The Influence of Music and Anxiety on Weaning from Mechanical Ventilation

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Dedication

This dissertation is dedicated to my patients and their families who have so generously let me be a part of the most tragic yet precious times of their lives. Critical illness is a journey that many do not understand but far more will be so unfortunate to experience. As a nurse, I am honored to not only touch the lives of those I serve, but to also be greatly impacted by the lessons and insights provided to me by the patients I encounter.

Abstract

Background: Mechanical ventilation is an invasive, life supportive treatment modality for respiratory failure that can heighten anxiety and elicit a psychophysioloical stress response in critically ill patients. Weaning, a gradual decrease in ventilator assistance, which leads to termination from ventilator support, requires increased respiratory effort that can exacerbate the stress response and prolong the need for mechanical ventilation. Timely, effective weaning is critical to decreasing the economic and personal impact of mechanical ventilation. Music is an integrative, holistic, cost-effective intervention that has been shown to decrease the psychophysiological symptoms of mechanical ventilation. However, few studies have evaluated the influence of music intervention specifically during weaning from mechanical ventilation.

Objective: This dissertation project sought to determine the influence of music and anxiety on the weaning process in patients receiving mechanical ventilator support.

Methods: The purpose of this dissertation was to: 1) conduct a narrative literature review to describe the state of the science on music as an integrative intervention during mechanical ventilation and ventilator weaning, and to identify current gaps in knowledge regarding use of music intervention for symptom management, specifically during weaning; and 2) to examine the relationship among music, anxiety, and ventilator weaning to better understand factors that facilitate successful weaning by completing a secondary data analysis from a

randomized clinical trial that tested a self-direct music intervention with mechanically ventilated patients.

Results: The narrative review illustrated that: 1) the duration, frequency, and timing of music intervention varied greatly across studies; 2) consensus for the most effective appropriate means for implementing music intervention could not be determined from the literature; 3) the desired level of patient wakefulness deemed appropriate by investigators for study inclusion varied, and it is not known if music intervention is more effective if the patient is more awake; 4) all studies implemented music styles that were considered “relaxing”, but an assortment of music genres were used; 5) music intervention was found to reduce the physiological signs of anxiety such as respiratory rate, heart rate, and blood pressure for patients undergoing mechanical ventilation; 6) music intervention can decrease the need for sedatives during mechanical ventilation; 7) music intervention is effective in reducing self-reported anxiety during mechanical ventilation; 8) the connection between biomarkers and clinical observations of anxiety like increased heart rate and respiratory rate remains unclear; 9) both patients and nurses expressed positive feelings towards music intervention.

The results of the secondary data analysis showed that: 1) music listening (PDM) and anxiety were not statistically significant predictors of time to first weaning trial after enrollment; 2) music listening (PDM) and anxiety were not statistically significant predictors of duration of weaning trials during the study

period; 3) subjects with higher illness severity were more likely to experience a shorter time to first weaning trial after study enrollment; 4) individuals with a tracheostomy were able to tolerate longer weaning trials; 5) the duration of weaning trials increased progressively from the enrollment day; 6) subjects who did not attempt a weaning trial during the study were more likely to die during their hospitalization than subjects who attempted at least one weaning trial; 7) subjects with a history of experiencing mechanical ventilation in a prior hospitalization were more likely to undergo a weaning trial; 8) the majority of the subjects that attempted at least one weaning trial during the study protocol, did so within the first 24 hours of study enrollment.

Conclusion: The narrative review demonstrated music can decrease the psychophysiological symptoms and reduce sedative exposure in patients undergoing mechanical ventilation which could potentially improve patient satisfaction and promote overall recovery. However, there is a noticeable lack of research that examines the influence of music intervention specifically during ventilator weaning.

The secondary data analysis found that music (PDM) and anxiety were not significant predictors of time to first weaning trial or duration of weaning trials. However statistically significant findings included subjects with higher illness severity (APACHE III) were more likely to experience a shorter time to first weaning trial after study enrollment, for each weaning trial a subject underwent per day, their weaning trial increased in duration, and subjects with

tracheostomies had weaning trials that were longer in duration than those who were orally intubated.

Recommendations for Future Research: This dissertation study was the first study in which a large randomized clinical trial data set was used to examine the influence of music intervention and anxiety on the physiological and psychological stressors that prolong weaning and delay extubation. Music may be a valuable non-pharmacological, adjunctive intervention to reduce burdensome symptoms, but additional studies with prospective designs and adequately powered sample sizes are needed to advance the science in this field. Continued research should aim to develop a better understanding of the most effective and appropriate means for implementing music intervention to facilitate weaning in order to determine if music intervention can favorably impact important clinical factors such as time to weaning trials, length of weaning trials, successful weaning readiness, and ultimately, total ventilator days and ICU length of stay.

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List of Abbreviations

ACCM – American College of Critical Care Medicine

APACHE – Acute Physiology, Age, Chronic Health Evaluation

ASHP – American Society of Health-System Pharmacists

FiO_2 – Fraction of inspired oxygen

HP – Noise Canceling Headphones

ICU – Intensive Care Unit

LTACH – Long term acute care hospital

MV – Mechanical Ventilation

NINR – National Institute of Nursing Research

NRSA – National Research Service Award

PDM – Patient Directed Music

PEEP – Positive End Expiratory Pressure

PRISMA – Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PTSD – Post traumatic Stress Disorder

SCCM – Society of Critical Care Medicine

UC – Usual Care

VAS-A – Visual Analogue Scale for Anxiety

BACKGROUND ON THE DISSERTATION FORMAT

Selection of the Manuscript Option to meet the Dissertation Requirements

The manuscript option was chosen to meet the requirements for a dissertation to assist the author in developing a publication record to address a training goal of developing into an independent, extramurally funded clinical researcher in critical care in a timely, and efficient manner.

Chapter 1 – Introduction. This dissertation begins with an introductory chapter that provides background information essential to illustrating the foundation for the topic as well as presents an overall unifying theme to the contents. The overall need and significance of the research as well as the originality of the study and the results are discussed.

Chapter 2 – Specific Content. The introduction chapter is followed by presentation of specific content, which includes two manuscripts. The first manuscript is a review of the literature that was first submitted to *Heart & Lung: The Journal of Acute and Critical Care* in January 2015; a revised version was submitted April 2015; the manuscript was accepted for publication in June 2015 (doi: 10.1016/j.hrtlng.2015.06.010). This manuscript, titled, “The influence of music during mechanical ventilation and weaning from mechanical ventilation: A review”, was developed from the NRSA grant application, and was enhanced with information presented in the author’s first comprehensive written exam, the Critical Review Paper. This manuscript mainly focusses on a narrative review of previously conducted studies examining the use of music intervention during

mechanical ventilation (MV), highlighting the evident lack of literature testing music intervention specifically during ventilator weaning. A strong argument is given to support the need for more research regarding the use of music during weaning; thus illustrating a foundation for the second manuscript.

The first manuscript is followed by a detailed explanation of the conceptual framework that was drafted to guide the dissertation project and the statistical analyses used to address the study aims. This conceptual framework was adapted from the conceptual model used to guide the parent study.

The second manuscript, titled, “The influence of music and anxiety on weaning trials in patients undergoing mechanical ventilation” focuses on the methods and results of the dissertation research. It was guided by the author’s NRSA grant application and further developed by the second written comprehensive exam, the Doctoral Research Prospectus. This paper briefly explains the parent study, methods employed for data analysis to address the study aims, results, as well as the discussion of the findings. The authors plan to first submit the manuscript to the *American Journal of Critical Care*. If not accepted, the manuscript will subsequently be submitted to the *Western Journal of Nursing Research.* This second manuscript concludes the specific content section of the dissertation.

Chapter 3 – Synthesis Chapter. A synthesis chapter was constructed to provide an overview of the findings from both manuscripts as well as further expand on the discussion of the research results and the impact of the project on

nursing practice. Support is given for the knowledge the project provides not only to nursing, but also to the interdisciplinary care providers who interact with critically ill individuals receiving MV and undergoing weaning trials. References and appendices can be found at the end of the dissertation.

CHAPTER 1 – INTRODUCTION

The purpose of this introduction chapter is to present background content to describe the dissertation theme, discuss the overall need and significance of the research topic, and address the construction of the dissertation in its entirety. This introduction chapter begins with a summary of content related to the dissertation titled, “The Influence of Music on Anxiety in Weaning from Mechanical Ventilation” followed by evidence that supports the need for the dissertation study. An overview of the dissertation is provided beginning with an explanation of the original study that inspired the dissertation topic and concluding with details about funding support and specific chapter content.

Overview of Mechanical Ventilation

Mechanical ventilation (MV) is a life support measure necessitated by respiratory insufficiency or failure. Over 50% of patients in the intensive care unit (ICU) require MV (Metnitz et al., 2009). This number is expected to rise continuously as the population ages in the United States (Zilberberg & Shorr, 2008). MV is a high risk intervention that can cause consistently elevated levels of anxiety and increase the incidence of complications. It results in higher rates of morbidity and mortality and lengthens hospital stays (Dijkstra, Gamel, van der Bijl, Bots, & Kesecioglu, 2010; Korhan, Khorshid, & Uyar, 2011; SCCM, 2012; Wong, Lopez-Nahas, & Molassiotis, 2001; Wunsch et al., 2010). In addition, MV is very expensive and leads to a disproportionate utilization of hospital resources

by those that require it (Wunsch et al., 2010). The adjusted cost per patient day for MV is approximately $1,500 (Zilberberg, Luippold, Sulsky, & Shorr, 2008). Dasta and colleagues (2005) found that mean hospital costs for patients who require MV are more than double those who do not require MV. The financial impact of MV is substantial considering that mechanically ventilated patients stay four days longer in the ICU and an extra six days in the hospital compared to non-mechanically ventilated patients (Dasta, McLaughlin, Mody, & Piech, 2005). In 2005, it was estimated that approximately 800,000 patients underwent MV in the US with a total estimated cost of over $27 billion. This represents 12% of all hospital costs (Wunsch et al., 2010).

MV requires the patient to be intubated. Intubation is a term used to describe the insertion of an artificial tube (airway) into a patient's throat, nose, or to surgically place it directly into the trachea. Oxygen is then forced through the tube and into the lungs via a mechanical ventilator. The mechanical ventilator has a variety of modes and settings that can be adjusted by trained ICU staff. Ventilators can be programed to deliver a targeted volume, a constant pressure, or a combination of both with each breath (Grossbach, Chlan, & Tracy, 2011). Volume targeted modes are the most commonly used; they deliver a fixed rate of breaths per minute at a consistent volume. In pressure control modes, breaths are triggered by the patient and designated pressure is provided to support spontaneous breathing. Newer ventilators offer duel control modes that combine facets of both pressure and volume targeted settings (Grossbach et al., 2011).

The mode is chosen based on the needs of the patient; all ventilator modes allow for spontaneous breathing but vary in the level of control they give patients over their own breaths (Neligan, 2006).

Specific ventilator settings are based on the patient's underlying condition and reason for mechanical ventilatory support. These settings include: tidal volume, positive end expiratory pressure (PEEP), fraction of inspired oxygen (FiO_2) and pressure support. Tidal volume is the volume of oxygen gas, either inhaled or exhaled during a breath. PEEP is the amount of positive pressure remaining in the lungs at the end of expiration; it helps keep the alveoli inflated to facilitate gas exchange. FiO_2 is the concentration of oxygen in the inspired gas; room air has a FiO_2 of 0.21 (21%), whereas ventilators can be set to deliver a FiO_2 up 1.0 (100%). Pressure support refers to a preset level of positive pressure delivered during inspiration (Grossbach et al., 2011). Various modes, pressures, volumes, and levels of oxygenation can be employed for ventilator assisted breaths to promote the most ideal oxygenation and gas exchange for the patient (Neligan, 2006).

