Music therapy reduces stress and anxiety in critically ill patients: a systematic review of randomized clinical trials

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Abstract

Background: The underlying clinical condition and the ICU environment make critical illness ~~is~~ a stressful event, Although the usual management consists of sedation, non-pharmacological interventions such as music therapy have been suggested for their drug-sparing effect. Aim of the present review is to assess the current evidence on the effectiveness of music therapy in reducing stress and anxiety in critically ill, adult patients.

Methods: A systematic review of publications was undertaken using MEDLINE, CINAHL, Cochrane Library, Scopus, Web of Science, Indice Italiano di Letteratura di Scienze Infermieristiche. We included studies of critically ill patients that assessed any effect of–music therapy on stress and anxiety, which were variably assessed according to each study's definition

Results: 11 studies were included~~, consisting of~~ (10 RCTs and 1 quasi-experimental design), for a total of 959 patients (range 17-373The overall quality of the studies was satisfactory; several potential sources for bias were identified. Music therapy was generally provided as a single, 30'-intervention ranging from 15 to 60'. Only in two studies was the intervention repeated more than once daily. The control groups were standard care, relaxation, headphones with no music or noise-cancelling headphones. Music therapy determined a significant reduction in the levels of anxiety and stress, as assessed by self-reported scales and physiologic parameters Pooled analysis was not performed due to the heterogeneity of the interventions.

Conclusions: Despite significant heterogeneity in trial designs, timing and features of the intervention, music therapy is consistently associated with a reduction in anxiety and stress of critically ill patients.

Trial registration: PROSPERO CRD42018100036, Registered on 1 august 2018

Keywords: music therapy, critical illness, intensive care unit, anxiety

Introduction

Critically ill patients undergo a significant amount of environmental and psycho-physical stress [1]. Indeed, not only is their severe and debilitating underlying clinical condition stressful, but they also are subject to a wide array of stressors, related to the harsh environment in which they are cared and to the procedures to which they undergo, which all have been associated with significant discomfort [2]. Stress itself is a factor able to influence the body homeostasis and to activate (mal)adaptive behavioral, physiological, and cellular responses [3]. Anxiety is a common finding in hospitalized patients, and even more in those who are critically ill. It was suggested that up to 80% of patients in the ICU may suffer from anxiety, especially in those undergoing mechanical ventilation [4]. Of note, despite 20 years of advances in the treatment, critically ill patients still report as stressful events of their stay in the intensive care unit (ICU) factors such as pain, the unfamiliar environment, the loss of interaction with friends and their loved ones, the limitation in movements, the lack of sleep [1,5-10].

The mainstay of therapy to manage the stress response is administration of antipsychotics, analgesics and sedatives, either by IV [11] or the enteral route [12], with the aim of reducing the sympathetic outflow from the nervous system. However, drugs used for this purpose are characterized by significant side-effects, such as hemodynamic impairment, respiratory depression, ileus, delayed weaning from mechanical ventilation, prolonged immobility and ICU-acquired weakness, development of delirium and gut dysfunction, prolonged ICU stay, increased costs, development of post-ICU syndrome (cognitive dysfunction, PTSD, etc.) and long-term disability [13-15].

While the administration of drugs plays an undoubtful role in the management of ICU-related stress, there are a variety of non-pharmacologic interventions and protocols, that have shown to be able to effectively prevent and treat the neuropsychologic manifestations of ICU stay, as recently reviewed [16]. Among such strategies, music therapy (defined as an interpersonal process in which the therapist uses music to help patients improve, or maintain health [17]) has proved effective in the modulation of the stress response, reducing the signs and symptoms of anxiety and promoting relaxation in critically ill patients [18,19].

Several randomized studies have investigated the impact of music therapy in critically ill patients [19-31]. Despite different criteria of patient selection and a heterogeneous array of interventions, all of them suggested a reduction in anxiety and physiologic measures of stress in critically ill patients. A Cochrane Collaboration meta-analysis found that music therapy had a beneficial effect on anxiety in the ICU[32].

However, that study was performed only in mechanically ventilated patients and included also studies that investigated only the changes in hormone levels. While it is represents the main form of support of patients with respiratory failure, mechanical ventilation is reported by patients as one of the most stressful factors in the ICU [33,34]. However, it was shown how up to 1 in 5 critically ill patients may develop agitated delirium requiring some sort of sedation even if they are not subject to mechanical ventilation [35,36], with a much higher risk for the effects of oversedation that may necessitate intubation for airway protection.

The effect of a music therapy intervention on the levels of stress and anxiety in critically ill patients who are not undergoing mechanical ventilation has not so far been summarized in review studies. The aim of the present study is to perform a systematic review of the literature on the effect of music therapy in critically ill adult patients independently of being subject to mechanical ventilation.

