base for music interventions in premature infants.

Music for perioperative care

Since our meta-analysis from 2015 (7), two new studies on the effects of music for children undergoing surgery have been published (8, 9). One is an RCT including 52 children which showed a statistically significant reduction of preoperative anxiety in the music group compared with a standard care control group (8). The other study compared an active with a passive music intervention (no control group) in 40 children and found a significant reduction in preoperative anxiety in both groups, but saw no superiority between the interventions (9). The findings of these additional RCTs and a recent meta-analysis in adults (10) are sufficient reasons to perform an implementation study on peri-operative music interventions.

Music in the emergency room

Over the past few years no new studies have been performed on music interventions in the paediatric ER. In our study we found music listening more effective than watching cartoons in reducing pain during painful procedures. Hartling et al. also found music beneficial in reducing pain and distress in children in the ER (11). A Cochrane review from 2013 shows strong evidence for distraction (including music interventions) during needle procedures in children (12). The previous studies on distraction during ER procedures indicate a willingness of clinicians to provide complementary care for their patients. Still, implementation might prove to be more difficult due to the hectic environment of the ER setting. Developing intervention research for this particular patient group is imperative (see below "Considerations for the implementation of music in medicine")

Music in burn wound care procedures

In our articles on children with burns we raise the question of the benefits and barriers of parental presence during painful and distressing wound care procedures. A recent study among parents of Dutch burns victims suggests that parents should be offered the choice to be present (13). The parents explained that despite the distress associated with seeing the wound care procedure, the benefits of being able to support their child weigh heavier. Research on music interventions in children with burns is very limited and needs to be further investigated, especially for children with burns younger than 3 years old and their parents.

Considerations for clinical research on music in medicine

Evidence-based medicine is 'the conscientious, explicit, judicious and reasonable use of current best evidence in making decisions about the care of individual patients'(14, 15). The RCT is considered the state-of-the-art study design in evidence-based-medicine as randomisation assures that confounders are equally distributed between the intervention and control groups, and thus that selection bias is minimized. Still, there are some challenges with performing RCTs in the context of evaluating nonpharmacological therapies that aim to provide a personalized psychological intervention (16-18). The parallel group RCT requires homogeneity in the patient group and diagnosis, the timing and duration of the intervention and the outcome measurements. Furthermore, ideally both the patients and the assessors of the outcome measurements are blinded to the assignment of the experimental vs. control group. In our studies we encountered difficulties regarding the above-mentioned aspects, which are detailed below.

The RCT revisited: patient groups

Both our studies and other studies show conflicting results of music interventions in premature infants (1), neonates (19), young infants (11) and older children (20). This could possibly be explained by a heterogeneity in the patient populations, particularly the variety in ages.

The stage of cognitive development could influence the child's responses and observable effects of the music (21). Survival and neurological outcomes differ between infants born very early (<28 weeks gestational age), early (28+0 – 31+6 weeks gestational age), moderate (32+0 – 33+6 weeks gestational age), late (34+0 – 36+6 weeks gestational age) (22). These differences notwithstanding, our systematic review in premature infants included 20 RCTs studying premature infants in NICU between the ages of 24 and 40 weeks gestational age (1). Standley has provided guidelines for interventions per gestational age group, which however were not adhered to in all the studies (23). These factors could have influenced the RCTs included in our systematic review and give an unclear perspective on the effects of music in preterm infants.

In our RCTs we found significant effects of both live and recorded music in children older than 4 years old, but not in younger children (24, 25). This is in line with a systematic review on music therapy including children over the age of 3 years undergoing medical procedures (20). Older children might express their emotions in a more understandable way for us adults. Also, they may have a better understanding of why they have to undergo a painful procedure and will better understand instructions. Furthermore, older children are usually more comfortable with strangers than are infants or toddlers, which is particularly important when studying live music therapy.

Besides age, there was heterogeneity in the types of medical procedures the patients underwent in our systematic review and meta-analysis (1, 7). Although medical procedures are never pleasant, some procedures may be scarier and more painful than others. In our own RCT during painful procedures in the ER, we chose to perform a pragmatic trial and included all types of medical procedures in order to reflect the typical patient mix of the ER. This may have limited the effect size because procedures are not equally painful or scary.

The RCT revisited: the intervention

We found heterogeneity in the studies included in our systematic review and meta-analysis in terms of: the type and content of the music intervention offered, and the timing and duration of the intervention. It appears there is no consensus on these matters and that the different options regarding the timing and duration of the intervention have not been compared in well-designed studies.

Recorded or live music therapy?

What are the considerations for a recorded music intervention? The following aspects should be carefully taken into account: genre, tempo, instruments, vocalists' gender, rate of change that occurs in the music (dynamics, melodic line, predictability) (26). Many studies used classical instrumental music, although they did not provide a clear rationale for this choice. In our RCT in the ER the recorded music intervention, composed by a music therapist, consisted of slow guitar music including vocals by a female singer. The lyrics were playful and there was a lot of repetition both lyrically and melodically. Our rationale for the playfulness and repetitiveness of the intervention was that we aimed to distract the child undergoing a medical procedure, rather than soothe or lull the child to sleep. The choice of type of music genre could also be based on the child's preference, in which case the parents could help choose the recorded intervention. The way of offering recorded music might also influence the experience of the intervention. Headphones, instead of speakers, might work well for older children but could inflict extra tension in very young children who are not used to wearing headphones.

While recorded music is a passive intervention that can soothe or distract the child resulting in less pain and distress, live music therapy is of a more interactive character. Live music therapy is, by nature, a tailored therapy depending on the needs, personal preference and mood of the patient in the moment. There are different therapeutic strategies. The music therapist uses the music as a vehicle to help the child go from one emotional state to another, this is called entrainment. Other therapeutic strategies can include song writing and improvising (27). Therefore, the live music intervention is never homogenous for all patients, making it more difficult to compare.

The best timing and duration of the intervention?

The timing of the music intervention depends on the therapeutic goal. Recorded music is often used with the goal to reduce pain and distress by soothing or distracting and can be offered at the convenience of the patient. Live music therapy often takes place "in between events" because its therapeutic goals are broader and can also include other aspects of hospitalization such as coping with trauma or strengthening the parent-child bond. Burns patients, for example, not only suffer from the painful procedures but also from the traumatic experience of obtaining the injury, the bodily disfigurement and the fear of stigmatization. Parents of a burns patient are often also traumatized by the burns incident and by seeing their child suffer. Therefore, the timing can be quite ad hoc and at the convenience of the medical staff, the therapists and the patient. The current evidence is insufficient to conclude on the best timing of recorded or live music interventions.