Respiratory failure necessitating MV is caused by a variety of conditions such as trauma, cardiac arrest, an inability to protect the airway, infection, cancer masses, sepsis, surgery, and organ failure (Hall & McShane, 2013). Individuals may require temporary MV to bridge them through acute critical illness while others may need MV for an extended period of time. MV can lead to severe

complications such as pneumothorax, bronchopleural fistula, and nosocomial pneumonia (Pierson, 1990).

Symptoms Associated with Mechanical Ventilatory Support

MV is a major physical and psychological stressor that complicates the overwhelming symptom burden of ICU patients (Silverman, 2002). Anxiety, which is defined as a sustained state of apprehension and arousal in response to a real or perceived threat, is a debilitating and common symptom of MV (Chlan et al., 2013; Chlan & Savik, 2013). It is associated with headache, nausea, insomnia, anorexia, dyspnea, palpitations, dizziness, dry mouth, chest pain, diaphoresis, hyperventilation, pallor, tachycardia, tremors and hypervigilance (Fuchs & Bellamy, 2014). In a study that used a survey to explore the symptoms experienced by ICU patients at a high risk of dying, the prevalence of anxiety was significantly higher in patients who were mechanically ventilated (74.2%) versus those who were not (25.8%) (Puntillo et al., 2010). Patients who are mechanically ventilated are forced to rely on health care providers and medical equipment for survival. In addition, they have extremely limited mobility and capacity for communication, which exacerbates intense feelings of vulnerability and fear (Baumgarten & Poulsen, 2014; Nystrom, Sundelin, & Rattray 2013).

In addition to anxiety, it has been determined (Puntillo et al., 2010) that ICU patients at a high risk for dying reported symptoms of fatigue (75%), extreme thirst (71%), restlessness (49%), hunger (45%), shortness of breath (44%), pain (40%), sadness (34%), fear (33%) and confusion (27%); of the 405 symptom

assessments that were completed to garner the above data, only 138 (34%) were completed by mechanically ventilated patients. Because of this, the authors of this study predicted the true prevalence of symptoms experienced by mechanically ventilated patients may be underreported (Puntillo et al., 2010).

In a study related to psychological experiences during MV, Rotondi and colleagues (2002) found that individuals who underwent MV reported psychological experiences such as having spells of terror, feeling nervous when left alone, and disturbed sleeping patterns. Jablonski (1994) uncovered the striking awareness that some patients had while on the ventilator. They not only realized their own mortality, but they also reported experiencing a tremendous range of emotions while they attempted to come to terms with the mechanical ventilator. The emotional and psychological stress induced by MV affects patients long after ICU discharge. A recent study found that one in three patients who underwent MV showed symptoms of post-traumatic stress disorder (PTSD) up to two years after being ventilated (Bienvenu et al., 2013). Half of those ICU survivors were dependent on psychiatric medications after their hospitalization. The long term impact of MV can slow patient's recovery and keep individuals from returning to work or performing usual daily activities, further expanding the financial drain of MV (Bienvenu et al., 2013). The physical symptoms of MV and psychological side effects associated with this intervention can increase recovery time and patient mortality (Puntillo et al. 2010; Silverman, 2010).

Weaning from Mechanical Ventilation

After the cause of acute respiratory failure or insufficiency is identified and addressed, patients must be able to breathe and maintain adequate gas exchange independent of the ventilator before the artificial airway can be removed, which is called extubation. Extubation is achieved through a series of "weaning trials" or "spontaneous breathing trials." Weaning trials are designated periods of time in which the patient must demonstrate the ability to initiate spontaneous respirations and maintain adequate ventilation and gas exchange. Ventilator settings are adjusted to decrease the amount of ventilator support provided, which requires increased respiratory effort from the patient. ICU staff can adjust the amount of PEEP, pressure support and FiO_2 in order to "exercise" the lungs (Neligan, 2006; Nickson, 2015) and determine a patient's readiness for extubation. Some institutions have developed weaning protocols, but generally the frequency and specific settings employed for weaning trials is up to the discretion of the physician.

Current research suggests that weaning trials should be attempted daily (Pruitt, 2006). In order to be considered "successful", a patient must complete a 30 minute trial free from negative side effects such as increased heart rate, increase respiratory rate, drop in oxygen saturation, and physical signs of stress and anxiety such as restlessness and diaphoresis (Nickson, 2015). Successful weaning from MV depends on respiratory muscle strength, adequate respiratory drive, acid base balance, electrolyte status, hemodynamic stability, nutrition, level

of alertness, as well as psychological readiness (Blackwood, 2000; Conti, Mantz, Longrois, & Tonner, 2014; Dasta & Cawley, 2007; Eskandar & Apostolakos, 2007). A patient is considered “ready to extubate” after two or more successful weaning trials. Extubation occurs when the artificial airway is removed and the patient breathes independently. If a patient fails a weaning trial, extubation is not safe. The cause of the respiratory insufficiency must be addressed and the weaning trials should be re-attempted within 24 hours (Pruitt, 2006). Up to 20% of ventilated patients experience extreme weaning difficulty and fail their first weaning attempt, thus delaying extubation (Eskandar & Apostolakos, 2007; Stawicki, 2007; White, O’Connor, & Kirby, 2008).

Weaning can further exacerbate the physical and emotional symptoms experienced during MV. Anxiety may be greatly increased during weaning because it requires increased respiratory effort. In addition, anxiety precipitates a myriad of problems by tightening the chest muscles, which may lead to hyperventilation and feelings of panic, thus inducing early fatigue during weaning (Blackwood, 2000; Schou & Egerod, 2008; Twibell, Siela, & Mahmoodi, 2003). In addition, patients can sometimes differentiate between mechanical breathing and natural breathing and reported frustrations with adjusting to this transition during weaning (Jablonski, 1994). It is important that patients be properly informed of the process and encouraged throughout, to prevent them from feeling increasingly anxious which leads to increased dyspnea and fear of abandonment as mechanical support is decreased (Blackwood; 2000; Twibell et al., 2003). One

study found that patients who did not wean successfully from the ventilator reported more fatigue, dyspnea and less weaning self-efficacy (Blackwood; 2000; Twibell et al., 2003). It has been predicted that patients' subjective perceptions of weaning may strongly influence weaning outcomes, but the exact association between perceptions and outcomes remains unclear.

For some, weaning to extubation may only take a day or two, but for others it can be an extended process that occurs over many weeks or even months. Delays in extubation can be due to severe respiratory muscle deconditioning, poor nutrition, upper airway edema, and decreased level of consciousness secondary to over-administration of sedatives and analgesics (Kulkami & Agarwal, 2008). In some cases, patients are extubated but subsequently require reintubation. The inability to sustain spontaneous breathing and adequate gas exchange after weaning and extubation with the need for reintubation within 24-72 hours is called extubation failure; it occurs at least once in up to 47% of mechanically ventilated patients (Kulkami & Agarwal, 2008). Continuous sedation is considered a major risk factor for extubation failure in the mechanically ventilated patient (Kulkami & Agarwal, 2008). Extubation failure carries a high risk for further complications such as airway trauma, ventilator associated pneumonia, gastrointestinal bleeding, and blood clots. These complications lead to increased overall cost, longer ICU lengths of stay, and increased patient morbidity and mortality (Eskandar & Apostolakos 2007; Kulkami & Agarwal, 2008).

Symptom Management during Mechanical Ventilation and Weaning

Because MV is both physiologically and psychologically stressful, it is almost always synonymously associated with the administration of large doses of sedative and analgesic medications (Girard et al., 2008). Nurses are primarily responsible for medication management during MV and weaning. At times, the administration of these medications is necessary to promote comfort, decrease oxygen consumption, facilitate nursing care, and ensure patient safety (Girard et al., 2008; Rotondi et al., 2002). However, overuse of sedative medications can cause hypotension, increased risk for ventilator associated pneumonia, fatigue, delirium, muscle weakness, and PTSD. Deep pharmacological sedation can also lead to prolongation of MV, increased length of ICU stay, and increased rates of organ failure and reintubation (Brush & Kress, 2009; Chlan, 2002; Girard et al., 2008; Silverman, 2002; Tracy & Chlan 2011; Volk & Grassi, 2009). In addition, over-sedation can greatly alter routine neurological assessments, which in turn leads to the ordering of unnecessary, costly diagnostic exams (Brush & Kress, 2009). Long-term use of sedative agents puts the mechanically ventilated patient at a high risk for withdrawal from these potent intravenous medications (Brush & Kress, 2009).

The need for sedative and analgesic medications should be assessed on an individual basis because consistent use of these medications can cause severe short-term and long-term issues with memory and cognition. There is growing evidence that mechanically ventilated patients can benefit from an

increased awareness of their environment and understanding of their condition (Brush & Kress, 2009). When interviewed, patients who had been mechanically ventilated appreciated the symptom relief provided by sedatives and analgesics but expressed reservations about the amnesic effects of these medications and how they interfered with the ability to understand and accept the mechanical ventilator (Jablonski, 1994). One study showed that patients felt like they had to "fight the sedation." They struggled to maintain clear thinking due to the sedatives they were receiving (Egerod, 2002). In a recent study by Karlsson, Bergbom & Forsberg (2014), eight out of 12 patients would have chosen consciousness over sedation if given the choice. They desired to be aware of what was going on and they felt being more awake was better for their body and their muscles. Continuous high doses of sedative medications can cause severe long-term psychological problems such as depression and paranoid delusions (Kress, Gehlbach, Lacy, Pliskin, Pohlman, & Hall, 2003; Strøm, Stylsvig, & Toft 2011). In a recent study, patients who were most awake and aware of their surroundings during MV had the lowest PTSD-like symptoms after hospital discharge (Kulkami & Agarwal, 2012).

Sedation and Weaning Protocols

Weaning can worsen the already substantial symptom burden of MV. It is challenging for nursing staff to appropriately manage distressing symptoms and maintain patient safety while optimizing mental alertness in order to facilitate successful weaning trials. Unfortunately, because there is a lack of evidence

regarding the optimal delivery of sedation in preparation for weaning, the type, amount, and frequency of sedative administration is largely opinion based (Conti et al., 2014).

Current research supports minimum sedation is a prerequisite for weaning because patients are likely to have weaning successes when they are awake and alert (Girard et al., 2008; Lacoske, 2015). Thus, the concept of pairing sedation interruption with a spontaneous breathing trial continues to be advanced through research (Conti, et al., 2014). A typical protocol recommends stopping sedation for a specific amount of time to allow the patient to wake up and successfully perform a weaning trial. The goal after the trial is completed is to reduce the continuous sedation to half the rate it was previously infusing so long as the patient's condition permits (Lacoske, 2015). Results from previous studies suggest that having patients "wake up and breathe" resulted in more time off of MV, less time in a coma, and less time in the ICU and the hospital compared with usual care and should be the standard practice (Girard et al., 2008). The patients had similar cognitive and emotional outcomes at three and 12 month follow up, which challenges the existing assumption that decreasing sedation may cause long-term mental harm (Jackson et al., 2010). However, debate remains regarding the safety of an alert and weaning patient as the perceived risk for self-extubation is a paramount concern among care providers, despite the fact that this risk has not been adequately demonstrated (Girard, 2008).

Current guidelines for the management of pain, agitation, and delirium in adult ICU patients were developed by a 20-person multidisciplinary, multi-institutional task force supported by the American College of Critical Care Medicine (ACCM) in conjunction with the Society of Critical Care Medicine (SCCM) and the American Society of Health-System Pharmacists (ASHP). These guidelines recommend maintaining “light” levels of sedation and implementing daily sedation interruptions unless clinically contraindicated (Barr et al., 2013). Lighter sedation has been shown to improve clinical outcomes by decreasing total ventilator time and overall ICU lengths of stay. These guidelines recommend attempting intense efforts to reduce anxiety before administering sedatives through strategies such as maintaining comfort, providing adequate analgesia, frequent reorientation, and environmental modification to promote sleep (Barr et al., 2013).