Materials and methods

For the present systematic review, the PRISMA statement (preferred reporting items for systematic reviews and meta-analyses) was followed. The PICO (Patient/Intervention/Comparison/Outcome) model was used as the strategy for formulating the research question. The review protocol was registered on the International Prospective Register of Systematic Reviews (PROSPERO CRD42018100036).

Study population

We conducted a systematic review of published randomized, controlled studies of critically ill, adult patients in a medical or surgical ICU, treated with music therapy.

Intervention

All studies in which a music therapy intervention was administered to critically ill patients with the aim of reducing their levels of anxiety, stress, agitation or pain were included in the present review.

Comparator

Our comparators were the group of patients in the studies included who did not receive the intervention.

Outcomes

Randomized controlled trials available in the literature which considered the levels of stress, state anxiety, pain and agitation as outcomes were included; other physiologic outcomes, such as the levels of stress hormones, have not been considered in the current review.

Study identification

A comprehensive bibliographic search strategy was developed. The search accessed the following databases: PubMed, CINAHL, Cochrane Library, Scopus, Web of Science, ILISI – Indice Italiano di Letteratura di Scienze Infermieristiche, from inception to the cutoff date of April 30th, 2018. We restricted our search to publications in English or Italian. To supplement our search, we also manually screened the reference list of every paper to identify additional potentially eligible studies.

Search strategy

The following key-words were used, alone or combined with appropriate boolean operators, to search the different databases: music, “music therapy”, “intensive care unit”, “non-pharmacological interventions”, anxiety, stress, pain, “vital signs”, nursing, “critical care” “critically ill patients”, “critical illness”. A similar search was also performed using the PubMed MeSH thesaurus.

We excluded studies enrolling patients less than 18 years old or patients with known psychiatric disorders and studies investigating interventions other than music therapy (such as natural sounds) or whose outcome was the analysis of biochemical pathways (such as stress hormones).

Study selection and quality assessment

Two authors (TS, ST) independently screened the studies selected from the search strategy to identify potentially eligible studies. Studies considered to be potentially eligible then underwent full-text review. In case of disagreement the authors reviewed the article in question together until they reached a consensus. The Phisiotherapy Evidence Database (PEDro) scale [37] was used to assess the methodological quality of the studies included.

Data extraction and synthesis

Two authors (TS, ST) independently extracted data from all the included studies. A specific data sheet was created to record the following information: author, year, design of the study, inclusion and exclusion criteria, population, intervention, outcomes, potential sources of bias, adverse effects of the intervention.

Definition of study outcomes

The self-reported scales of anxiety used to assess the effect of the music intervention differed among the different studies. Some authors [20-22,27,31] used the short version of the Spielberger State-Trait Anxiety Inventory Scale (STAI) [38] as the outcome measure for anxiety, which is composed of six out of the 20 items of the full version. Some studies [21-23,28] also considered the effect of music therapy on physiologic ~~vital~~ parameters such as the average blood pressure, respiratory rate and heart rate. Other studies used the Faces Anxiety scale [25], or the 100-mm Visual Analog Scale [24,30]. Agitation and sedation were assessed as the intensity and frequency of sedative drugs administered [30], with the Richmond Agitation Sedation Scale (RASS) [23], or with the Ramsay Score [26]. Pain was assessed with the numerical rating scale [23,25].

Results

A total of 511 citations were initially identified, of which 493 were subsequently excluded. The search strategy identified 18 studies, of which 17 randomized controlled clinical trials (four with a cross-over design) and one quasi-randomized trial (Figure 1) .

Excluded studies

Seven out of the 18 studies selected were excluded from the systematic review (six RCTs and one randomized crossover trial), as some assessed the effects of nature sounds (rain, wind, forest sounds) on the levels of anxiety and stress in mechanically ventilated patients [39], some other investigated the possible biochemical pathways and plasma levels of stress mediator, such as the modification in plasma levels of epinephrine, norepinephrine, cortisol and corticotropins [40], the levels of IL-6, growth hormone, epinephrine and dehydroepiandrosterone [41] the daily excretion of free urinary cortisol [42] or the plasma levels of cortisol, prolactin and adrenocorticotropic hormone[43] Two studies [23,24] were excluded after abstract retrieval, as they have been published in French and Chinese, respectively.

Included studies and outcomes reported

In total, 11 studies (10 RCTs and one quasi-experimental) met the inclusion criteria and were included in the systematic analysis. Study sizes ranged from as small as 17 to as large as 373 patients (median sample size 60 patients), for a total of 959 patients. Table 1 describes the main outcomes of the different studies included. Table 2 summarizes the inclusion and exclusion criteria, the study design and setting and the population enrolled. Table 3 reports the types of music therapy interventions and the main findings, as well as the possible sources of bias of each study.