Furthermore, the repetition, length and frequency of interventions vary greatly in most studies. Our systematic review on premature infants showed a wide range in duration and frequency of the recorded music interventions. The minimum was a once-only session of listening to music for 10 minutes; the maximum was 3 daily sessions of 30 minutes during 14 days. Live music therapy, on the other hand, is personalized which influences the duration of the session. For the sake of the RCT, we standardized the music therapy sessions to 3-5 minutes in our study on live music therapy in burns (24). This meant that the music therapist had to change the normal practice of playing as long as needed.

Based on our review of the literature and our own trial experience, we tentatively conclude that the type of music intervention, its timing and duration should ideally be adjusted for the context and the situation of the patient in the moment. Especially a live music intervention is difficult to protocolize, therefore making it difficult to perform a rigorous RCT.

The RCT revisited: outcome measurements

Music interventions have been shown to reduce pain and anxiety in hospitalised adults undergoing surgery (10, 28, 29); adults with burns (30, 31); patients with coronary heart disease (32); in mechanically ventilated patients (33) and to reduce preoperative anxiety in adults (27). Our research group conducted a systematic review and meta-analysis on the effects of music in hypertension treatment and revealed a trend towards a decrease in blood pressure in hypertensive patients listening to recorded music (34). Studies in adults used predominantly self-reported outcome measurements alongside physiological outcome measurements. Self-report is obviously not possible in non-verbal or preverbal children. In our clinical studies the primary outcomes were therefore assessor-observed. Furthermore, certain physiological parameters such as heart rate, oxygen saturation, and blood pressure are not standardly measured in the burns unit and in the ER. We feared that placing a pulse oximeter on their fingers would inflict extra distress in these young children (35). Therefore, in children younger than 5 years we could only use scales that measure observed changes in pain and distress (36-41). To give an unbiased score of observed pain and distress, the RCT requires assessment by an independent assessor blinded to the study group. This is why we used video footage. The disadvantage of this is that the filming is likely to have an effect on the child's behaviour. In future research a possible solution could be to use small Go Pro® filming equipment hidden in the researcher's clothing.

Ideally, for non-verbal and preverbal children outcome measurements include neurological and physiological parameters and behavioral measurements. Gathering neuroscientific evidence through for example EEG and fMRI is a costly procedure and not readily accessible in all hospitals. However, this can provide a valuable insight in understanding the relationship between music processing and brain development in preterm and hospitalised newborn infants (3, 5, 42-44).

A prerequisite of a rigorous RCT is well-defined and measurable outcomes, but how do we decide what to measure and when do we deem a therapy successful and beneficial for the patient? When studying live music therapy in burns we used the outcomes pain and distress, however we also observed other effects of the therapy that we could not measure objectively such as emotional release, joy, relaxation, connection between the child and the therapist or between the child and the parent or amongst the other children in the ward. Researchers studying the effects of other non-pharmacological interventions come across similar problems. For example, massage interventions show positive effects in an observational study research but not in a RCT (35, 45). Both music interventions and massage interventions aim to increase relaxation and wellbeing and decrease pain and distress, both interventions de-medicalise the hospital environment and distract from the current situation. However, as of yet there are no measurement tools for these outcomes in young children. Furthermore, we do not know when to best collect data in order to measure the effects of these type of interventions. Should we look at the effects after the therapy or might the effect take place during the therapy? For example, in our RCT in children with burns we measured pain and distress before going in for wound care procedures and after the music therapy session. Therefore, there was quite some time between the first measurement and the second (median 32; interquartile range 26 to 39 minutes).

When listening to music we can experience feelings of joy and pleasure that we might not express noticeably. We might experience goose bumps or positive chills. When witnessing a child listening to recorded music or participating in a music therapy session, we can observe “something in their eyes” or “you can feel something is happening”. But of course, these are not measureable observations. In an attempt to systematically assess music therapy, two tools have been developed by music therapists (46-50). One is the Music Therapy Rating Scale, which aims to evaluate the progression of the non-verbal and sonorous musical relationship between children with autism and their music therapist during the sessions (47, 48). The other, the Paediatric Inpatient Music Therapy Assessment Form, aims to evaluate music therapy in hospitalised children but does not provide a scale of measurable outcomes (46). It consists of 8 descriptive categories discussing background information: referral information, physiological information, physical and motor skills, cognitive skills, social and emotional behaviors, communication skills, and musical behaviors. Both scales evaluate effects from a music therapy point of view, but for a medical researcher they would not provide enough objective and quantifiable information. Based on our research in children with burns we are currently developing a music therapy assessment tool specifically aimed at clinical research on music therapy in young hospitalised children. Ultimately, this tool could be used in RCTs in addition to other measurements. The tool consists of 4 categories: 1) level of patient engagement 2) level of patient relaxation 3) level of parent engagement 4) therapeutic strategies used by the music therapist. Patient and parent categories consist of items to be scored: items regarding behavior of engagement and levels of relaxation. Occurrences of these items are scored from videos per 15-second time interval. The music therapist category concerns the occurrence and frequency of specific therapeutic strategies (see Table 7.1). We are yet to validate the tool and make it quantifiable.

Considering the parent-child dyad

Although our research did not include parents, we recognize their importance and role in the care for the hospitalised child. There is some debate about whether or not a parent should be present during their child's painful procedure (51, 52). Parental distress and anxiety could be more detrimental than helpful for the child (53-55). On the other hand, it is of great importance that a child feels safe and emotionally supported during medical procedures (55-58). Young children with burns have a high risk of developing posttraumatic stress disorder directly after the burn injury (59-61). The child's family is also at risk to develop posttraumatic stress disorder and it has been recommended to target interventions for both children with burns and their families (62). A systematic review on the effects of music therapy on posttraumatic stress in adults concluded that live music therapy can improve functioning and increase resilience (63). Further research should assess the effects of music therapy on reducing posttraumatic stress symptoms in children and their parents. In our study in burns parents were not allowed to be present during the WCP, which was justified by a fear of infection and lack of space. However, in our study in the ER of Red Cross War Memorial Children's Hospital, parents were present during the procedure. Music therapists can help in supporting the parent-child dyad. They can give the parents a specific task during the music making which will make them feel useful and a part of the process (64).