Nationwide, the mean number of ventilator days is 5.6 but 5 to 20% of intubated patients require support for at least 21 days (Dasta et al., 2006; White et al., 2008) In fact, up to 40% of the time patients spend on the ventilator can be spent weaning. Patients who require mechanical ventilator for more than 3 weeks account for more than 50% of total ICU costs (Wunsch et al. 2010). Timely, effective weaning is critical to decreasing the personal and economic costs of MV (Blackwood, 2000; Twibell et al., 2003). It is vital to encourage efficient weaning by approaching weaning holistically and employing a variety of interventions designed to promote timely extubation.

Music Intervention to Promote Successful Weaning

The literature supports pairing weaning trials with sedation interruptions, but in doing so, some individuals may be more alert and more aware of their anxiety during ventilator weaning. The experience of increased awareness and a loss of control may add to the stress of the patient (Shou & Egerod, 2008). This increased stress creates the need for additional symptom management strategies that can alleviate anxiety but maintain alertness. Music intervention can be used as an adjunct to sedative and analgesic medications in order to reduce dependence on these medications and promote comfort and relaxation (Tracy & Chlan, 2011). In this dissertation project, it is hypothesized that patients may benefit greatly through music intervention during weaning from MV. It is hypothesized that patients who partake in music intervention will report less anxiety, have a shorter time to first weaning trial, and have weaning trials that are longer in duration. In addition, they will be extubated sooner than those who did not receive music intervention.

A variety of studies have been conducted examining the use of music during MV (Hetland, Lindquist, & Chlan, in press). Collectively, these studies support the use of music intervention to reduce psychological and physiological symptoms associated with MV. Incorporating music into the care of the mechanically ventilated patient has strong potential to alleviate the symptom burden and the high cost of conventional treatments as well as increase patient satisfaction and

promote efficient weaning (Chlan et al., 2013; Disch & Kreitzer, 2003; Hunter, Olivia, Sahler, Gaisser, Salipante, & Arezina, 2010; Tracy & Chlan, 2011).

Significance of the Research Problem and Overall Need for the Dissertation

Music is an ideal therapeutic modality to alleviate anxiety and promote wellbeing in the mechanically ventilated patient (Bradt, Dileao, & Grocke, 2010). Incorporating music during ventilator weaning trials is an innovative approach that warrants a more thorough investigation for the following reasons (Hetland, et al., in press): 1) close to 1 million individuals endure MV each year in the United States (Wunsch et al., 2010); 2) weaning is a necessary process for MV to be terminated and for independent respirations to commence; 3) close to half of the total duration of MV is spent undergoing weaning (Eskandar & Apostolakos, 2007); 4) sustained anxiety lengthens the weaning process and further complicates recovery; and 5) music is a feasible non-pharmacological intervention to help alleviate anxiety and promote more effective ventilator weaning.

While music has been studied previously in mechanically ventilated patients, a large knowledge gap exists regarding music's influence during ventilator weaning trials. Only one article identified in the literature specifically evaluated music intervention during weaning from MV. These study results indicated that music decreased the physical signs of anxiety during weaning and both patients and nurses were very satisfied with the intervention, which adds to its feasibility in practice (Hunter et al, 2010). While the results of this study are

encouraging, there is a great need for additional studies in this area that have stronger designs and adequately powered samples sizes. The results from this dissertation study will begin to fill this knowledge gap by evaluating the impact of music on anxiety during weaning from MV from a large, randomized controlled clinical trial.

Integrative approaches for symptom management, specifically in those mechanically ventilated, weaning patients is a relatively new area of research. Existing studies demonstrate music positively influences patient outcomes, but few studies consider factors such as: the importance of individual music preferences, the impact of medication dosing before, during, and after music intervention, or the impact of illness severity on the measured outcomes. In addition, previously completed studies have relatively small sample sizes and employ weaker designs and inconsistent measurement techniques.

This project provides an in-depth analysis of the influence of anxiety on ventilator weaning trials as well as the influences of music on anxiety during weaning trials by evaluating objective data from a large randomized controlled clinical trial parent study. The further evaluation of music intervention during weaning trials is essential to determine if music can reduce anxiety during weaning trials and have an impact on factors such as time to weaning trials, length of weaning trials, successful weaning readiness, and, ultimately, the reduction of total ventilator days and ICU length of stay.

This project is significant because it illustrates the potential clinical benefit of music specifically for mechanically ventilated patients undergoing weaning trials. The knowledge gained from this study can reform current practices of anxiety management during weaning trials in mechanically ventilated patients. This project relates directly to national research agendas. The research content is closely aligned with the National Institute of Nursing Research's (NINR) 2011 Strategic Plan to advance quality of life through symptom management during acute and critical illness (National Institute of Nursing Research, 2011). The knowledge gained from this project can be used to guide innovative perspectives and develop strategies for critical care symptom management of the mechanically ventilated patient as well as promote the use of integrative therapies as a viable option for the millions of patients who experience critical illness each year in the United States. This dissertation focus is also consistent with the recommendations from the Critical Care Societies' Collaborative Strategic Planning Task Force for Critical Care Research (Deutschman, Ahrens, Cairns, Sessler, & Parsons, 2012). One of the key research priorities established by this task force is to, "explore new approaches to enhance patient comfort while reducing the need to manipulate consciousness," as well as to "examine the effectiveness of interventions to measure and treat prevalent/distressing patient symptoms (Deutschman et al., 2012, p. 199).

Composition of the Dissertation

Secondary Analysis and Explanation of the Parent Study

This dissertation project is a secondary data analysis of a previously conducted study by Dr. Linda Chlan and colleagues (1RO1NR009295). A secondary analysis was chosen to gain valuable learning in a timely, efficient manner for the following reasons: 1) high-impact research questions can be answered effectively using fewer resources than primary data collection (Smith, et al., 2011); 2) novice researchers can learn valuable research techniques while still completing and publishing research in a timely manner; 3) successfully completed analysis demonstrates a specific skill set and foundational understanding of methodological and statistical concepts (Smith et al., 2011); and 4) conducting a high quality analysis requires both research and statistical expertise (Smith et al., 2011).

The parent study (Chlan et al., 2013) used a three group experimental design with repeated measures in which 373 subjects were recruited from 12 adult ICUs in five teaching and non-teaching hospitals in the urban Midwest. Subjects were randomized to one of three conditions: experimental condition of patient-directed music (PDM), or one of two control conditions; usual ICU nursing care only or noise-canceling headphones (HPs). All subjects were eligible to receive appropriate sedative and analgesic medications as requested or as deemed necessary by nursing staff.

To address the aims for this dissertation research project, a subset of 307 subjects from the parent study who had been enrolled in the parent study for at least 24 hours, were intubated less than 40 days prior to study enrollment, and

had at least one recorded weaning trial after enrollment were included for analysis. In collaboration with a statistician, survival analysis, Cox proportional hazards regression, and linear regression with mixed modeling were used to address the specific aims. The specific aims were to determine the following for patients receiving mechanical ventilation: 1) the influence of music on time to first weaning trial after study enrollment; 2) the influence of anxiety on time to first weaning trial after study enrollment; 3) The influence of music on the duration of weaning trials during the study period; 4) the influence of anxiety on the duration of weaning trials during the study period. It was hypothesized that individuals who received music intervention and those with lower anxiety scores would have shorter times to first weaning trial after study enrollment. Individuals who received music intervention and those with lower anxiety were expected to have weaning trials that were overall longer in duration.

Results of the study did not support the hypothesis. Statistical analysis demonstrated that music intervention did not shorten time to first weaning trial after study enrollment or lengthen the duration of weaning trials overall. Neither group assignment nor anxiety were significant predictors of time to first weaning trial after study enrollment when controlling for other covariates such as sedation frequency, sedation intensity score, total days in ICU prior to enrollment, APACHE III, and history of ventilation during a prior hospitalization. APACHE III was the only significant predictor in the models ($p=.004$ and $p=.005$); subjects with higher APACHE III scores were likely to undergo their first weaning trial

sooner after study enrollment. In addition, neither group assignment nor anxiety were significant predictors of duration of weaning trials during the study period when controlling for other covariates such as sedation frequency, sedation intensity score, study day, trial number, VAS-A, age, days ventilated prior to enrollment, days in ICU prior to enrollment, FiO_2, and tracheostomy. For each day from study admission, weaning trials increased by 8.4/8.6 minutes ($p<.001$). If a subject had a tracheostomy on the day of the weaning trial, weaning trials for that day increased by 53.6/54.6 minutes ($p=.04$ and $p=.03$).

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CHAPTER 2 – SPECIFIC CONTENT

This chapter begins with the first manuscript, a narrative review of the literature, titled, “The Influence of Music during Mechanical Ventilation and Weaning from Mechanical Ventilation”. It was developed from the NRSA grant application and then expounded upon during the construction of the author’s first comprehensive exam, the Critical Review Paper. This narrative review of previously conducted studies examining the use of music intervention during MV and ventilator weaning highlights the evident lack of literature testing music intervention specifically during ventilator weaning. A strong argument is given to support the need for more research regarding the use of music during weaning; thus illustrating a foundation for the second manuscript. The manuscript was first submitted to *Heart & Lung: The journal of Acute and Critical Care* in January 2015. The manuscript was returned in March 2015 with critique and request for resubmission. A revised version was submitted in April 2015; the manuscript was accepted for publication in June 2015 (doi: 10.1016/j.hrtlng.2015.06.010). Extensive guidance was provided by Dr. Linda Chlan and Dr. Ruth Lindquist during the revision process.

MANUSCRIPT 1

Title. The influence of music during mechanical ventilation and weaning from mechanical ventilation: A review

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Summary

Background: Mechanical ventilation (MV) causes many distressing symptoms. Weaning, the gradual decrease in ventilator assistance leading to termination of MV, increases respiratory effort, which may exacerbate symptoms and prolong MV. Music, a non-pharmacological intervention without side effects may benefit patients during weaning from mechanical ventilatory support.

Methods: A narrative review of OVID Medline, PsychINFO, and CINAHL databases was conducted to examine the evidence for the use of music intervention in MV and MV weaning.

Results: Music intervention had a positive impact on ventilated patients; 16 quantitative and 2 qualitative studies were identified. Quantitative studies included randomized clinical trials (10), case controls (3), pilot studies (2) and a feasibility study.

Conclusions: Evidence supports music as an effective intervention that can lesson symptoms related to MV and promote effective weaning. It has potential to reduce costs and increase patient satisfaction. However, more studies are needed to establish its use during MV weaning.

Key Words (Max of 6):

Artificial Respiration, Mechanical Ventilator, Weaning, Airway Management, Music, Music Therapy

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Introduction

Initiation of mechanical ventilation (MV)[a] to treat acute respiratory failure is a lifesaving intervention. Causes of acute respiratory failure include pulmonary disease, neuromuscular disease, shock, and major surgery.[1] Recent estimates have found that over half of all ICU patients require MV.[2] An estimated 800,000 patients undergo MV in the U.S. each year with a cost of approximately $27 billion.[1] On average, patients who receive MV stay 4 days longer in the ICU and an additional 6 days in the hospital compared to ICU patients who do not.[3]

Generally, as patients recover from acute illness, they can be "weaned" from ventilatory support. Weaning is a gradual decrease in ventilator settings that leads to termination of MV support.[4] Successful weaning depends on respiratory muscle strength, adequate respiratory drive, acid base balance, neurological status, as well as psychological readiness.[5-7] Nationwide, the mean number of ventilator days is 5.6, but 5% to 20% of intubated patients require support for at least 21 days.[3,8] Delays in extubation can be due to severe respiratory muscle deconditioning, poor nutrition, upper airway edema, and decreased level of consciousness secondary to over-use of sedative medications.[9] Extubation failure can lead to ventilator-associated pneumonia, airway trauma, increased costs and high mortality rates.[10] Patients who require MV for greater than 3 weeks account for more than 50% of total ICU costs.[1] MV and MV weaning lead to an array of distressing symptoms such as pain, agitation, lack of sleep, and especially anxiety.[13] Unmanaged anxiety stimulates the sympathetic nervous

[a] MV – mechanical ventilation

system, increases work of breathing and fatigue, and severely impedes ventilator weaning;[4] it can be particularly severe for the ventilated patient, and, if not treated promptly, can increase recovery time and patient mortality.[11,12]

Current symptom management practice for patients receiving ventilatory support primarily involves the administration of numerous sedative and analgesic medications which can prolong ventilation and increase length of ICU stay.[11,13] Overuse of these medications can lead to fatigue, delirium, muscle weakness, and post-traumatic stress disorder (PTSD).[14] However, sedative administration is only one symptom management strategy used to help alleviate anxiety. A number of integrative, non-pharmacological interventions have been shown to be beneficial for anxiety symptom management in non-ICU patients such as music, imagery, massage, and animal assisted therapy.[13]

Music intervention is the non-pharmacological, integrative therapy of interest in this review; it has been shown to decrease anxiety during MV.[15] Decreasing anxiety could help promote more efficient ventilator weaning and hasten ICU discharge. This is significant in that “even nominal decreases in length of time spent in the ICU or the duration of mechanical ventilation have the opportunity to significantly reduce hospitalization costs.”[3(p. 1271)] Incorporating music into the care of the ventilated patient has strong potential to alleviate the symptom burden and the high cost of conventional treatments as well as increase patient satisfaction and promote efficient weaning.[4,13,16,17]

The purpose of this narrative review was to describe the state of the science on music as an integrative intervention during MV and ventilator weaning, and to identify current gaps in knowledge regarding use of music intervention for symptom management, specifically during weaning. This review provides an evidence-based background for music intervention and supports the need for future studies on music intervention during weaning.