Evaluation of the quality of the evidence

The quality of the evidence coming from each study was assessed with the PEDro checklist. Since none of the studies included in the present review was blinded (due to the intrinsic characteristic of the intervention), the highest possible score on the scale is eight (out of the theoretical 11 items). The summary of the quality of the assessment and the items on the PEDro scale of each study is presented in table 4.

Effect of music therapy in state anxiety

No statistically significant baseline differences between the groups were found in any the studies included in the present review. All the studies reported a significant reduction in the level of anxiety at the end of the music intervention (Table 3). In all the studies, music therapy led to an increase in the sedation level or a reduction in the amount of sedatives administered, as well as to changes in physiologic parameters such as heart and respiratory rate and blood pressure. A lower level of pain was reported in the groups exposed to music.

Adverse effects

Music therapy is generally considered a safe intervention with no side effects. Nevertheless, none of the studies included in the current review specifically investigated the occurrence of adverse effects. Only two studies [26,27] report mortality rates in patients randomized to music therapy or control, and both did not find any statistically significant difference.

Potential sources of bias

All the trials included in the current review present some sources of bias, the main being the lack of blinding, which however is unavoidable in music medicine studies that use subjective outcomes. Moreover, the majority of the studies used a single, time-limited music intervention [19-21,27,31]. Moreover, many studies were of limited sample size [21,22,25,26,29,31]; some are exposed to the presence of a halo-effect in the self-assessment of anxiety or stress, given the cross-over design [21] or a short interval between the withdrawal of sedation and the music intervention [28]. In some studies, patients had a low baseline level of anxiety and discomfort, and the confounding effect of sedation and analgesia could not be ruled out [25,29]. Moreover, no long-term assessment of patient status has been performed in any of the studies.

Discussion

The present systematic review suggests that music therapy is associated with significant reductions in self-reported scales of anxiety and physiological parameters used as proxy of stress in critically ill patients who are or are not treated with mechanical ventilation; the mechanism of action of the intervention was not investigated in the studies included. These results were achieved even when music therapy was provided as a short, single intervention, and are consistent in the different studies included in the analysis.

Unlike a previous meta-analysis [32], we decided to include in our review also studies which included critically ill patients who were not receiving mechanical ventilation. It is known that sedation is even more problematic in these patients, given the additional risk of respiratory depression and the consequent need for securing the airway as compared to patients who are already mechanically ventilated [35]. We think that the current review widens the knowledge on the possible positive effects of music therapy in critically ill patients.

We chose not to perform a formal meta-analysis of the finding of the studies included, as they differed widely in terms of the features of the music intervention, the time during the course of ICU stay in which it was administered, its duration, as did the outcomes considered and the tools used to assess the effects of music therapy. Indeed, the lack of a meta-analytic approach is also the main limitation of the current review, which can impact the validity of the findings.

Despite the heterogeneity of the interventions, the results of the different studies still consistently show a significant effect of music therapy on self-reported measures of anxiety and physiologic parameters indicating stress in critically ill patients with or without mechanical ventilation. The quality of the evidence, as evaluated by the PEDro scale, is satisfactory, as all the studies are methodologically sound in terms of patient selection and administration of the intervention. However, the intrinsic characteristics of music interventions make the lack of blinding in participants, therapists and assessors unavoidable.

Potential effects of music on stress and anxiety

Music has an intrinsic effect on the mind and feelings of persons. In consideration of its properties, it has long been considered as a therapeutic tool. Music therapy is defined as listening to music with the aim of a change in the emotional or physical state of health, and it has been used in a wide range of pathologic conditions, with special attention in the perioperative period and during ICU stay [27,41,43-48].

From a technical and scientific point of view, music is defined as a complex network of organized sounds, characterized by various features, such as the rhythm, melody, harmony and time. It can be used as a therapeutic tool with the aim of an interruption in the stress response. Listening to music was shown to lead to a reduction in the level of anxiety through a complex array of effects in a neurohumoral pathway that involves the brain and autonomic system at several conscious and uncoscious levels, with modifications in the production of endorphins, cytokines and endogenous opiates [27,41,49-51].

Music therapy has proven effective in the treatment of postoperative pain[46,52,53], in reducing the need of sedation and analgesia during surgical and endoscopic procedures [45,54-57], in reducing the levels of anxiety in critically ill mechanically ventilated patients [20-22,28], for the reduction of endogenous stress levels after myocardial infarction [50,58]. Two meta-analyses reported positive effects of music therapy in reducing the levels of anxiety in hospitalized patients [59,60]; however, the authors pointed out how the different methodologies of music administration and the limited power of the majority of the studies made the comparisons difficult.