Considerations for the implementation of music in medicine

Earlier I proposed that music is harmless and beneficial and can therefore be used in hospitalised children. How can we make sure the beneficial effects of music are available to all hospitalised children and to establish firmer ground for music in medicine? Providing evidence alone is not enough; successful implementation of a beneficial intervention depends on the way scientific evidence is translated into practice and policy (65-67). Every doctor and nurse wants to provide the best care for their patient, but going 'from best evidence to best practice' involves change, and bringing about change is notoriously difficult (68-71). Grol et al. defined the following barriers to the uptake of evidence by medical staff: cognitions (not convinced of the evidence), motivation, working routines of the individual professional (ownership), interaction within the team (accountability, control and leadership) and functioning of the hospital (financial commitment and allocating time) (70). Providing evidence-based music interventions for hospitalised children may sound like a simple task, but in order to ensure actual change in patient care we should address possible barriers on knowledge and attitude, prevailing opinion and the practice environment (see Table 7.2) (70). Grol argued that 'evidence-based medicine should be complemented by evidence-based implementation' (72). Implementation projects should make use of various change strategies (73). An appeal to the intrinsic motivation of healthcare workers can be achieved by actively teaching about the benefits of music. Extrinsic motivation for change happens on a group and organisational level and involves planning for financial resources and time allocation. At the moment some hospitals sporadically include music interventions in

Table 7.1 - The Sophia Red Cross Music Therapy Assessment Tool

Category 1: Level of patient engagement											
Items engaged:							**Items not engaged:**				
Eye contact	Fixed look	Nodding head in response	Smile	Verbal	Touches the instrument	Play (+/++)	Turning away (including seeks comfort from parent)	Active rejection			
Category 2: Level of patient relaxation											
Body tense	Body relaxed	Face tense	Face relaxed	Cry	Moaning	Calm	Awake	Drowsy	Asleep		
Category 3: Level of parent engagement											
Engaged:							**Not engaged:**				
Looks at child	Looks at MT*	Smile	Encouraging	Moving body	Responsive		Not looking	Preoccupied**	Active rejection***		
Category 4: Music therapist											
Matching: general	Matching: volume	Matching: tempo	Matching: mimicking	Asking child question	Asking parent question	Offering child music instrument	Offering parent music instrument	Show use of instrument	Singing song	Inviting other people in the room to join in	Type of instrument used in session

Table 7.2 - Possible barriers to implement music interventions in patient care

Compulsion to act	Do clinicians and hospital management agree certain problems should be addressed (e.g. peri-operative and peri-procedural pain and anxiety) and that current practice is lacking in its approach?
Appraisal of evidence and opinion leaders	Is the evidence on the benefits of music widely accepted amongst clinicians and hospital management?
Standards of practice	What needs to change in daily routine of health care providers to facilitate the implementation of music interventions?
Ownership and organisational constraints	The use of music is not limited to one specific patient group and therefore does not belong to one specific department. Who will be responsible for communication and execution of the intervention?
Financial considerations	Who is responsible for funding music interventions in the hospital? Can music interventions be reimbursed by health insurance companies?
Clinical considerations	Live or recorded music? Depending on the patient group, both interventions have clinical benefits

Based on Grol R, Grimshaw J. From best evidence to best practice: effective implementation of change in patients' care. Lancet. 2003

patient care. In the Erasmus MC in Rotterdam, a music therapist is employed part-time but only for adolescents admitted to the psychiatry ward and is paid by that specific department. Other hospital music programmes in the Netherlands include the initiative 'Muziek aan Bed' (Music at the Bedside) by two cellists who perform music in the wards. This is funded through an individual private foundation. Depending on the hospital and the patient group, music interventions might belong to the domain of the medical specialist, anaesthesia team and/or the nursing teams. Music interventions can offer a valuable contribution to patient care, but more research is needed on the practical implementation and its costs. Given the evidence in (paediatric) surgical patients, an implementation study on peri-operative music interventions might be a good place to start.

The following steps should be taken (73):

1. Develop intervention guidelines based on research findings
2. Define best practices
3. Describe specific change targets
4. Analyse target group, current practice and local context
5. Select change strategies (intrinsic or extrinsic)
6. Develop and execute implementation plan
7. Continuously evaluate and adapt plan

Successful evidence-based implementation depends on a plan for knowledge translation, identification of barriers, communication with all stakeholders, interventions to support and facilitate behavioural change (69, 74, 75). In the end, what is clinical research worth if it does not positively change patient care?

Recommendations

Based on this thesis we recommend the following:

- Children seem to benefit from listening to music before and after surgery. Similarly, older children undergoing procedures in the ER benefit as well. Future research should include what type of music works best and from what age children can decide their preference in music.
- Implementation studies should explore different ways of offering music by speakers or headphones. We recommend including certified music therapists and parents in compiling a playlist
- Staff offering music in the NICU should prevent overstimulation of the child and measure the decibel levels of music interventions.
- Live music therapy seems promising in promoting sleep in premature infants. Future research should focus on how live music therapy can promote the parent-child dyad in the NICU and reduce distress in the parents. Music therapy could be a part of a family-centred approach in the NICU.
- Implementation studies are required to develop guidelines to best introduce music in hospital to help patients cope.
- Children with burns are at high risk of pain and distress, and subsequently at developing posttraumatic stress symptoms. Moreover, family members of children with burns are at risk of developing posttraumatic stress symptoms. More research is needed on the potential benefits of repeated live music therapy sessions for children with burns and their families.

In conclusion

Music should not only be appreciated for its entertainment value, but also for the value it can have for children who are suffering from pain and distress. There should be a future for music in medicine.

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CHAPTER 8

Summary | Nederlandse Samenvatting

"Music gives a soul to the universe, wings to the mind, flight to the imagination and life to everything"

- Plato -

MUSIC IN MEDICINE

The value of music interventions for hospitalised children

This thesis addresses the question: 'music in medicine: does it work and should we use it in hospitalised children'? The overall aim was to find if live music therapy and recorded music interventions could reduce pain and distress from medical procedures. The findings could help convince the medical field of the benefits of music interventions in hospitalised children. Earlier publications on this topic demonstrated a great variety in the music interventions offered to sick children, the outcomes with which the effect of music is measured and the results in various groups of hospitalised children.