Background

Weaning from Mechanical Ventilation

The weaning process involves a gradual decrease in ventilator settings as a patient's respiratory status improves, leading to termination of MV support.[4] As the acute cause of respiratory failure resolves and the patient can tolerate independent respirations, the artificial airway is removed.[9,10,18] For some, weaning can be a lengthy process. Recent estimates state that more than 40% of the total duration of MV is spent enduring the weaning process.[6] While advancements in ventilator management protocols have been made, a universal protocol to determine readiness to wean based on strict physiological measures has not been established.[10] It has been predicted that patients' subjective perceptions of weaning may strongly influence weaning outcomes, but the extent of their role in successful outcomes remains unclear.[19] Most weaning guidelines require a formal assessment of readiness to wean before beginning weaning trials. Weaning trials generally require a patient to tolerate spontaneous respirations for at least 30 minutes. A patient is usually ready for extubation after

two or more successful weaning trials. If a patient fails a weaning trial, extubation is not safe and weaning is continued. Up to 20% of ventilated patients experience extreme weaning difficulty and cannot be extubated.[6,8,10]

Extubation failure is the inability to sustain spontaneous breathing after removal of the artificial airway with the need for reintubation within 24-72 hours.[9] Extubation failure can lead to airway trauma, ventilator-associated pneumonia, gastrointestinal bleeding, and blood clots. It can increase costs, result in longer ICU stays, and increase morbidity and mortality.[6,9,10] It has been estimated that extubation failure occurs at least once in up to 47% of mechanically ventilated patients.[9] Timely, effective weaning is critical to decreasing the personal and economic cost of MV and extubation failure.[19]

Anxiety during Mechanical Ventilation and Ventilator Weaning

Anxiety, a state marked by dread, fear, apprehension, increased motor tension and autonomic arousal, is a major psychological stressor with harmful physical manifestations that are often experienced during MV and ventilator weaning.[17,20] High stress and anxiety levels in mechanically ventilated patients have been associated with increased patient morbidity and mortality.[15,21] Up to 85% of ventilated patients experienced anxiety,[12] and 60% of those patients reported feeling scared most of the time.[22] Sustained high levels of anxiety activate the sympathetic nervous system, which causes an increase in heart rate, blood pressure, and respiratory rate, and initiates an unfavorable neurohormonal response.[23-25] Arousal of the sympathetic nervous system can cause serious

complications including arterial and venous constriction, myocardial stimulation, and bronchoconstriction.[23] Arterial and venous constriction in the lungs severely impedes the ability to oxygenate tissues effectively,[26] which increases the work of breathing, induces fatigue, and can extend the need for MV.[7]

Weaning requires increased respiratory effort and can further exacerbate anxiety and its manifestations. If patients are not properly educated and encouraged during weaning, they may feel increasingly anxious, which can lead to increased dyspnea, panic, and a fear of abandonment as ventilator support is decreased.[7,19] It has been shown that patients who did not wean successfully reported more fatigue, dyspnea, and less weaning self-efficacy.[19]

Symptom Management with Sedative Medications

Nurses are responsible for ICU patient symptom management. Current practice to alleviate distressing symptoms involves the administration of sedative and analgesic medications which can lead to prolonged ventilation and increased lengths of ICU stays.[11,13,17] At times, medication is necessary to facilitate patient comfort, safety, and promote recovery.[27] However, these highly potent medications can contribute to a multitude of complications such as fatigue, weakness, delayed weaning, and PTSD.[14] Indeed, many side effects have been associated with sedative agents such as hypotension, increased risk for ventilator-associated pneumonia, and delayed ventilator weaning.[28,29-33] Overall, deep pharmacological sedation during MV increases patient morbidity. A strong correlation exists between continuous sedation and prolonged ICU stays,

increased rates of organ failure and reintubation.[28,34] Over-sedation with continuous infusions can greatly alter routine neurologic assessments which may lead to the ordering of unnecessary costly diagnostic exams (i.e., CT scans, MRIs).[34] Sedative agents can cause severe short-term and long-term issues with memory and cognition.

There is growing evidence supporting the notion that mechanically ventilated patients can benefit from an increased awareness of their surroundings.[34] Recent studies indicate that patients who were most awake and aware of their surroundings during MV had the lowest PTSD-like symptoms after hospital discharge.[34] Continuous high doses of sedative medications can cause severe long-term psychological damage such as continued anxiety post-ICU discharge, depression, and paranoid delusions.[28] Neurological impairment from sedatives can necessitate reintubation and negatively impact the weaning process.[9] Continuous sedation is a major risk factor for extubation failure.[9] Integrative therapies such as music, in addition to sedative and analgesic medications, can synergistically enhance comfort and relaxation during MV.[13]

Symptom Management with Music Intervention

Music is a non-pharmacological intervention that integrates physiological and psychological components to reduce stress and anxiety and promotes overall well-being.[23,24] Music intervention can abate the stress response, decrease anxiety during MV, and induce an overall relaxation response by reducing stimuli that cause stress, synchronizing body rhythms such as breathing

and heart rate, and by positively influencing emotional feelings of the listener.[35] This relaxation response can lower cardiac workload and oxygen consumption, which promotes more effective ventilation and accelerates ventilator weaning.[23,36] Music that contains simple repetitive rhythms, low pitch, slow tempos, harmony and lack percussive instruments and vocals have been shown to reduce anxiety.[25,28]

Although it is noted in the literature that music is commonly used in nursing care, there are currently no standard protocols or guidelines to direct ICU staff on the most appropriate and useful methods to incorporate music into daily care of the ventilated patient. Music is inexpensive when compared to sedative and analgesic medications,[17,23] and has been shown to reduce anxiety and sedative exposure, which decreases the time the nurse must spend providing calming techniques and other pharmacological intervention to ventilated patients.[5,17,23-25] The success of weaning could be significantly impacted by music intervention, but this assertion requires further examination of existing evidence to determine the influence of music on the weaning process in patients receiving MV. The following research methods were employed to identify the most relevant literature regarding music intervention and MV.

Methods

A narrative review was guided by the flowchart described by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement.[37] A comprehensive computerized search of the literature on music

intervention during MV was conducted using the OVID Medline, PsychINFO, and CINAHL databases with the guidance of an expert professional biomedical librarian. Subject headings used in the searches included “respiration, artificial”, “ventilators, mechanical”, “ventilator patients”, “airway management”, “music”, and “music therapy”. The subject headings were exploded to yield adequate resources for review. Cross- referencing was used to identify additional relevant articles for review. Title and abstract review was used to identify primary research studies. The review was not limited by study design or date published. Quantitative and qualitative studies that examined the use of music intervention during MV and ventilator weaning to reduce physical and psychological symptoms, as well as studies that evaluated the patient experience of music intervention during MV were examined. Studies that assessed the infant and pediatric populations and studies not published in English or translated into English were excluded from the review. Duplicate studies were also excluded.

The initial review yielded 156 potentially relevant articles. After duplicates were removed, 86 abstracts were reviewed; 27 potentially relevant articles were reviewed in full-text. Those not meeting inclusion criteria were excluded (not published in English [n=3], involved infants or pediatrics [n=2]. Four unpublished manuscripts were identified by title. Additional attempts were made to obtain the unpublished manuscripts but were unsuccessful. In total, 18 studies were eligible for review (See Figure 1 for the PRISMA Flowchart used to document the progression of this review). Using the Matrix Method,[38] a standardized data

display was used to chronologically evaluate and extract information from each study such as author, journal, and year, study purpose, setting, number of subjects, methodical design, sampling design, variable measurement, subject characteristics, findings and limitations, and information related to weaning.

Results

Most studies investigated music intervention during MV; only one study explored music intervention during ventilator weaning (see Table 1). One qualitative study that explored patients' experiences with music while ventilated was reviewed. One study used both quantitative and qualitative methods. The remaining 16 studies used quantitative methods to evaluate physiological signs of anxiety as well as a variety of anxiety, agitation, and sedation scales to measure the effectiveness of music intervention. The quantitative studies included randomized clinical trials (n= 10), case controls (n=3), pilot studies (n=2), and a feasibility study (n=1). A variety of control conditions were used such as headphones to promote a relaxing environment, ICU usual care, and historical controls. The results of the review are presented using the following eight subject headings. The first two subheadings relate to methodological aspects of studies: 1) Duration, Frequency and Timing of Music Intervention, 2) Patient Wakefulness, Music Styles, and Music Selection. The remaining six subheadings refer to outcomes and interventions of studies: 3) Influence of Music on Sedation and Agitation, 4) Influence of Music on Physiological Arousal, 5) Influence of Music on Biomarkers of the Stress Response, 6) Influence of Music

on Anxiety, 7) Patients' Self Report of Experiences with Music, and 8) Nurses' Evaluation of Music Intervention.

Duration, Frequency and Timing of Music Intervention

The duration, frequency, and timing of music intervention varied greatly across studies. All studies implemented music for a minimum of 30 minutes once per day, but some music listening sessions lasted up to 90 minutes and intervention frequency ranged from one to three times per day. The duration of study protocols ranged from one day to up to 30 days. Four studies implemented music intervention during the late afternoon or early evening.[35,39-41] Others implemented the intervention during the morning and then again in the evening [21,34] or randomly throughout the day depending on unit and nurse schedules.[23,24] One study implemented music listening during nighttime sleep[42] and another allowed patients to listen to music continuously during the post-operative period.[43] In a study that evaluated music during weaning, the timing of the music intervention depended on where the patient was in the weaning process (early versus more progressed).[4] Chlan et al. used a unique approach that allowed patients to self-direct the frequency, length, and timing of the music intervention.[17,44] Ultimately, consensus regarding the most effective and appropriate duration, frequency and timing of music intervention could not be determined from the literature.

Patient Wakefulness, Music Styles, and Music Selection

Investigators required varying levels of patient wakefulness for study inclusion. Most investigators required patients to be alert and mentally competent in order to participate in study consent.[4,17,23,35,39,40,43-45] Many studies mentioned conditions such as “alert and oriented”, “following commands”, “not confused”, and “able to effectively communicate” as inclusion criteria but few required official screens for delirium as part of the pre-enrollment process. It is not known to what extent wakefulness impacts the physiologic results of music intervention during MV and ventilator weaning.