Few studies have investigated the effects of music listening in the critical care setting. This intervention was shown to be associated with a reduction in self-reported levels of anxiety and reduced values of respiratory rate, heart rate and blood pressure [20-22,48,61]. It was shown in physiologic studies how heart and respiratory rate may synchronize with the characteristics of the music to which one listens, mainly through an activation on the autonomic system [62]. Although reactions to music are considered subjective, several studies suggested that cardiorespiratory variables increase with faster tempo, independent of individual preference [63]. It was recently shown how music emphasis and rhythmic phrases are tracked consistently by physiological variables such as skin vasomotor tone, mid-cerebral artery blood flow, R-R intervals on the EKG, and blood pressure. Autonomic responses are synchronized with music, which might therefore convey emotions through autonomic arousal during crescendos or rhythmic phrases, both in music-experienced and in naïve listeners [64].

Characteristics of the studies included in the current review

Despite the consistent finding of reduced levels of anxiety and stress after a music therapy session, the studies differed significantly regarding the sample size and the time during the ICU stay in which the intervention was performed. Moreover, the duration of the intervention was also different among the studies, as was the possibility for the intervention to be repeated over time. In particular, the majority of studies used a single-intervention, in six of which [19-22,27,31] the duration was 30', in one [29] it lasted 45', in the study by Korhan et al. [28] it was a 60' intervention, in one [25] the duration was 15' ~~and in another 20'~~. Only in two of the studies included was the intervention administered more than once. Dijkstra et al [26] administered 30' music therapy three times in a 48h-period, while Chlan et al. [30] designed a "self-initiated music listening" study, thereby allowing patient to decide whether and when to start listening to music, for as long as the whole day; nurses and researches asked each patient to listen to the music at least twice per day, for a period of up to 30 days.

The studies included in the present review also show differences in the control group. All the studies but two have one control group; Chlan et al. [30] and Han et al. [27] have two different controls. Moreover, the control group was either a placebo intervention (headphones and music player with no music playing) [22,25,27,30], or no music.

Moreover, the music therapy intervention was heterogeneous in the various studies. It was a playlist selected by the researchers and consisting of classic music [26,28] or a generally-defined "relaxing" music [29], or the patients had the possibility to choose among playlists of different genres [18,20-22,25,27,31].

The investigations included in the current review differ in the inclusion criteria: seven studies only enrolled mechanically-ventilated patients [20-22,26-28,30], of which the studies by Lee et al [22], Wong et al [21], Dijkstra et al [26] and Korhan et al [28] require a patient-triggered mode. The studies by Cooke et al [25], ~~Jaber et al~~ Chan et al [19], Su et al [29] included critically ill patients independently of the presence of mechanical ventilation, while the study by Lee et al [31] only included critically ill patients who were not mechanically ventilated.

Clinical implications

Despite the increasing interest of this field of research, the exact role of music therapy in the care of critically ill patients has yet to be defined. The studies included in the present review consistently

showed how music is an inexpensive, easy to administer intervention with likely no adverse effects, which may reduce anxiety and sedation compared with usual care both in patients who are mechanically ventilated and in those who are not. However, despite these beneficial effects, this kind of non-pharmacologic intervention is still rarely observed in the daily practice. Even if we acknowledge that further studies are required, particularly with regards to the number and the duration of music sessions to be administered and the impact on longer-term outcomes such as the development of delirium and post-traumatic stress symptoms, the current evidence seems sufficient to consider the ~~suggest the routine~~ prescription of music therapy for patients in the intensive care unit. Administration of music therapy could be triggered by a nursing assessment of either elevated CAM ICU scores, or patient reported anxiety.

Limitations

As mentioned earlier, one of the main limitation of the current study is the lack of formal meta-analysis of the findings, which can impact the validity of the findings. We chose not to perform a forma meta-analysis of the results of the randomised trials because of their significant heterogeneity in terms of design, type and duration of intervention. The evidence arising from this review has to be considered in the context of the possible bias of the trials included in the analysis, which may preclude the generalizability of the results. All the studies but one [30] are single-centre trials with limited sample size; several studies [19,21,22,24,27,29,31] have been conducted in Asia and may suffer the confounding effect of cultural aspects; only few studies [20-22,24,25,27,30] allowed the patients included to choose the type of music they wanted to listen to; the use of physiologic proxies of anxiety and stress, such as heart rate or blood pressure, may be influenced by other factors (especially sedatives, vasoactive and antiarrhythmic drugs) whose administration was non-protocolized or controlled.