The studies in this thesis focused on different patient groups, ranging from prematurely born children admitted to a neonatal intensive care unit (NICU); children aged 0 to 18 years undergoing surgery; young children hospitalised with burns; and children from age 3 years upwards undergoing painful procedures in the emergency room. The question of whether music 'works' requires a nuanced answer, but the overall conclusion is cautiously positive. Premature infants receiving live music therapy showed a significant improvement in sleep. Older children with burns and children undergoing surgery or receiving a music intervention during procedures in the ER self-reported a significant reduction in pain and/or distress. In younger children under the age of 3 we could not show a significant improvement in pain and distress outcomes.

Systematic reviews and meta-analysis

Chapter 2 presents our systematic review on the effects of music interventions in premature infants. Nine reviews on this topic had been previously published, but ours was the first to include only RCTs. The increasing and worldwide interest in music interventions in the NICU is demonstrated by the fact that our review, published six years after the last, included 15 new studies, from the USA, Israel, Iran, Turkey, Australia, Lithuania, Germany and Brazil. We could not draw a solid conclusion, although we can cautiously infer that live music interventions seem to improve sleep quality of critically ill premature infants. The biggest limitation of this systematic review was the heterogeneity in type and duration of interventions, and in the gestational age of the included patients. Furthermore, there was a great variety in outcome measurements.

In *chapter 3*, our meta-analysis showed that children undergoing surgery benefit from both live and recorded music interventions, in that they have significantly less pain and distress. However, we could include only three randomised controlled trials. As with our systematic review on premature infants, this meta-analysis was limited by the heterogeneity in types of music interventions, patient population and outcome measurements.

In both our systematic review and meta-analysis the overall risk of bias was moderate. Blinding was often not reported at all or it was unclear to what extent the researcher was blinded to group allocation. Both studies also showed there is a lack of consensus on the most relevant outcome measures to address the effects of music. Furthermore, the systematic reviews did not conclude the best timing and duration of music interventions.

Clinical studies in the Burns Unit and the Emergency Room at Red Cross Children's Hospital, Cape Town, South Africa

A hospital is often a distressing place for a child especially when the child is brought to hospital after sustaining a traumatic injury, as is the case with children admitted to the burns unit or the emergency room. Increasingly, music interventions are studied for their added value in pain and distress management. However, most of these studies have been performed in the USA, Australia, Western Europe and South America. We carried out two RCTs at the Red Cross War Memorial Children's Hospital (RCWMCH) in Cape Town, South Africa. The RCWMCH is an academic teaching hospital connected to the University of Cape Town and one of the best specialised children's hospitals in southern Africa. To our knowledge our studies were the first carried out in Sub-Saharan Africa.

Children hospitalised with burn wounds suffer on a physical and emotional level from the pain, discomfort, the traumatic experience of sustaining a burn and being hospitalised for it, and the long road to recovery. In order to bring distraction, enhance relaxation and help processing the traumatic experience, many burns units around the world offer complementary interventions such as massage therapy, art therapy and music therapy.

In *chapter 4* we used the COMFORT Behavioural Scale (COMFORT-B) to measure the level of pain intensity and distress across four phases of the wound care procedure: removal of bandage; washing the wound; administering wound care; putting on new dressings. We included 124 children, with a median age of 21.2 months old, undergoing wound care procedures (WCP) in the burns unit of the RCWMCH. A previous study carried out by other researchers in a comparable patient population in the Netherlands found that most children experienced severe pain and distress during WCPs. Similarly, in our study this was the case across the four phases for respectively 76%; 89%; 81% and 62% of the patients. In our study we found that younger age was a predictor for pain and distress, as the younger children were assigned higher scores – indicative of more pain and distress – than older children ($p<0.001$). It is difficult to unravel whether pain or distress is the specific primary cause for high COMFORT-B scores. The parents were not present during WCP.

Recommendation: There is a need for better pain and distress management during WCPs, particularly for very young children. We recommend clinicians to better evaluate pain and distress using the COMFORT-B scale during WCPs. Furthermore, future research should focus on interventions tailored per age group.

In *chapter 5* we describe an assessor-blinded RCT on the effects of live music therapy in 135 young children with burn wounds after WCP. Their median age was 22.6 months (IQR 15.4 to 40.7 months). In 135 children levels of distress and pain before undergoing WCP procedures were compared with levels of pain and distress after receiving live music therapy directly after WCP. Distress was measured with the Observational Scale of Behavioural Distress-revised (OSBD-r) and pain was assessed with the COMFORT-B scale. Older children self-reported distress and pain with the Wong Baker scale (FACES) and the Faces Pain Scale-Revised (FPS-R), respectively.

We did not find an effect of live music therapy on distress and pain levels estimated by assessors. However, self-report by eighteen over 5year-olds (n=18) indicated a significant reduction in distress after live music therapy (p=0.05) and there was a strong correlation between observed and self-reported distress and pain.
This study is one of the first with a large population of pre-verbal children.

Recommendation: As the parent is the primary support giver in the burns unit, future research should include interventions aiming at the parent-child dyad. Live music therapy could encourage a positive engagement between child and parent. Music therapy seems valuable for older children with burns.

For children with trauma who are rushed off to the emergency room (ER) the hospital can be a frightening place. In *chapter 6* we describe our RCT in 198 children older than 3 years admitted to the emergency room. Children would listen to recorded music, watch a cartoon or receive standard care as a control. Independent assessors used the Alder Hey Triage Pain Scale (AHTPS) to assess pain and the OSBD-r to assess distress from video footage. Children older than 4 years self-reported pain using the FPS-R. Furthermore, heart rate was measured as an indicator of distress. Based on the AHTPS, children in the music group had significantly less pain than children in the cartoon and control groups (p=0.003). The other outcome measurements did not show a statistically significant difference.

Recommendation: Recorded music is non-invasive, not expensive, and can be implemented independently by nurses, which is particularly useful in resource-limited settings. Future studies should investigate whether self-selected music might increase effectiveness.

Conclusion

Music should not only be appreciated for its entertainment value, but also for the value it can have for children who are suffering from pain and distress. There should be a future for music in medicine.

NEDERLANDSE SAMENVATTING

Muziek in de geneeskunde: De waarde van muziekinterventies in het kinderziekenhuis

'Muziek: welke effecten heeft het luisteren naar muziek en kunnen we muziek gebruiken in de zorg voor kinderen in het ziekenhuis'? In dit proefschrift is onderzocht wat de toegevoegde waarde is van muziekinterventies – live of recorded – voor kinderen die in het ziekenhuis pijnlijke procedures ondergaan: vermindert hierdoor eventuele pijn en angst?