All studies in this review implemented styles of music that were considered “relaxing” including nature-based sounds, classical, and easy listening. Previous research has demonstrated music most effective at reducing anxiety is familiar to the patient, contains 60-80 beats per minute with simple arrangements and lacks words.[13] However, whenever possible, patients should be solicited personally for their specific musical preferences because certain styles of music can trigger music memories that evoke profound emotional responses.[13] Chlan et al. and Hunter et al. encouraged patients to self-select their preferred music styles.[4,17] Some investigators allowed patients and families to choose from a predetermined list of music selections.[23,25,35,36,40,41,45,46] One study had patients select their music choice prior to undergoing cardiac surgery. Upon awakening, patients were allowed to change their music choice if desired.[43] Hunter and colleagues utilized live music at the bedside.[4] Many investigators

used the expertise of a music therapist to help design the music portfolio or help implement intervention and evaluate patient preferences.[4,17,44,47] It was common for investigators to enhance the environment of both control and experimental groups to promote relaxation by dimming lights, closing curtains/doors, and placing signs outside to alert staff and visitors to the intervention[23,25,35,40-42] Some also provided patients with verbal instructions to think of pleasant thoughts during the intervention.[35,40] In summary, inconsistencies exist concerning ideal patient wakefulness for study inclusion. However, increased patient wakefulness affords greater patient control and independence in regards to music choice.

Influence of Music on Sedation and Agitation

Several studies have evaluated and confirmed the hypothesis that music intervention can decrease the need for sedatives during MV. In a study designed to test whether listening to self-initiated, patient-directed music (PDM) reduced sedative exposure during MV, investigators used a sedative drug intensity score which revealed sedative exposure was significantly reduced in the PDM group.[17] In a study by Conrad et al., a continuous infusion of propofol was suspended prior to the intervention for both the experimental and control groups and was reinitiated after the intervention.[48] Patients in the experimental group did not require additional doses of propofol during the intervention, whereas patients in the control group occasionally needed extra doses of propofol to maintain ventilator compliance.[48] In a study by Saadatmand et al., the Richmond Agitation Sedation Scale (RASS), a 10-point scale with four levels of agitation ranging from

combative, to calm and alert, to unarousable, was used as a measurement of sedation effectiveness.[39] Results demonstrated the odds of having higher agitation in the control group was approximately 11.24 times that of the intervention group, suggesting that the music intervention, which consisted of nature-based sounds, could decrease agitation levels in sedated, mechanically ventilated patients.[39]

Influence of Music on Physiological Arousal

Evidence reveals music can reduce the physiological signs of anxiety such as respiratory rate, heart rate, and blood pressure among patients who are mechanically ventilated. In several studies, music intervention groups experienced a significant decrease in respiratory rate. [23-25,35,40,41] The significant reduction was seen over time, suggesting a cumulative dose effect.[24,35] A number of studies found that music intervention significantly reduced heart rate.[24,25,35,40,41,48] The literature also reveals a trend of decreasing heart rates both during and after music intervention. The reductions were also seen over time suggesting a cumulative dose effect.[24,35,40] Music intervention was effective at decreasing blood pressure.[24,25,35,39,42,48] Conrad et al. found that not only did arterial blood pressure decrease significantly in the music group, it also increased significantly in the control.[48] Similarly, Almerud et al. noted a significant decrease in blood pressure during music intervention as well as a corresponding rise after cessation of treatment.[42]

Influence of Music on Biomarkers of the Stress Response

Several studies explored the influence of music on biomarkers of the stress response by testing blood and urine samples in patients undergoing MV.[45,47-49] These biomarkers included blood levels of corticotrophin, cortisol, epinephrine, norepinephrine, dehydroepiandrosterone (DHEA), growth hormone, adrenocorticotropin hormone (ACTH), interleukin-6 (IL-6), prolactin and prolactin monomer, leptin, MET-enkephalin, and C-reactive protein.[45,47,48] Chlan et al. evaluated urinary free cortisol (UFC).[49] While not significantly different among groups, less profound spikes in urinary free cortisol (UFC) levels were observed. Beaulieu-Boire et al.[47] found that blood cortisol and prolactin decreased after music listening. In another study by Conrad et al., decreases were seen in plasma concentrations of IL-6, DHEA, and epinephrine.[48] Chlan et al. did not find any statically significant decreases in serum biomarkers, but attributed the results to a wide variability in mean levels of biomarkers and small sample size.[45] The connection between biomarkers and clinical observations of anxiety such as increased heart rate and respiratory rate remains unclear. Some hypothesized explanations for inconsistent results provided by investigators were drug administration, number of ventilator days, and large variability in baseline biomarker levels and variability among critically ill patients.

Influence of Music on Anxiety

Over half of the articles reviewed included a self-reported assessment of anxiety. The reliability of these self-reported measures is difficult to assess

because most subjects receive sedative medications during MV. A number of instruments were used to measure anxiety across studies with varying results. These included: Visual Analogue Scale for Anxiety (VAS-A), Anxiety Faces Scale (FAS), The Spielberger State-Trait Anxiety Scale (STAI) [20 items and 6 items]. Music was found to be an effective intervention to reduce anxiety in the mechanically ventilated patient.[35,40,43] In one study, both the music condition and the rest condition experienced reduced state anxiety scores, but the music intervention was more effective than a rest period in reducing anxiety.[23] Another study found that at any point, the music group had a VAS-A score that was significantly lower than the usual care control group. One study detected a significant difference between anxiety scores using the FAS.[39] The odds of having a high anxiety score in the control group was 4.5 times the same odds of having higher anxiety scores in the music group.[39]

Patients' Self Report of Experiences with Music

Two studies primarily aimed to investigate patients' experiences of music intervention by interviewing patients after extubation.[42,46] Both interviewed patients while they were still in the hospital, shortly after being extubated. When interviewed, no patients were immediately able to recall that they had listened to music.[42,46] In one study, the music played during MV was also played during the interview to jog patients' memory, which was a successful tactic.[46] It is unknown whether the timing of the interviews affected patients' ability to recall information

accurately due to the administration of sedative medications in the days before the interviews.

Patients who underwent music intervention during MV were able to recall memories of pain, anxiety and discomfort, as well dreams and delusions. For many, music was a happy memory among traumatic memories while undergoing MV.[46] Lee et al. conducted a post intervention satisfaction survey, and 88% of subjects expressed satisfaction with music.[25] Another study reported that 95% of the time, participants felt that music was helpful, and 100% of study subjects would participate in a music intervention again.[4] In addition, 98% of music sessions that were surveyed, the participant felt less anxious, and after 80% of the music sessions surveyed, the participant reported less stress than expected.[4]

Nurses' Evaluation of Music Intervention

Several investigators solicited nurses for their subjective evaluation of patients' response to music intervention. Nurses expressed positive feelings towards music intervention. Stubbs reported that none of the nurses' interviewed felt there were any disadvantages to music.[46] Chlan et al. did not receive any comments from nurses that would suggest the music protocol was burdensome to their patient care practices.[17] Lee et al., created a resting behavior observation list which was a checklist for research staff to identify four types of behavior: restlessness, facial distortion, restfulness, and sleep.[25] A greater increase in the proportion of "comfortable behaviors" were observed in the music group compared to the control group.[25]

Hunter and colleagues [4] administered Likert-type scale surveys [1 = strongly disagree, 5=strongly agree] to bedside nurses to investigate their observations and satisfaction with the protocol. Nurses ranked the statements "patient appeared less anxious" and "there was less need for medical intervention" with a mean score of at least 4.2 or greater. In addition, nurses felt that music reduced their personal stress, was incorporated unobtrusively, and was useful for their patient. Chlan et al. found that nurses were willing to use the music intervention and had a positive view of the intervention.[44] This is important, since nurses are primarily the ones who are responsible for promoting and implementing music intervention at the bedside.

Discussion

This narrative literature review supports the use of music intervention in patients undergoing MV. While the aim was to focus on music to reduce psychophysiological symptoms, especially anxiety, during weaning trials, there is a striking lack of studies testing music listening during weaning. Of the three studies that examined music during ventilator weaning, only one was in English[4] and it was a feasibility study. While a majority of the evidence centers on symptom management with music during MV, important aspects are gained from the review.

Hunter et al.[4] specifically evaluated music during ventilator weaning. This study demonstrated that music is an effective complement in difficult to wean patients by decreasing the physical signs of anxiety.[4] Music was well received by

both patients and staff, which adds to its feasibility in practice. [4] Failure to wean from the ventilator is a complex physical and psychological setback that frequently impacts ventilated patients. Little is understood regarding the influence of psychophysiological symptoms on weaning trials and ways in which music can lessen these symptoms during weaning trials to promote efficient ventilator termination. There is a critical need for more studies that investigate music to reduce distressing symptoms during ventilator weaning.

Incorporating music during weaning trials is an innovative intervention that warrants more thorough investigation for the following reasons: (1) Close to 1 million individuals endure MV each year in the United States.[1] (2) Weaning is a necessary process for MV to be terminated and spontaneous independent breathing achieved. (3) More than 40% of the total duration of MV is spent enduring the weaning process.[6] (4) Music is a feasible non-pharmacological intervention to help alleviate anxiety and other distressing symptoms in order to promote successful weaning.[4]

Limitations to this Review

There are several limitations to this review. A single author evaluated the studies and only studies published in English were included. Three original non-English studies were identified in the search of the literature but were not used in this review. In addition, only published literature was included. Unpublished literature such as abstracts and unpublished dissertations and theses were not included in this review. Only adults over 18 were included in the studies

reviewed. Music has a strong influence on the psychological wellbeing of adolescents, and it is not known how music intervention can impact adolescent ventilated patients. Many studies had small sample sizes. There is a need for randomized clinical trials that are adequately powered to answer questions asked, and a need for consistent measures and protocols so that findings can be compared across studies. The majority of studies focused on music to manage symptoms of anxiety; examination of additional symptoms of MV weaning such as agitation, lack of sleep, and pain is warranted.

Conclusion

Collectively, the studies included in this review indicate that music can decrease psychophysiological symptoms for patients undergoing MV, which may lead to improved patient satisfaction and promote overall recovery from conditions requiring MV.[43] A decrease in distressing symptoms could encourage a beneficial relaxation response. Achieving a more relaxed state can help reduce the necessity for sedative medications and may eventually decrease the overall length of time ventilatory support is needed.[24] While ICU staff can easily implement music as a non-pharmacological intervention,[42] patient initiated music listening is a plausible and effective intervention strategy.[17] The evidence from the studies evaluated for this review suggests that music can decrease the physiological and psychological symptoms as well as reduce sedative exposure in the ventilated patient. However, this review reveals the noticeable absence of research that examines the influence of music intervention during weaning from

MV. Further research in this area is warranted in order to determine if music intervention can reduce distressing symptoms and favorably impact important clinical factors such as time to weaning trials, length of weaning trials, successful weaning readiness, and ultimately, total ventilator days and ICU length of stay.