Despite the abovementioned limitations, the findings of reduced state anxiety and physiologic parameters of stress were consistent among the different studies, and similar to what was found when the analysis was restricted to mechanically-ventilated, critically-ill patients [32] and in other categories of non-critically ill patients (namely, coronary heart disease patients [65], cancer patients [66], and pre-surgical patients [67]).

Conclusions

In conclusion, this systematic review suggests how music listening may have beneficial effects on reducing state anxiety as well as limiting the physiological stress response, as assessed by heart and respiratory rate, and blood pressure in critically ill patients with and without mechanical ventilation. Since music therapy is an easy intervention to implement, we suggest to consider among the non-pharmacological strategies for anxiety and stress management to critically ill patients. Further studies are warranted to investigate the number and the duration of music sessions to be administered, as well as the impact on more clinically relevant end-points such as the long-term development of delirium and post-traumatic stress symptoms.

Key messages

- Critical illness is associated with a significant amount of stress, both because of the underlying clinical condition and for the ICU environment. Moreover, up to 80% of patients in the ICU develop anxiety.
- Even if mechanical ventilation is one of the most important stressors, also patients in the ICU who are not undergoing mechanical ventilation can develop stress and agitation.
- Although the usual management of the stress response and anxiety consists of sedation, neuroactive drugs used for this purpose are characterized by significant side-effects
- Despite significant heterogeneity in trial designs, timing and features of the intervention, we found that music therapy was consistently associated with reductions in self-reported scales of anxiety and physiological parameters used as proxy of stress in critically ill patients who are or are not treated with mechanical ventilation.

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Notes

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1 Table 1 – Outcomes of the studies included in the systematic review

OUTCOMES									
STUDY	**PHYSIOLOGICAL PARAMETERS**				**ANXIETY**	**PAIN**	**AGITATION**	**STRESS**	**OTHER OUTCOMES**
	BP	**HR**	**RR**	**SpO_2**					
Chlan et al (1998)		•	•		•			•	Relaxation
Wong et al (2001)	•		•		•				
Lee et al (2005)	•	•	•		•				Relaxation, personal satisfaction
Chan et al (2008)	•	•	•						
Cooke et al (2010)					•	•			Discomfort
Dijkstra et al (2010)	•	•	•		•		•	•	
Han et al (2010)	•	•	•	•	•			•	Relaxation
Korhan et al (2011)	•	•	•	•	•				
Su et al (2012)	•	•	•						Relaxation, sleep, personal satisfaction
Chlan et al (2013)					•		•		
Lee et al (2017)	•	•			•			•	Cortisol levels

2 BP: Blood pressure; HR: heart rate; RR: respiratory rate; SpO_2: Peripheral oxygen saturation.

3

1 Table 2 – Summary of study designs

STUDY	SETTING AND COUNTRY	DESIGN	INCLUSION CRITERIA	EXCLUSION CRITERIA	SAMPLE SIZE	MEAN AGE	MALE SEX
Chlan et al (1998)	Multi-centre 4 urban ICU USA	RCT	Mechanically-ventilated, critically-ill patients Age ≥18 Alert, mentally competent, adequate hearing, English as primary language Not receiving continuous intravenous sedation	Simmetrical to inclusion	n = 54 (M: 27; C: 27)	57.1 (range: 18-89)	41%
Wong et al (2001)	Single-center Urban ICU Hong Kong	crossover RCT	Mechanically-ventilated, critically ill patients, undergoing assisted, self-triggering ventilation Age 18-85, Chinese nationality, understanding Cantonese or English, able to communicate by holding up fingers Alert, mentally competent, without hearing problems Not receiving any continuous intravenous analgesia, hemodynamically stable	Simmetrical to inclusion	n = 20 (M: 20; C 20)	58.3 (SD: 15.5)	75%
Lee et al (2005)	Single-center Urban ICU Hong Kong	RCT	Mechanically-ventilated, critically ill patients, undergoing assisted, self-triggering ventilation Alert, no psychiatric illnesses, able to hear, able to obey to researcher's command	Hemodynamically unstable patients	n = 64 (M: 32; C: 32)	69.4 (SD: 15.2)	28%
Chan et al (2008)	Multi-centre 3 urban ICU Hong Kong	Quasi-experimental	Critically ill patients Age >18, understanding Cantonese or Mandarin, mentally alert and competent, able to communicate by body gestures, without hearing defects	Simmetrical to inclusion	n = 101 (M: 101)	Not stated	67.3%
Cooke et al (2010)	Multi-centre 2 urban ICU Australia	crossover RCT	Critically ill, postoperative patients with scheduled ICU admission, both ventilated and non-ventilated; Expected ICU stay >8h, able to respond to pre- and post-turning discomfort and anxiety questions.	Neurosurgery; Age <18; Did not like music; Impaired hearing; difficulty wearing earphones	n = 17 (M: 17; C: 17)	72 (range: 19-87)	71%
Dijkstra	Single-center	RCT	Critically ill, mechanically-ventilated patients, undergoing self-	Simmetrical to	n = 20	52.2	60%