In eerdere publicaties over dit onderwerp zijn helaas geen eenduidige uitkomstmaten of muziekinterventies gebruikt en waren de patiëntengroepen sterk verschillend. Dit maakt het lastig een duidelijk antwoord te geven.

De studies in dit proefschrift betroffen verschillende patiëntengroepen: prematuur geboren kinderen opgenomen op de neonatologie intensive care unit (NICU), kinderen van 0 tot 18 jaar oud die een operatie ondergaan, jonge kinderen die met brandwonden in het ziekenhuis zijn opgenomen, en kinderen vanaf 3 jaar oud die pijnlijke procedures ondergaan op de spoedeisende hulp. De vraag 'werkt muziek' vereist een genuanceerd antwoord, maar de algemene conclusie van dit proefschrift is positief. Prematuur geboren baby's die live muziektherapie kregen leken beter te slapen. Oudere kinderen met brandwonden en kinderen die rondom een operatie of tijdens een pijnlijke procedure muziek te horen kregen gaven zelf aan significant minder pijn en angst te ervaren. Bij kinderen jonger dan drie jaar oud konden we geen significant verschil in geobserveerde pijn en angst aantonen.

Systematic reviews en meta-analyses

Hoofdstuk 2 bevat onze systematic review naar de effecten van muziekinterventies bij prematuur geboren kinderen. Hoewel er voorheen negen reviews over dit onderwerp zijn gepubliceerd, is onze review de eerste die alleen maar gerandomiseerde, gecontroleerde studies (RCT's) heeft geïncludeerd en daarmee van hoge kwaliteit is. Wereldwijd is er steeds meer aandacht voor het gebruik van muziek bij deze kinderen. Dit blijkt uit het feit dat onze review, gepubliceerd zes jaar na de laatst uitgevoerde review, 15 nieuwe studies uit Amerika, Israël, Iran, Turkije, Australië, Litouwen, Duitsland en Brazilië bevat.

Live muziektherapie lijkt de slaapkwaliteit van prematuur geboren baby's te verbeteren. Maar deze conclusie moet voorzichtig worden geïnterpreteerd omdat er grote verschillen waren tussen de studies wat betreft het type muziekinterventie, de duur daarvan, en de zwangerschapsduur van de baby's. Bovendien werden er verschillende uitkomstmaten gebruikt.

Uit onze meta-analyse in *hoofdstuk 3* blijkt dat kinderen die een operatie ondergaan bij zowel live muziektherapie als luisteren naar recorded muziek significant minder angst en pijn ervaren dan kinderen in de controle groep. Echter, deze conclusie is gebaseerd op drie RCT's en dient ook voorzichtig te worden geïnterpreteerd in verband met de bovengenoemde verschillen.

Voor zowel de systematic review als de meta-analyse is er een gerede kans op bias. Het was namelijk niet duidelijk, of het werd niet gerapporteerd, of en hoe de onderzoekers geblindeerd waren voor groepstoewijzing. Uit beide studies werd ook niet duidelijk wat de beste uitkomstmaten zijn om muziek te testen bij jonge kinderen, noch werd duidelijk wat de beste timing en lengte van een interventie zou moeten zijn.

Klinische studies op de brandwondenafdeling en spoedeisende hulp in Red Cross War Memorial Children's Hospital, Kaapstad, Zuid-Afrika

Het ziekenhuis is een stressvolle, beangstigende plek voor een kind, en dit geldt zeker voor kinderen met zware brandwonden of ander ernstig letsel. Er vindt steeds meer onderzoek plaats naar de waarde van muziekinterventies voor met name pijn- en angstbestrijding. De meeste van deze studies zijn uitgevoerd in de Verenigde Staten, Australië, West-Europa en Zuid-Amerika. Wij hebben twee grote RCT's uitgevoerd in het Red Cross War Memorial Children's Hospital (RCWMCH) in Kaapstad, Zuid-Afrika. Dit academisch kinderziekenhuis is een van de beste kinderziekenhuizen in zuidelijk Afrika.

Kinderen met brandwonden lijden zowel fysieke als emotionele pijn, niet in het minst door de traumatische ervaring van het verbranden, de ziekenhuisopname en de lange weg naar herstel. Om het leed te verzachten, ontspanning te brengen en de traumatische ervaring te verwerken, worden in brandwondencentra over de hele wereld complementaire therapieën aangeboden zoals massage, creatieve therapie en muziektherapie.

In *hoofdstuk 4* hebben we gemeten hoeveel pijn en angst kinderen met brandwonden ervaren tijdens wondverzorging. Voor dit doel hebben we bij 124 kinderen met een gemiddelde leeftijd van 21.2 maanden de COMFORT Behaviour Scale (COMFORT-B) toegepast tijdens vier fases: verband verwijderen; wond wassen; wondzalf aanbrengen; nieuw verband aanbrengen. Gemeten over de vier fases lieten respectievelijk 76%, 89%, 81% en 62% extreem veel pijn en angst zien. Uit een soortgelijke studie van andere onderzoekers onder Nederlandse kinderen met brandwonden is gebleken dat die ook extreem veel pijn en angst hadden tijdens de wondverzorging. Wij konden concluderen dat de pijn en angst significant sterker waren bij jongere kinderen in vergelijking met oudere kinderen ($p<0.001$).Het is lastig te bepalen of de hoge COMFORT-B scores voornamelijk op het conto komen van de pijn of de angst. De ouders waren niet aanwezig tijdens de wondverzorging.

Aanbeveling: Met name voor jonge kinderen moet er betere pijn en angstbestrijding tijdens de wondverzorging komen. Pijn en angst tijdens wondverzorging moet beter gemeten en geregistreerd worden bij alle kinderen. De COMFORT-B is hier een goed instrument voor. Tevens raden we aan dat vervolgonderzoek zich richt op interventies specifiek per leeftijdsgroep.