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Figure 1

Audit Trail of Literature Search Using PRISMA Flowchart

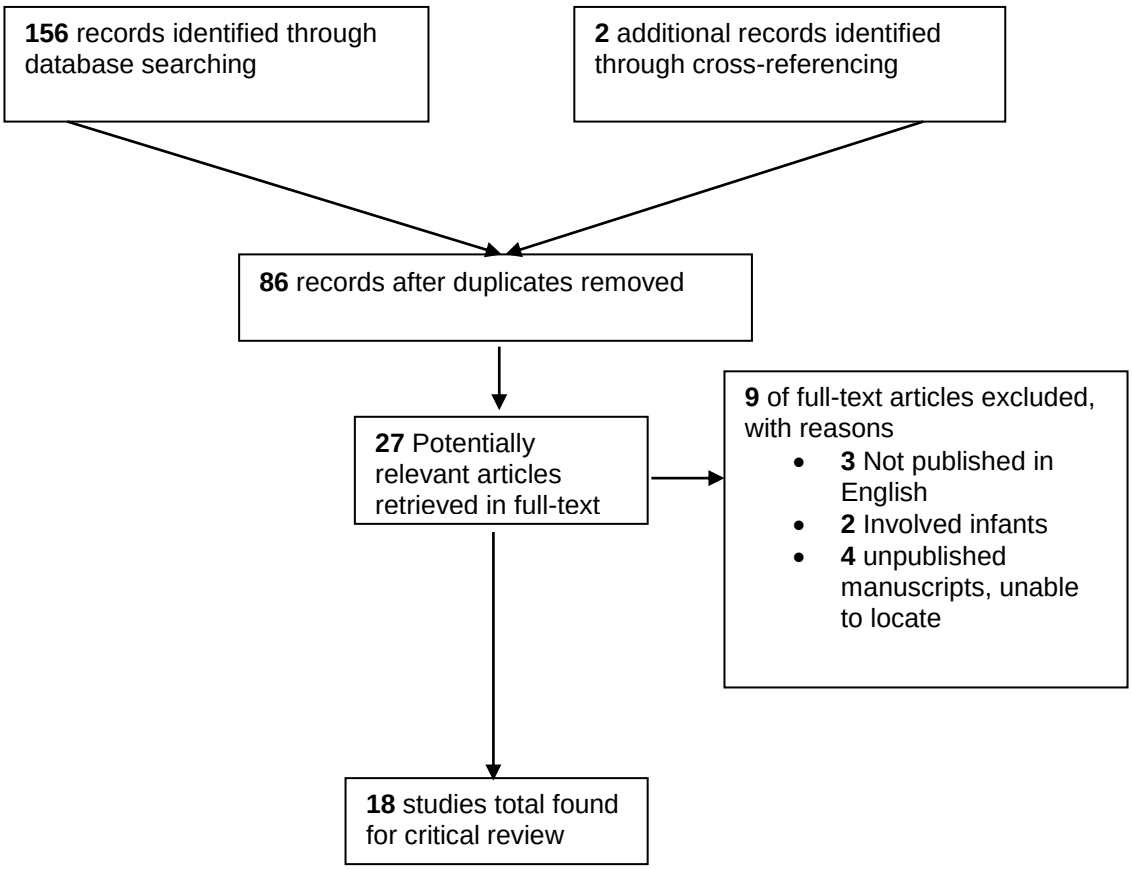


Table 1

Summary of Reviewed Studies

Author/Year	Design	Purpose	Setting/Subjects	Variables Measured	Findings
Almerud & Petersson, (2003)[35]	Mixed Methods • Intervention: Classical music for 30 minutes in conjunction with night sleep • Control: Rest under similar circumstances as the intervention group	Purpose: to discover whether music therapy had a measurable relaxing effect on patients who were temporarily on a respirator in an ICU and after completion of respirator treatment investigate those patients' experiences of music therapy	16 bed ICU in Sweden • 20 subjects for quantitative data • 6 subjects for qualitative interviews	1) Quantitative: Vital signs every 5 minutes during intervention 2) Qualitative: Interview questions about memories of MV after ventilation terminated	- Statistically significant drop in BP[2] during intervention - Non-statistically significant drop in HR during intervention - Subjects had poor memory of time on the ventilator. No subjects recalled listening to music while ventilated - Three themes identified: 1) Anxiety and discomfort, 2) Illusory Feelings, 3) Close Relationship
Beaulieu-Boire, et al. (2013)[34]	Randomized Crossover (3 days with a washout on day 2) • Intervention: Slow tempo music for 1 hour, 2 times per day • Control: Rest with headphones with no music	Purpose: to evaluate the impact of slow tempo music listening periods in mechanically ventilated intensive care unit patients	16 bed ICU in a tertiary hospital in Canada • 49 subjects	1) Vital signs before and after intervention 2) Sedative drug consumption 3) Blood tests for biomarkers before and after intervention	- No significant change in vital signs observed - Trend towards decrease in Fentanyl in intervention group - Blood cortisol and prolactin decreased after intervention
Chlan	Two group experimental	Purpose: to examine	Single ICU at a	1) Vital signs before, at 5	- Statistically significant

[b] HR-heart rate, BP – blood pressure, RR – respiratory rate

(1995)[33]	design • Intervention: Classical music listening for 30 minutes during late afternoon/evening • Control: Rest with headphones with no music	selected psychophysiological responses of mechanically ventilated patients to music	tertiary care center in the US • Intervention group: 11 subjects • Control group: 9 subjects	minute intervals during intervention, and 5 minutes after intervention 2) Anxiety measured using Profile of Mood States (POMS) 30 item short form	decreases in HR, BP, and RR observed in the intervention group - Statistically significant difference found in POMS scores between groups
Chlan (1998)[32]	Two group experimental design • Intervention: Non lyrical, relaxing music with 60-80 bpm for 30 minutes • Control: Rest with no headphones for 30 minutes	Purpose: to test the effects of music therapy on relaxation and anxiety reduction for patients receiving ventilator assistance	4 urban ICUs in the US • Intervention group: 27 subjects • Control group: 27 subjects for control	1) Vital signs at baseline, every 5 minutes, and at 30 minutes 2) Anxiety measured by pretest/posttest 6 item version of Spielberger State Anxiety Inventory	- Statistically significant difference between pretest and posttest anxiety scores for the intervention group - HR and RR decreased over time for the intervention group
Chlan et al. (2007)[38]	Pilot Study: two group experimental design • Patient selected music listening for 60 minutes • Control: Rest with no headphones for 60 minutes	Purpose: to explore the influence of music on serum biomarkers of the stress response in patients receiving ventilator support	11 bed ICU in a University medical center in the US • Intervention group: 5 subjects • Control group: 5 subjects	1) Levels of corticotropin, epinephrine and norephinephrine measured 4 times during each 60 minute session 2) HR: measured 4 times during each 60 minute music listening session	- No clear pattern of SNS activity was apparent from the levels of biomarkers - Levels of biomarkers did not differ significantly between intervention and control group - Levels of corticotrophin and cortisol decreased over time for the music group, but this decrease was not statistically significant
Chlan et al. (2012)[41]	Three group randomized clinical trial • Patient Directed Music (PDM): self-initiated, PDM with	Purpose: to explore the influences of music on stress in a sample of patients of the duration of ventilator support	12 ICUs at 5 urban hospitals in the US • PDM group: 19 subjects	1) 24 hour Urinary free cortisol (UFC) collected from 0700 hours to 0700 hours each day the subject	- No significant differences in UFC among groups over the course of ventilator support - Extremely high variability in study entry levels of UFC

	preferred selection tailored by a music therapist • Headphones (HP): self initiated application of noise canceling headphones • Control: Usual care (UC)		• HP group: 27 subjects • UC group: 19 subjects	was enrolled in the study	noted which could have impacted results
Chlan et al. (2001)[37]	Descriptive pilot study	Purpose: to test feasibility of patient-initiated music intervention protocol over a 3 day trial and to discern the associated barriers to adherence by study participants and nursing staff	1 ICU at a tertiary care center in the US • 5 subjects	1) Vital signs measured at baseline and after completion of the intervention 2) Anxiety measured by a visual analogue scale, given before and after each intervention session	- Patient initiated music is a feasible intervention protocol - Subjects were able to independently request music - Nurses were cooperative in offering the intervention
Chlan et al. (2013)[17]	Three group randomized clinical trial • Patient Directed Music (PDM): self-initiated, PDM with preferred selection tailored by a music therapist • Headphones (HP): self-initiated application of noise canceling headphones • Control: Usual Care (UC)	Purpose: to test whether listening to self-initiated PDM can reduce anxiety and sedative exposure during ventilator support in critically ill patients	12 ICUS at 5 urban hospitals in the US • PDM group: 126 subjects • HP group: 122 subjects • UC group: 125 subjects	1) Daily anxiety measured by visual analogue scale 2) Sedative exposure measured by sedative drug intensity score	- PDM subjects had significantly lower anxiety scores than subjects in the UC group - By the 5th study day, anxiety was reduced by 36.5% in PDM patients - PDM significantly reduced measures of sedative exposure - By the 5th study day, PDM subjects received 2 fewer sedative doses than subjects in the UC group

Conrad et al. (2007)[40]	Two group randomized clinical trial • Intervention: slow movements of Mozart's piano sonatas for 1 hour • Control: Rest for 1 hour with headphones with no music	Purpose: to identify mechanisms of music-induced relaxation using a special selection of slow movements of Mozart's piano sonatas	1 ICU • 10 subjects	1) Vital signs, continuously during intervention 2) Brain electrical activity, continuously during intervention 3) Serum levels of stress hormones and cytokines before and after intervention 4) Requirements for sedative drugs 5) Level of sedation before and after music intervention	- The intervention significantly reduce the amount of sedative drugs needed to achieve a comparable degree of sedation - Subjects that received music had increased levels of growth hormone and decreased levels of interleukin-6 and epinephrine - The reduction in stress hormones in the subjects that received music was associated with a significantly lower blood pressure and heart rate
Dijkstra, et al. (2010)[21]	Two group randomized clinical trial • Intervention: Listened to music 3 times for 30 minutes over 2 days • Control: had 3 rest periods for 30 minutes of 2 days	Purpose: to determine the effects of music on physiological responses and sedation scores in sedated, mechanically ventilated patients	3 ICUs in a university hospital in the Netherlands • Intervention group: 10 subjects • Control group: 10 subjects	1) Vitals signs at baseline, after 5, 10, 20, 30, 60 minutes 2) Sedation scores measured by the Ramsay Sedation Scale measured at baseline and after music or rest	- Subjects in the intervention group had higher sedation scores, indicating music leads to a deeper level of sedation - No significant decreases in physiological parameters were observed
Han et al. (2010)[28]	Three group randomized clinical trial • Listening to relaxing music for a single 30 minute session • Headphones with no	Purpose: to examine the effects of music intervention on the physiological stress response and the anxiety level among mechanically	A single ICU at a large teaching hospital in China • Music listening group: 44 subjects	1) Vital signs, baseline, every 5 minutes during intervention and at 5 minutes after intervention 2) Anxiety measured by	- Significant differences among groups for HR, BP, RR, and anxiety - Significant reduction in physiological stress response over time in music listening

	music for a single 30 minute session • Control with quiet rest for a single 30 minute session	ventilated patients in the intensive care unit	• Headphones group: 44 subjects • Control group: 49 subjects	the Spielberger State-Trait Anxiety Scale, measured before and after 30 minute session or all groups	group - Significant increase in physiological stress response over time in control group - Significant reduction in anxiety score for the music group and headphone group
Hunter et al. (2010)[4]	Feasibility study with historical controls • Intervention: 45-60 minute MT sessions offered 3 times/week during weaning trials; time of session determined by where patient was in weaning process	Purpose: to determine the feasibility of incorporating music therapy in to the weaning process and to evaluate the efficacy of the intervention based on levels of anxiety, days to wean and patient/nurse satisfaction	A single pulmonary stepdown unit of a large tertiary teaching hospital in the US • 61 subjects	1) Anxiety measured by a patient survey and a staff survey 2) Vital signs before and after each music therapy session 3) Days to Wean (DTW) 4) Satisfaction measured by a patient survey and a staff survey	- Patient and nurse satisfaction with the intervention were both high - Significant difference in HR and RR found from beginning to the end of the music therapy session suggesting a more relaxed state had been achieved - Staff assessment of anxiety demonstrated patient appeared to be less anxious after intervention
Korhan et al. (2011)[23]	Case control experimental study • Intervention: Classical music listening for 60 minutes • Control: Usual ICU care	Purpose: to investigate if relaxing music is an effective method of reducing the physiological signs of anxiety in patients receiving mechanical ventilator support	A single ICU in a teaching hospital in Turkey • 30 subjects for the intervention • 30 subjects for the control	Vital Signs measured immediately before the intervention, at the 30th, 60th, and 90th minutes of the intervention, and 30 minutes after the intervention	- Subjects in the music group had significant lower mean RR and BP than the control group - The decrease in RR and BP improved progressively in the 30th, 60th, and 90th minutes of the intervention suggesting a cumulative dose effect
Lee et al.	Two group randomized	Purpose: to investigate	A single ICU in	1) Vital signs measured	- Significant decreases in HR,