et al (2010)	3 Urban ICU Netherlands		triggering ventilation. No hearing impairment, continuous dedative infusion (midazolam or propofol), Ramsay score: 2-4	inclusion	(M: 10; C:10)	(SD: 15.3)	
Han et al (2010)	Single-center Urban ICU China	RCT	Chinese nationality, understanding Mandarin; Alert, mentally competent, able to communicate by holding up fingers, responsive to researchers' questions; Mechanically-ventilated, undergoing synchronised intermittent mandatory ventilation and/or pressure control mode; Not receiving any continuous intravenous analgesia or sedative; No previous experience of music intervention.	Hearing impairment or skull injury that affect listening to music and use of headphone Patients on CMV or CPAP mode ventilation.	n = 137 (M:44; C:49; P:44)	46.2 (range: 18-84)	43.8%
Korhan et al (2011)	Single-center Urban ICU Turkey	RCT	Turkish nationality, age 18-70; Hemodynamically stable, mechanically-ventilated in pressure support mode; No psychiatric or neurological illnesses, not receiving inotropic support, not taking any neuromuscular blocker and antihypertensive drug; able to hear and with Glasgow Coma Scale Point 9 or above.	Simmetrical to inclusion	n = 60 (M: 30; C:30)	45.3 (SD 14.7)	53.3%
Su et al (2012)	Single-center Urban ICU Taiwan	RCT	Age>18; Acute Physiology and Chronic Health Evaluation II score ≤25; ability to communicate in either Mandarin or Taiwanese; Conscious and clear, length of ICU stay > 24 hours Arterial catheter inserted.	hearing impairment; physical restraint; alcoholism; infectious disease; haemodynamic instability	n = 28 (M: 14; C: 14)	61.7 (SD 9.8)	60.7%
Chlan et al (2013)	Multi-centre 12 ICU 5 urban hospitals USA	RCT	Mechanically-ventilated patients for acute respiratory failure; Alert, participating in their daily care routines, appropriately following commands, cognitively intact to participate in the consent process; Adequate or corrected vision and hearing.	aggressive ventilatory support, vasopressors, unresponsive or delirious, chronic ventilator support prior to hospitalization, documented mental incompetence	n = 373 (M: 126; P: 122; C: 125)	59.2 (SD 14.4)	48.3%

Lee et al (2017)	Single-center Urban ICU Taiwan	RCT	Critically ill patients, admitted to the ICU for >24h Age 18–85, understanding the study purpose, able to understand and communicate in Mandarin Chinese, Taiwanese (Southern Min), or both; Conscious and mentally clear, able to communicate using body gestures, writing, or both	Impaired hearing, skull injury restricting the use of headphones, Use of physical restraints, alcoholism, infectious disease, hemodynamic instability, Treatment with continuous intravenous analgesic or sedatives, or cortisol	n = 85 (M: 41; C: 44)	59.5 (SD: 9.1)	43.5%

1 ICU: Intensive care unit; RCT: randomized controlled trial; M: music therapy group; C: control group; P: placebo group; SD: standard deviation.
2