In *hoofdstuk* 5 bespreken we onze RCT naar de effecten van live muziektherapie ná wondverzorging bij 135 jonge kinderen met brandwonden. De gemiddelde leeftijd was 22.6 maanden (IQR 15.4 tot 40.7 maanden). Een deel van de kinderen kreeg live muziektherapie aangeboden na de wondverzorging, terwijl de controlegroep alleen standaardzorg kreeg. De mate van pijn en angst werd voor beide groepen gemeten vóór en na de wondverzorging; bij de interventiegroep na de muziektherapie. Bij alle kinderen werd hun angst gemeten met de Observational Scale of Behavioural Distress (OSBD-r) en hun pijn met de COMFORT-B. Kinderen ouder dan 5 jaar rapporteerden daarnaast ook zelf angst en pijn op gezichtjesschalen, respectievelijk de Wong-Baker scale (FAC-ES) en de Faces Pain Scale-revised (FPS-R).

Na analyse van de scores bleek er wat betreft pijn en angst van de jongere kinderen geen significant verschil tussen de interventie- en de controlegroep. Uit de zelf-rapportage van de kinderen ouder dan 5 jaar (n=18) bleek echter wel een significante vermindering van angst na de muziektherapie. Er een sterke correlatie tussen de angst- en pijnscores van de OSBD-r en COMFORT-B en de gezichtjesschalen.

Deze RCT is een van de eerste met een grote groep jonge kinderen die nog niet zelf kunnen aangeven of ze pijn en angst hebben.

Aanbeveling: Omdat ouders een belangrijke rol spelen in de zorg voor kinderen met brandwonden zouden verdere interventies in het ziekenhuis zich moeten richten op de ouder-kind band. Live muziektherapie zou hierin een positieve rol kunnen spelen. Muziektherapie lijkt waardevol voor oudere kinderen met brandwonden.

Voor kinderen die met letsel naar de spoedeisende hulp worden gebracht is het ziekenhuis ook een beangstigende plek. In *hoofdstuk 6* bespreken we onze RCT onder 198 kinderen ouder dan 3 jaar die zijn opgenomen op de spoedeisende hulp. De kinderen werden in drie groepen verdeeld. Een groep kreeg tijdens een pijnlijke procedure een tekenfilm te zien, een tweede groep luisterde naar muziek, en de derde was een controlegroep die alleen standaardzorg kreeg. Onafhankelijke onderzoekers gebruikten de Alder Hey Triage Pain Scale (AHTPS) om pijn te scoren. Angst werd gescoord met de OSBD-r. Kinderen ouder dan 4 jaar rapporteerden zelf pijn met de FPS-R. Hartslag werd gemeten als een indicator van angst.

Kinderen in de muziekgroep hadden significant minder pijn, gemeten met de AHTPS ($p=0.003$), tijdens de procedure dan kinderen in de controlegroep en kinderen die naar een tekenfilm hadden gekeken. Wat betreft angst en hartslag was er geen significant verschil tussen de groepen.

Aanbeveling: Luisteren naar recorded muziek is een niet-invasieve, relatief goedkope interventie die gemakkelijk zou kunnen worden geïmplementeerd. Vervolgonderzoek zou zich moeten richten op het verschil in effect tussen voorgeselecteerde en zelf-geselecteerde muziek.

Conclusie

Muziek wordt meestal alleen gewaardeerd voor plezier en vermaak, maar kan ook meerwaarde hebben voor kinderen met pijn en angst. Muziek verdient een toekomst in de geneeskunde.

FIELD NOTES

"Anthropology demands the open-mindedness with which one must look and listen, record in astonishment and wonder that which one would not have been able to guess"

- Margaret Mead -

FIELD NOTES

Clinical observations, August 2013
Red Cross War Memorial Children's Hospital, Cape Town, South Africa

"There are two sorts of music", Chris (the music therapist) says as I follow him into the ward, "music to stimulate you and to wake you up, and music to help you relax and go to sleep". It is my first week of participant observation in the burns unit at RCWMCH in Cape Town. We are standing in front of the dressing room and we hear the loud screams of Janda, a ten-year-old boy, who has a big burn on his bum and lower back. Janda's mother is standing next to us, with a look of sadness and guilt on her face. Chris says he will play some music later and the mother responds: "I think he will like it".

Minutes later Janda comes out of the dressing room crying and shaking, and expressing a lot of pain and anger. He asks his mother over and over again "why he had to go there, it hurts so much". The mother looks stressed and takes him back to his bed. With great effort Janda lies down on his belly, continuing to cry and scream, while his mother tries to calm him down by stroking his back and head and telling him 'to be a strong boy'.

Chris sits next to the bed and starts playing his guitar while minding his own business, without really engaging with Janda. The guitar music sounds like reggae and Chris starts humming softly. It takes a while for Janda to interrupt his crying and to show interest. Chris waits for Janda to interact first before making eye-contact. He smiles and puts a tambourine on the bed in reach of the boy.
"Do you wanna play?" he asks Janda, who stares back at the man with the guitar and nods his head.

Chris picks up the rhythm of his song and starts singing to Bob Marley:

Here at Red Cross Hospital we will make you very well
Here at Red Cross Hospital we will make you very well
You are the red cross soldier, red cross soldier
Wow wow wow wow

I look at the mother as she is joining the music making by clapping her hands. She looks relieved by the distraction that Chris provides. Chris takes the tambourine and asks the boy: "show me how you feel". Janda bangs uncontrolled on the tambourine and stops. Chris mimics him and strums the guitar like he is an angry rock-and-roll artist while singing 'lalala'. "Good", he says, "you're showing anger".
Now, let's see, what other emotions can we think of to express? Together Chris and Janda start jamming, a process of communicating through the music and exploring different emotions. Janda smiles when Chris plays funny music while singing 'lalala' exploring the emotion happy.

Following this, Chris puts the guitar next to Janda's head so he can put his fingers on the strings and together they start jamming to a new song. Janda is still in pain, but he is also having fun discovering the music. After ten minutes Chris starts to end the session. "Wow Janda, this was great! Let's play a goodbye song now.

Goodbye everyone
Thank you for the music
Thank you for the fun we had

Chris says goodbye to the child and the mother and we leave the room. I turn around to hear Janda say: "Mommy eina [au] my bum, eina". His mother responds by stroking him on his back while softly singing a new song. Both Janda and his mother look less distressed.

"You see", Chris says, "the boy is still in pain, of course he is, but he has also transformed. That is what I like about the music, it does many things at once. For this child I used the music to distract him, to allow him to express his emotion, to explore different emotions and to help him go from anger to smiling, to explore the guitar and to relax in the moment. Also, by making music together mother and son have a shared experience that they can remember, that they can talk about. If she wants she can repeat the song, or make up a song of her own.