(2005)[24]	clinical trial • Intervention: 30 minute relaxing music listening • Control: 30 rest period with headphones with no music	effects of music on the anxiety of patients on mechanical ventilators as assessed by objective parameters and a subjective validated anxiety scale	Hong Kong • Intervention group: 32 subjects • Control group: 32 subjects	before and after the intervention 2) Anxiety measured by the Chinese version of the Spielberger State Trait Anxiety Inventory Scale measured before and after the intervention 3) Resting Behavior Observation checklist 4) Patient Satisfaction measured before and after the intervention	RR, systolic BP and diastolic BP were noted after the music intervention in the music group - An increased in observed resting behaviors was observed in the intervention group
Saadatmand et al. (2013)[31]	Two group randomized clinical trial • Intervention: 30-90 minutes of listening to nature-based sounds • Control: 30 minute rest period with headphones with no music	Purpose: to identify the effect of the nature-based sounds' intervention on agitation, anxiety level, and physiological stress responses in patients under mechanical ventilation support	A single ICU in a teaching hospital in Iran • Intervention group: 30 subjects • Control group: 30 subjects	1) Vital signs measured before the procedure, at the 30th , 60th , and 90th minutes of the procedure and 30 minutes after procedure 2) Anxiety measured by the FACES anxiety scale 30 minutes after the intervention 3) Agitation measured by the Richmond Agitation Scale during the intervention	- The intervention group had significantly lower systolic BP, diastolic BP, anxiety and agitation levels than the control group - The reductions observed were progressive over time, indicating a cumulative dose effect
Stubbs (2005)[39]	Qualitative Study • Intervention: 30 minutes of relaxing music listening on 2 prescribed occasions	Purpose: to gain insight into patients' and nurses' perception of the benefit of music therapy during critical illness and to add to	A single ICU in a community hospital in the US • 5 patients • 4 nurses	1) Unstructured interviews after ICU discharge but before leaving the hospital. 2) Results were analyzed	- When interviewed, no patients remembered listening to music. Nursing staff made timetables of music interventions which

		the body of knowledge in nursing around the use of therapies complementary to medicine		according to Burnard's framework	was successful in jogging patients' memories - Patients' notable comments concerned 1) imagery, 2) being somewhere else, 3) pain perception altered by music, 4) sleep relaxation, 5) music dreams - None of the nurses interviewed felt there were any disadvantages and found the results to be positive
Twiss et al. (2006)[36]	Two group randomized clinical trial • Intervention: listened to music continuously throughout surgery and while in ICU • Control: received usual post-operative care	Purpose: to determine the effect of music listening on postoperative anxiety and intubation time in patients undergoing cardiovascular surgery	A single ICU in the US • Intervention group: 28 subjects • Control Group: 32 subjects	1) Anxiety measured by the Spielberger State Trait Anxiety inventory administered the night before surgery and the 3rd post-operative day 2) Intubation time – measured by the time patient left the OR until they were extubated	- Subjects in the music group had significantly lower anxiety scores - Subjects in the music group had fewer minutes of postoperative intubation after cardiovascular surgery
Wong et al. (2001)[22]	Crossover design with random assignment • Randomized to get 30 minutes of music therapy then 30 minutes of uninterrupted rest or vice versa • Music: relaxing music via headphones • Control: uninterrupted rest	Purpose: to assess the effectiveness of music therapy in decreasing anxiety in ventilator dependent patients	A single ICU in Hong Kong • 20 subjects	1) Vital signs measured before intervention and at 5 minute intervals throughout intervention 2) Anxiety measured by the Chinese version of the Spielberger State Trait Anxiety Inventory measured before and immediately after intervention	- Music listening was more effective in decreasing state anxiety than uninterrupted rest period - Significant difference of BP and RR were observed at the end of the intervention between the two conditions, with music being superior to the rest period

The next section of Chapter 2 contains the conceptual framework that was created to guide the development of the dissertation project and provide a foundation for the secondary analysis. Figure 1 was developed to provide an illustration of the framework whereas Figure 2 provides greater detail of the specific study variables available for examination during the statistical analysis.

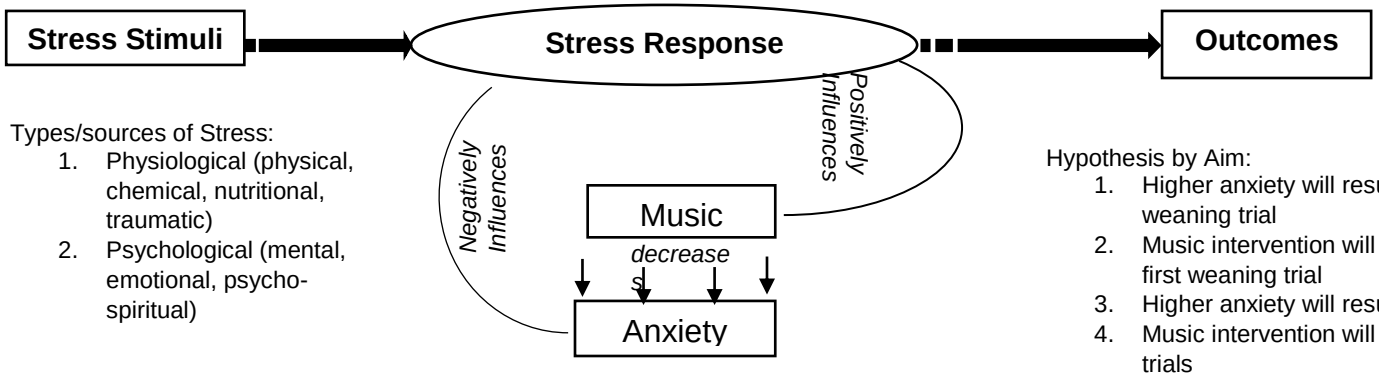
CONCEPTUAL FRAMEWORK

The conceptual basis of this study (See Figure 1) was guided by a thorough review of the literature related to the use and effectiveness of music interventions during MV and during ventilator weaning. The conceptual basis used to guide the parent study (R01-NR009295) was adapted to direct the proposed secondary data analysis. MV is a common life-saving intervention; however the physiological and psychological stress induced by MV is exacerbated by acute illness severity and a variety of environmental factors. Enduring MV can provoke severe anxiety and elicit a harmful stress response (Silverman, 2002; Tracy & Chlan, 2011; Wunsch et al., 2010). This stress response can cause delays in extubation, lengthen recovery time, and increase morbidity and mortality (Hunter et al., 2010; Kulkami & Agarwal, 2008; Puntillo et al., 2010; Silverman, 2002; Tracy & Chlan, 2011; Wunsch et al., 2010). Music interventions can calm the stress response and decrease anxiety during MV and promote effective weaning from MV (Bradt, Dileao, & Grocke, 2010; Disch & Kreitzer, 2003; Hunter et al., 2010; Tracy & Chlan, 2011). It is unknown to what extent anxiety and music can influence the time to first weaning trial **[Aims #1,**

#2] and the duration of weaning trials **[Aims #3, #4]**. Individual factors that have been hypothesized to impact weaning trials have been extracted from the parent study and can be found in Figure 2.

Figure 1

Influence of Music on the Stress Response and Outcomes in Mechanically Ventilated Patients



Types/sources of Stress:

1. Physiological (physical, chemical, nutritional, traumatic)
2. Psychological (mental, emotional, psycho-spiritual)

Hypothesis by Aim:

1. Higher anxiety will result in increased time to first weaning trial
2. Music intervention will result in decreased time to first weaning trial
3. Higher anxiety will result in a shorter weaning trials
4. Music intervention will result in longer weaning trials

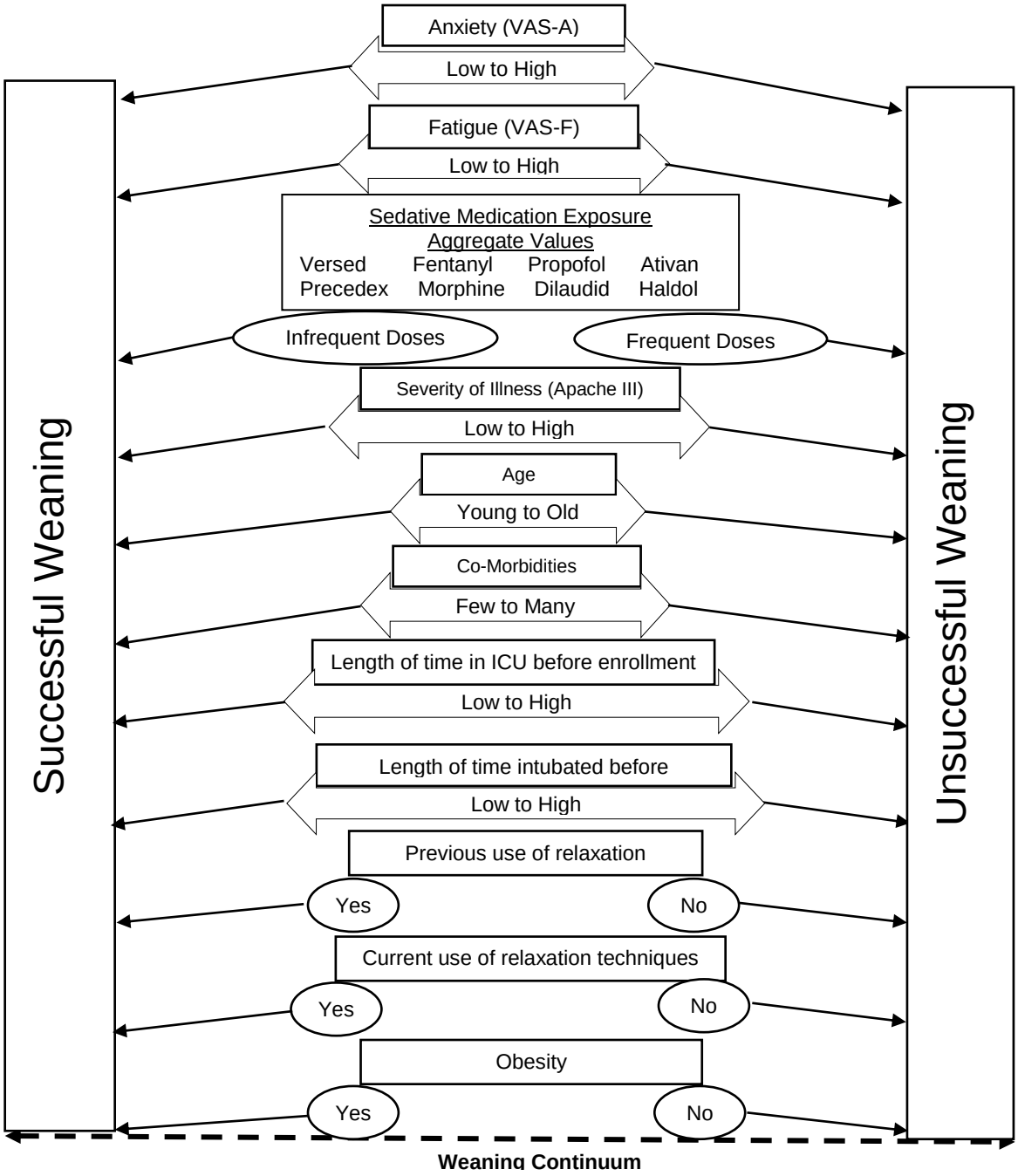
Anticipated Outcomes:

Music interventions will lower patient anxiety, resulting in more effective weaning trials thus:

1. Facilitate extubation
2. Accelerate recovery
3. Decrease morbidity and mortality

Figure 2

Variables that Impact Weaning



Conceptualized definition of a **successful weaning**

- Projected observed trend: shorter time to first wean, trials will be longer in duration overall

Conceptualized definition of an **unsuccessful weaning**

- Projected observed trend: longer time to first wean, trials will be shorter in duration overall

The final section of Chapter 2 contains the second manuscript, titled, “The influence of music and anxiety on weaning trials in patients undergoing mechanical ventilation”. It was developed from the NRSA grant application and then expounded upon during the construction of the author’s second comprehensive exam, the Doctoral Research Prospectus. This manuscript begins with an introduction to the process of weaning from MV and offers support for the purpose and need for the dissertation study. The manuscript continues by explaining the parent study and then focusses on the methods, results, and discussion of the dissertation research project. This manuscript concludes the Specific Content section of the dissertation. The authors’ plan is to first submit the manuscript to the American Journal of Critical Care. If it is not accepted, the manuscript will be submitted to the Western Journal of Nursing Research.