1 Table 3 – Comparison of interventions and outcomes and results

STUDY	INTERVENTION	CONTROL	OUTCOMES	RESULTS
Chlan et al (1998)	30' music tape through headphones via portable cassette player Choice among 4 non-lyric playlist (60-80 bpm, New Age, country, religious, classical)	30' rest period (Closing blinds, dimming lights, Do-Not-Disturb sign on the door)	State Anxiety: 6-item version of the Spielberger State-Trait Anxiety Inventory Scale (STAI-6), at baseline and after 30' Stress and agitation: heart rate and respiratory rate, at baseline, every 5' during assigned treatment and 5' after the end	Statistically significant difference in posttest state anxiety between groups: mean value 10.16 (M) vs. 16.15 (C), p<0.001 Reduction of heart and respiratory rate over time in both groups, with greater reduction in Music group
Wong et al (2001)	30' music tape through headphones Choise among a collection of 7 cassettes of relaxing, Chinese or Western music (Chinese folk song, music played by Chinese instrument, Chinese music played by Western instrument, Buddhist music, Western classic, Western movie music, piano music)	30' rest period, at least 6-hours apart from music intervention (drawing curtains, dimming lights)	Anxiety: 6-item version of the Spielberger State-Trait Anxiety Inventory Scale (STAI-6), at baseline and after 30' Stress and agitation: mean blood pressure and respiratory rate, at baseline, every 5' during assigned treatment	Subjects in both conditions had reduced state anxiety scores over time; music therapy was more effective than a rest period in reducing state anxiety (C 49.67±4.82 vs. M 38.67±5.23, p<0.01) Reduction of blood pressure and respiratory rate over time in both groups, with greater reduction in Music group
Lee et al (2005)	30' music tape through CD-player and headphones Music selected by the patient from researcher collection (Chinese classical music, religious music, Western classical music, music of natural sounds).	30' placebo, through CD-player and headphones but without CD playing.	Anxiety: 6-item version of the Spielberger State-Trait Anxiety Inventory Scale (STAI-6), at baseline and after 30'; Behavioural checklist developed by the researcher recorded during intervention Stress and agitation: heart rate, systolic and diastolic blood pressure and respiratory rate, at baseline, and after the intervention Self-reported satisfaction after the intervention	Subjects in the music group had reduced state anxiety scores over time: 15.4±4.6 vs. 13.8±2.8, p=0.048; state anxiety in the control group was similar to baseline value Respiratory rate, heart rate, systolic and diastolic blood pressure were all significantly lower than baseline in the music group, while only diastolic blood pressure was reduced after the intervention in the control group.
Chan et al (2008)	30' of music through headphones and mp3 or CD player Music chosen based on previous studies: relaxing music defined primarily as being low-pitched, having a simple and direct musical rhythm and having a tempo of approximately	No control group	Demographic variables: age, gender, religion, education level, previous or current use of relaxation techniques. Physiological parameters: Systolic and diastolic blood pressure, heart and respiratory rate	A higher therapeutic effect of music (significant reduction in heart and respiratory rate and blood pressure) was found in female patients, patients older than 65 years, and mechanically-ventilated patients. A lower effect was found in males and in

	60–80 bpm. Music used: Chinese classical music, religious music and Western classical music and Jazz		Data recorded at baseline, 15' and 30'	those with higher levels of education.
Cooke et al (2010)	60' of music through CD player and headphones before and during the turning procedure. Music chosen preoperatively from a selection of classical, jazz, country and western, new age, easy-listening or 'other' (mostly by contemporary artists) music provided by the researchers.	15' of headphones and CD player with no music playing.	Discomfort: measured by Numerical Rating Scale (NRS) Anxiety: measured through Faces Anxiety Scale (FAS) Both measured 15' before and 15' after intervention	No significant reduction of discomfort (M: 2.7 (1.7; 3.7) vs. 3.6 (2.0; 5.2) and C: 3.4 (2.2; 4.6) vs. 2.8 (1.3; 4.2); both p>0.05) or anxiety in both groups.
Dijkstra et al (2010)	3 sessions spread over 2 days, each lasting 30' of music through mp3 player and headphones. between 10 am and noon and between 8 and 10 pm Classical and easy-listening music chosen by patient or caregiver.	Control: 3 sessions spread over 2 days, each lasting 30' of rest period	Stress: systolic, diastolic and mean blood pressure, heart and respiratory rate, assessed at baseline and 5',10',20',30' and 60' from the beginning of the intervention. Sedation: Ramsay score, at baseline and at the end of the intervention.	No differences in blood pressure, heart or respiratory rate between groups. Significantly higher level of sedation in music group (Ramsay M 3.8±0.8 vs. 4.3±0.7; C 4.6±0.9 vs. 4.0±1.4; p=0.015)
Han et al (2010)	30' of music through headphones and mp3 player through foam-lined headphones. Music chosen by patients from the investigator's collection. 4 categories of relaxing music, including Western classical music, Western light music, Chinese traditional music and Chinese folk.	Placebo: patients wearing foam-lined headphone and resting with their eyes closed for 30', no music playing. Control: patients resting with their eyes closed for 30', with neither headphone nor music.	Anxiety measured by the Chinese version of the Spielberger State-Trait Anxiety inventory Scale (C-STAI), at baseline and at the end of intervention. Stress and relaxation: heart and respiratory rate, blood pressure, arterial oxygen saturation, at baseline and at 5' intervals.	Significant differences in heart and respiratory rate, systolic and diastolic blood pressure, and C-STAI, but not in SaO2 among the three groups Greater mean differences in music group (Delta pre-post M 10.7±6.82 vs. P 3.34±5.37 vs. C 0.76±4.97; p<0.001). Significant reduction in stress response (heart respiratory rate) over time in music group while a significant increase in heart rate and respiratory rate over time in control, no significant change over time in headphone.
Korhan et al (2011)	60' of music through mp3 player and disposable headphones Classic music (60-66 bpm), at least 30' after stopping of intravenous sedation.	60' of rest, standard care	Anxiety: physiological measurements as systolic and diastolic blood pressure, pulse rate, respiratory rate and oxygen saturation, at baseline, 30', 60' and 90'.	M: significantly lower respiratory rates, and systolic and diastolic blood pressure, than C; the decrease improved progressively at 30', 60' and 90', indicating a cumulative dose effect; No differences in heart rate and oxygen