"The trick is to know when to play which type of music and that's why you need to observe the child's needs in the moment and change your music accordingly. I'm not just some nice music man that's here for entertainment of the children and the staff. Music therapy is not the same as a clown coming into the hospital. Don't get me wrong, the clowns do great work but they perform for the children. We use music in a therapeutic way. Music can be like a vehicle of change and it represents change for the better. You can go from feeling sad to feeling less sad, from being in pain to getting lost in a world of music, even if it's just for one moment."

APPENDICES

"I have never tried that before,
so I think I should definitely be able to do that"

- Pippi Longstocking -

PHD PORTFOLIO

		Year	Hours	ECTs
PhD training				
PhD courses	NIHES summer school	2012	137	4.9
	Erasmus MC Medical library course “Systematic literature retrieval in PubMed”	2012	8	0.3
	Cochrane course “Developing a Cochrane review” Dutch Cochrane Centre	2012	28	0.5
	Good Clinical Practice (BROK)	2014	28	1.0
	Biomedical English Writing and Communication	2016	56	2.0
	Qualitative analysis	2016		1.3
Congresses, Seminars, Workshops				
Seminars	Weekly meetings Music as Medicine group	2012 – 2016		2.0
	TULIPS grant writing course	2013	28	1.0
	Sophia Research day	2016	8	0.3
Oral presentations	ZonMw presentatie	2014	28	1.0
	Hogeschool Leiden	2015	28	1.0
	Wassenaar International Chamber Music Festival	2016	28	1.0
	Muziek, een waardevol instrument in de zorg	2016	28	1.0
	Training KNO-artsen Albert Schweitzer Ziekenhuis Dordrecht,	2018	28	1.0
	International association for Music and Medicine	2018	42	1.5
Congresses	NICU Music therapy training, Orlando, Florida, USA	2013	28	1.0
	International Congress of Complementary Medicine Research, London, UK	2013	28	1.0
	Nordoff Robbins Conference “Evaluating music therapy: considering value, benefit and impact” London, UK	June 2015	14	0.5
Teaching				
	Supervision students Cape Town	2014 - 2016	56	2.0
	Amsterdam Dance Event - college	2016		2.0
Total Ects				**26.3**

CURRICULUM VITAE

Marianne Jocelyne Elisabeth van der Heijden was born on September 10th, 1984. In 2003 she completed secondary school at the Willem de Zwijger College in Bussum. After spending one year working and travelling in Ghana and South Africa, she went on to study a bachelor's degree in Cultural Anthropology and Sociology of Non-Western Societies, followed by a Master's degree in Medical Anthropology at the University of Amsterdam.

During her anthropology studies Marianne developed an interest for topics such as medical pluralism and integrative medicine: the study on the use, effects and integration of complementary, non-pharmacological and medical philosophies. In 2010 she graduated from her Master's degree in Medical Anthropology at the University of Amsterdam with her thesis "Acupuncture and AIDS in Africa. Exploring the experience, use and integration of acupuncture treatment in Uganda".

Between 2010 and 2012 Marianne worked as a freelance consultant and writer in the international field of integrative medicine on projects for the Trimbos Institute (Utrecht, the Netherlands), the College of Medicine Innovations Network (London, UK), Atrium Medical Center Parkstad (Heerlen, the Netherlands), Maxima Medical Center (Veldhoven, the Netherlands), and Global Advances in Health and Medicine (Portland, OR, USA).

Marianne is a member of several health innovations networks including the Dutch think tank on Integrative Medicine, through which she was in the organising committee of work visits to integrative medicine hospitals in respectively India, China and the East coast of the USA. She has had the opportunity to do a short internship with the Integrative medicine and Health team at the Mayo Clinic in Rochester, Minnesota, USA.

In 2012 she started working for Prof. dr. Hans Jeekel, Prof. dr. Monique van Dijk and Prof. dr. Myriam Hunink as the first PhD candidate on the topic 'Music as Medicine'. Under the supervision of Prof Monique van Dijk (Department of Paediatric Surgery) she was able to perform her clinical research at Red Cross War Memorial Children's Hospital in Cape Town, South Africa.

As of November 2017 Marianne works as a researcher for Prof. dr. Monique van Dijk, professor Nursing Science, department of Internal Medicine at the Erasmus Medical Center in Rotterdam, the Netherlands.

LIST OF PUBLICATIONS

This thesis

Marianne J.E. van der Heijden, Sadaf Oliai Araghi, Monique van Dijk, Johannes Jeekel, M.G. Myriam Hunink
The effects of perioperative music interventions in paediatric surgery: a systematic review and meta-analysis of randomised controlled trials.
PLoS ONE 2015, 10(8): e0133608
(Chapter 3)

Marianne J.E. van der Heijden, Sadaf Oliai Araghi, Johannes Jeekel, Irwin K.M. Reiss, M.G. Myriam Hunink, Monique van Dijk
Do hospitalized premature infants benefit from music interventions? A systematic review of randomised controlled trials.
PLoS ONE 2016, 11(9): e0161848
(Chapter 2)

Marianne J.E. van der Heijden, Alette de Jong, Heinz Rode, Roux Martinez, Monique van Dijk
Assessing and addressing the problem of pain and distress during wound care procedures in paediatric patients with burns
Burns 2018, Feb 44 (1)
(Chapter 4)

Marianne J.E. van der Heijden, Johannes Jeekel, Heinz Rode, Sharon Cox, Joost van Rosmalen, M.G. Myriam Hunink, Monique van Dijk
Can live music therapy reduce distress and pain in children with burns after wound care procedures? A randomised controlled trial
Burns 2018, Jan 30 (in press)
(Chapter 5)

Marianne J.E. van der Heijden, Hiske Mevius, Nicky van der Heijde, Joost van Rosmalen, Sebastian van As, Monique van Dijk
Children listening to music during ER procedures had lower pain scores than children watching cartoons or without distraction: a randomised controlled trial
South African Medical Journal (submitted)
(Chapter 6)

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"I've learned that people will forget what you said, what you did,
but people will never forget how you made them feel"
- Maya Angelou -

Something's got a hold on me (oh it must be love)
Something's got a hold on me right now child (yeah, it must be love)
Let me tell you now
I got a feeling, I feel so strange
Everything about me seems to have changed
Step by step, I got a brand new walk
I even sound sweeter when I talk

- Etta James -
Something's got a hold on me

For the past years I have had the great fortune of "getting a hold of love" - a love for discovering the world of medical science, discovering the effects of music, learning from and about hospitalised children and getting the opportunity to live and work in my beloved South Africa. As you can all attest to, my research on music in medicine has certainly gotten a hold of me.

My dear mentors, colleagues, friends and family, thank you for your endless support, laughter, critical questions, curiosity, friendship and outright awesomeness.
I am the luckiest person in the world to be able to do what I love and to receive your encouragement!

Therefore, true to the topic of my research, I would like to dedicate the following songs to you:

To the children and parents going through difficult times during their stay in the hospital, thank you for your participation in these studies,
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Thula Baba — Soweto Gospel Choir
A Brand New Day — Diana Ross, Michael Jackson
Ooh Child (Things Are Gonna Get Easier) — The Five Stairsteps

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I'm Every Woman — Whitney Houston
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It's A Man's World — James Brown
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I Can See Clearly Now — Johnny Nash

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Metamorphosis I-V — Philip Glass (Solo Piano Album)

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Truth — Kamasi Washington

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Mr Tambourine Man   Bob Dylan
Philna Badenhorst, bokkie ek sal nooit die pret tye vergeet nie!
If You Want To Sing Out, Sing Out   Yusuf/Cat Stevens
Karyn Stuart, for your great spirit and hard work,
Thank You For The Music   ABBA

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Sisters Are Doing It For Themselves   Eurythmics, Aretha Franklin
Love Will Save The Day   Whitney Houston

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Play That Funky Music   Wild Cherry
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Listen To The Music   The Doobie Brothers

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Take Ten   Paul Desmond
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Sweet Dreams Are Made Of This — **Eurythmics**
Repair: Zhouqiao, Ruth, Luca, Simone, Joel, An, Leonard,
Superfly — **Curtis Mayfield**
NA-1723: Esther, Aukje, Hamed, Robin, Ozge, Paola, Jennifer, Ser. Keep on swimming,
The Revolution Will Not Be Televised — **Gil Scott-Heron**
Tuintje Rg-5: Laura en Isabel,
Tuintje In Mijn Hart — **Damaru**
Artur Jaschke,
Seven Nation Army — **The White Stripes**

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Home — **Edward Sharp & The Magnetic Zeros**
Travel So Far — **Joan Armatrading**

Jooske	Everywhere	Fleetwood Max
	Two Of Us On The Run	Lucius
Myrugia	Graceland	Paul Simon
	I feel love	Donna Summer
Marlou	You've Got A Friend	James Taylor
	The Bear Necessities	Phil Harris
Melissa	Don't Worry Be Happy	Bobby McFerrin
	U Remind Me	Usher

Barbara V.	Rafiki	Zap Mama
Emilie	Girls Just Wanna Have Fun	Cindi Lauper
Elburg	What The World Needs Now	Jackie deShannon
Floortje M.	Break My Stride	Matthew Wilder
Esmee	Let The Sun Shine	Hair The Musical
Charnie	Our House	Madness
Viv	Blame It On The Boogie	The Jacksons
Sophie P.	Blister In The Sun	Violent Femmes
Fernande	Inner Ninja	Classified, David Myles
Pepijn	Scatman	Scatman John
Barbara B.	Cornerstone	Benjamin Clementine
Hans (Kluggie)	Disco Dancer	Kiki Gyan
Floor F.	Oh Carolina	Shaggy
Nicole	Sweetness	Pearl and The Beard
Sara B.	Can I Kick It?	A Tribe Called Quest
Roos v. K.	Sweet Disposition	The Temper Trap
Annebeth	Orinoco Flow	Enya
Sake	Midnight Train To Georgia	Gladys Knight & The Pips
Diederik v. D.	I'll Be There For You	The Rembrandts
Koennie	Clap Your Hands	Whilk and Misky
	Pick It Up	Redman
Kat	We Are Family	Sister Sledge
Sarah	Video	India Arie
Leila	Qongqothwane (Click Song)	Miriam Makeba
Emma	Mission To The Sun	Jeremy Loops
Marinke	Under African Skies	Paul Simon
Gute and Theo	C'mon And Swim	Bobby Freeman
Danielsun	Flight Over Africa	John Barry
Marli and Mitch	Klein Tambotieboom	Die Heuwels Fantastisch
Christiaan and Jay	Disco Highlife	Orlando Julius
Peter	Omaha	Counting Crows
The Boys: Rein, Kone, Gav, Reuben, Rox	Only The Wild Ones	Dispatch
De Berries: Roos, Mette,	Club Tropicana	Wham!
Christiaan, Raoul, Scato,	Super Freak	Rick James
Erik, Brechtje, Leonoor,	Without You	Mariah Carey
Floortje, Nard, Lizet,	What Is Love (Baby Don't Hurt Me)	Haddaway
Jochem, Carlijn, Annebeth	I'm Always Here	Jimi Jamison

To my (extended) family, how lucky I am to have you in my life,

Inx	There Will Be Time	Baaba Maal, Mumford & Son
Monique, Amber	The Wolves	Ben Howard
Stephen & Christie	Old Pine	Ben Howard
Meulemannen	Hold On, I'm Coming	Sam & Dave
Van der Heijdens	Dancing In The Street	Martha Reeves & The Vandellas
Evertse Family	Oh Happy Days	The Edwin Hawkins Singers
Selderbeek	Dance To The Music	Sly & The Family
De Wilde	Let's Dance	David Bowie
Antoinette	Vincent (Starry Starry Night)	Don Mclean
Jan-Hendrik	Pata Pata	Miriam Makeba

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Barbara P. C.	Mountain To Move	Nick Mulvey
Boudewien	Mogoya	Oumou Sangare

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Paul	Stand By Me	Otis Redding
Sophie C.	Ain’t No Mountain High Enough	Marvin Gaye, Tammi Terrell

To my parents, Paul, Lotte and the Boyband: Karel, Theo, Jacob en Kees.
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Your Love Keeps Lifting Me Higher	Jackie Wilson
Travelin’ Prayer	Billy Joel
Happy	Pharrell Williams
The Snowman Soundtrack	Howard Blake In The Air
Rusalka Song To The Moon	Antonin Dvorak
To Those We Love	Miriam Makeba

Take Yo' Praise!
(Camille Yarbrough)

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