				saturation.
Su et al (2012)	45' of music through CD player and headphones during nocturnal sleep time. Four pieces of sedating piano music composed by two of the authors; volume: 30-40 dB, 60-80 bpm).	Control: no music listening	Stress and relaxation: heart and respiratory rate, mean arterial pressure, at baseline and at 5' intervals Sleep quality: polysomnography and validated questionnaires (Verran and Synder-Halpern Sleep Scale)	Improved polysomnography quality of sleep in music group (shorter N2 and longer N3 sleep), and improved self-reported sleep quality, Music group had significantly lower heart rates than control
Chlan et al (2013)	Standard CD/MP3 player with comfortable, noise-cancelling headphones with a starter set of 6 CDs (relaxing music played on piano, harp, guitar, and Native American flute) Within 24h, the music therapist completed a music preference assessment on each patient using a specific tool Music offered at least twice per day (when feeling anxious and/or to provide relaxation), with self-initiation encouraged	Placebo: "self-initiated" use of noise-cancelling headphones whenever they wanted to block out ICU noise or have some quiet time. Control: normal care	Anxiety: 100mm visual analog scale (VAS-A) Sedation: Sedation intensity and sedation frequency scores	Patients in listened to music for a mean (SD) of 79.8 (126) minutes/day The intervention decreased anxiety and sedative exposure over time more effectively than usual care or placebo (noise-cancelling headphones). Patients in M group had 19.5 points lower VAS-A than usual care (p=0.003), as well as reduced sedation intensity by 0.18 points/day (p=0.05) and reduced frequency (0.21 points/day) vs. C and reduced sedation frequency (0.18 points/day) vs P (p=0.04).
Lee et al (2017)	30' music listening through mp3 player and headphones between 4-4.30 pm Music chosen by patients among researchers catalogue of slow-beat (60-80 bpm), relaxing music: Western classical music, Chinese classical music, music of natural sounds, or religious music	30' of rest between 4-4.30 pm; headphones with no music playing	Anxiety: measured as serum cortisol levels (objective indicator) and as the Chinese version of the Spielberger State-Trait Anxiety inventory Scale (C-STAI) and the Visual-Analogue Scale (VAS-A) scores (subjective indicators). Stress: heart rate and blood pressure.	Significant better values for all posttest measures and for pre–post differences for music as compared to control (C-STAI M 57.2±7.64 vs. 51.5±5.1, C 57.2±5.8 vs. 56.2±5.6, p<0.001; VAS-A STAI M 57.2±9.2 vs. 49.6±8.1, C 58.0±8.2 vs. 56.1±9.2, p<0.001) except for diastolic blood pressure

BIS: bispectral index; RASS: Richmond agitation-sedation scale; M: music group; C: control group; P: placebo group

Table 4 - Quality assessment of the included trials using the PEDRO scale

Study	1	2	3	4	5	6	7	8	9	10	11	Total
Chlan et al (1998)	✓	✓	✓	✓				✓	✓	✓	✓	8
Wong et al (2001)	✓	✓	✓	✓				✓	✓	✓	✓	8
Lee et al (2005)	✓	✓	✓	✓				✓	✓	✓	✓	8
Chan et al (2008)	✓		✓					✓	✓	✓	✓	6
Cooke et al (2010)	✓	✓	✓	✓					✓	✓	✓	7
Dijkstra et al (2010)	✓	✓	✓	✓						✓	✓	6
Han et al (2010)	✓	✓	✓	✓				✓	✓	✓	✓	8
Korhan et al (2011)	✓	✓	✓	✓				✓	✓	✓	✓	8
Su et al (2012)	✓	✓	✓	✓				✓	✓	✓	✓	8
Chlan et al (2013)	✓	✓	✓					✓	✓	✓	✓	7
Lee et al (2017)	✓	✓	✓	✓				✓	✓	✓	✓	8

1: eligibility criteria and source of participants; 2: random allocation; 3: concealed allocation; 4: baseline comparability; 5: blinded participants; 6: blinded therapists;7: blind assessors; 8: adequate follow-up; 9: intention-to-treat analysis; 10: between-group comparisons; 11: point estimates and variability.

Figure legends

Figure 1 Flow chart of the study selection process. CINAHL: Cumulative Index to Nursing and Allied Health Literature; ILISI: Indice della Letteratura Italiana di Scienze Infermieristiche.