MANUSCRIPT 2

The influence of music and anxiety on weaning trials in patients undergoing mechanical ventilation

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University of Minnesota

Summary

Objectives: Weaning from mechanical ventilation (MV) requires increased respiratory effort which heightens anxiety and prolongs MV. The purpose of this paper was to examine the relationship among music, anxiety, and ventilator weaning to better understand factors that facilitate successful weaning.

Design: A descriptive, correlational design was used to address the primary aims for this secondary data analysis project.

Methods: Music intervention was defined as self-initiated, patient directed-music via headphones. Anxiety was measured daily using a self-report visual analogue scale. Analyses consisted of descriptive statistics, graphing, survival analysis, Cox proportional hazards regression, and linear regression.

Results: Subjects (N=307) were 52% female, 86% white. Mean age was 59.3 ± 14.4 years; APACHE III scores were 62.9 ± 21.6. Length of ventilation was 8 days (range, 1-52). Length of ICU stay was 18 days (range, 2-71). Subjects with higher illness severity had shorter times to first weaning trial after study enrollment. For each day from study admission, weaning trials increased in duration. If a subject had a tracheostomy on the day of the weaning trial, weaning trials increased in duration for that day.

Conclusions: Music intervention and self-reported anxiety were not found to influence time to first weaning trial or duration of weaning trials, but clinical practice factors of illness severity, days of weaning trials, and tracheostomy

placement influenced weaning patterns in this sample of ventilated subjects. Further examination of music intervention and other psychophysiological factors during weaning from MV with prospective primary studies is recommended to better understand factors that facilitate successful weaning.

Introduction

Initiation of mechanical ventilation (MV) for respiratory distress or failure is a life supporting intervention for over 800,000 patients each year in the United States (Wunsch et al., 2010); that number is expected to rise significantly as the population ages (Zilberberg & Shorr, 2008). Successful ventilator weaning is necessary to terminate support and resume independent respiration (Eskandar & Apostolakos, 2007; Kulkami & Agarwal, 2012; Stawicki 2007; White et al., 2008). Up to 40% of the time that patients spend on the ventilator is spent weaning (Eskandar & Apostolakos, 2007). Patients who require mechanical ventilator support for more than three weeks account for more than 50% of total ICU costs (Wunsch et al. 2010). Thus timely, effective weaning is essential to decrease the personal and economic costs of MV (Twibell, Siela, Mahmoodi, 2003). There is a critical need to consider the physiological and psychological factors that prolong weaning and delay extubation and to develop innovative interventions to address those modifiable factors in order to promote efficient weaning and ventilator termination. The purpose of this paper is to examine the relationship among music intervention, anxiety, and ventilator weaning in order to better understand the factors that may facilitate successful ventilator weaning.

Background

MV is a common ICU intervention used to support respiratory function that involves the use of a mechanical ventilator to deliver oxygen gas into the lungs through an artificial airway in the mouth, nose, or through a tube inserted directly into the trachea in order to promote effective gas exchange (Neligan, 2006). Patients may require MV after suffering from respiratory distress or failure secondary to conditions such as trauma, cardiac arrest, an inability to protect the airway, infection, cancer masses, sepsis, surgery, and organ failure (Hall & McShane, 2013).

In order for MV to be terminated, patients must demonstrate their ability to breathe independent of the ventilator. Weaning trials, designated periods of time that patients must initiate and maintain ventilation, must be completed before the artificial airway can be removed. A weaning trial is generally considered successful if the patient is able to tolerate at least 30 minutes of spontaneous breathing that is free from negative responses such as increased heart rate or respiratory rate, decrease in oxygen saturation, restlessness, and diaphoresis (Nickson, 2015). Recommendations call for weaning trials to be attempted daily (Barr et al., 2013). Extubation, the term used to describe the removal of the artificial airway, may be feasible after the patient successfully completes two or more weaning trials (Pruitt, 2006). Weaning to extubation might only take a few days, but can be a complicated and extended process for some. Patients who require prolonged MV may receive a tracheostomy, which is an opening created

in the neck to allow direct access to the breathing tube. Tracheostomies improve airway security, promote mobility, enhance comfort, and facilitate ventilator weaning (Young, 2013; Siempos, 2015).

MV can cause distressing physical symptoms and psychological distress (Puntillo et al., 2010; Rotundi et al., 2002). Anxiety, a sustained state of apprehension and arousal in response to a real or perceived threat, is one of the most frequent and debilitating symptoms experienced by ventilated patients (Silverman, 2002). High stress and anxiety levels have been associated with increased patient morbidity and mortality in ventilated patients (Bradt et al., 2010). Weaning can further exacerbate the physical and emotional symptoms experienced during MV because it requires increased respiratory effort that can lead to hyperventilation and feelings of panic, thus inducing early fatigue during weaning (Blackwood, 2000; Schou & Egerod, 2008; Twibell, Siela, & Mahmoodi, 2003). Patients who did not wean successfully from the ventilator reported more fatigue, dyspnea, and less weaning self-efficacy (Twibell et al., 2003).

Anxiety is commonly managed through the administration of sedative and analgesic medications by nursing staff. At times, the administration of these medications is necessary to promote comfort, decrease oxygen consumption, facilitate nursing care, and ensure patient safety (Girard et al., 2008; Rotundi et al., 2002). Overuse of these medications can cause many negative side effects such as increased rates of organ failure, short-term and long-term issues with memory, cognition, and emotional stability, inaccurate neurological assessments,

reintubation, and medication withdrawal (Brush & Kress, 2009). Over-sedation can have grave consequences on weaning success, thus it is important to consider alternative methods to decrease the symptom burden of ventilator weaning while maintaining alertness and promoting physical and psychological wellbeing.

Current guidelines for the management of pain, agitation, and delirium in adult ICU patients recommend maintaining “light” levels of sedation to enable responsiveness and awareness sufficient enough to follow simple commands while mechanically ventilated (Barr et al., 2013). Lighter sedation has been shown to improve clinical outcomes by decreasing total ventilator time and overall ICU lengths of stay but lightening sedation may heighten the physiological stress response (Barr et al., 2013) as well as intensify psychological stressors (Shou & Egerod, 2008). This increased stress creates the need for adjunctive symptom management strategies that can alleviate anxiety but maintain alertness. Music intervention is a viable non-pharmacological option that can be used adjunctively to reduce sedative exposure and can effectively manage anxiety in the mechanically ventilated patient (Chlan et al., 2013; Dijkstra et al., 2010; Korhan et al., 2011; Lee et al., 2005; Wong et al., 2001). Evidence has shown that patients had a decrease in psychological and physiological signs of anxiety (Bradt et al., 2010) and a reduction in sedative exposure (Chlan et al., 2013) in response to music intervention, which could indicate a beneficial relaxation response.

Achieving a more relaxed state with little to no pharmacological therapy while maintaining alertness may greatly promote ventilator weaning. The influence of music intervention and anxiety during weaning from MV is not known. The purpose of this secondary analysis of data was to examine the relationships among factors that may facilitate ventilator successful ventilator weaning. The specific aims for this secondary data analysis were to determine the following for patients receiving MV: 1) the influence of music on time to first weaning trial after study enrollment; 2) the influence of anxiety on time to first weaning trial after study enrollment; 3) the influence of music on the duration of weaning trials after the study period; 4) the influence of anxiety on the duration of weaning trials after the study period.

Methods

Overview of the Parent Study

This secondary data analysis was based on a subset of individuals who participated in a randomized controlled clinical trial (1RO1 NR009295) between September 2006 and March 2011 (Chlan et al., 2013). This parent study, which included 373 subjects who underwent MV, aimed to test whether listening to self-initiated, patient directed-music (PDM) reduced anxiety and sedative exposure during ventilator support in critically ill patients. Subjects were recruited from 12 adult ICUs in five teaching and non-teaching hospitals in the urban Midwest. All participating ICUs were located in large regional referral medical centers in the Minneapolis/St. Paul metropolitan area. To be eligible for recruitment, subjects

had to 18 years of age or older, in the ICU, receiving acute mechanical ventilator support with anticipated continuation of support for at least 48 hours, deemed awake and alert based on nurse assessment, able to make daily care decisions, have free use of hands along with adequate vision and hearing, receiving IV sedative medications, and have English as a primary language. Subjects were maintained on protocol as long as they were receiving ventilator support, up to 30 days, or until they were extubated, chose to withdraw, were transferred from the ICU, or died.

The parent study used a three group experimental design with repeated measures. A stratified randomization approach was used to achieve a balanced group assignment across multiple sites. Subjects were randomized to one of three conditions: patient-directed music (PDM), noise-canceling headphones (HPs), or usual ICU care (UC). Subjects randomized to the PDM group received usual ICU nursing care and were prompted to listen to preferred music via noise-canceling headphones and a CD/MP3 player whenever they were feeling anxious or needed quiet time. PDM subjects were encouraged to listen to music at least twice per day whenever feeling anxious or wanting relaxation, but were able to use their own discretion to determine how long and how frequently they wished to listen. A complete music preference assessment was performed by a board certified music therapist. Then, a CD collection of a variety of relaxing music choices without lyrics that met established tempo, instrumental, and rhythm requirements was tailored by the music therapist based on subjects'

preferences. Subjects randomized to the HPs group also received usual ICU care, in addition, they were provided with noise-canceling headphones to apply when they desired quiet time. Subjects in the UC group received usual nursing care as designated by the protocols and procedures of the participating unit.

Sedative exposure was operationalized as a daily sedative drug intensity score and sedative dose frequency score (Weinert & Calvin, 2007; Chlan et al., 2013). Sedative administration practices and protocols used were specific to the units in which the study was conducted.

Procedures and data collection. Baseline demographic data were collected and subjects were assigned to one of the three conditions. Study subjects were visited daily by a trained research nurse to assess the most current level of anxiety. They were asked to rate their current level of anxiety on a visual analogue scale (0-100) in response to “How are you feeling right now?” Data collection was continued for the duration the subject remained in the study (up to 30 days) and mechanically ventilated or until the subject withdrew, was extubated, transferred, or died. Subjects were followed after extubation until their transfer out of the ICU to record length of ICU stay. If a study participant required long-term MV for more than 30 days, they were tracked until transfer out of the ICU or death. Subjects who were extubated and reintubated within 12 hours remained in the study. Subjects who were reintubated after 12 hours while still in the ICU were not re-enrolled.

Secondary Data Analysis Project

Design. A descriptive, correlational study design was used to address the study aims with a secondary data analysis project from a previously conducted randomized clinical trial (1RO1 NR009295).

Sample. Subjects were included in the secondary analysis if they were enrolled in the parent study for at least 24 hours, were intubated less than 40 days prior to study enrollment, and if they had recorded sedative exposure data. A study flow diagram is presented in Figure 1.

Conceptual framework*.* The development of the conceptual basis of this study (Figure 2) was guided by a thorough literature review of the influence of music intervention during MV and weaning from MV (Hetland, Lindquist & Chlan, in press). The framework was used to guide the selection of variables available for this secondary data analysis project.

Variables and their Measurement.

Demographic and Clinical Variables. Baseline demographic data included age, gender, race, history of ventilator support, and type of artificial airway. Severity of illness was measured by the Acute Physiology, Age, Chronic Health Evaluation (APACHE III) (Knaus et al., 1991) using variables from the day of ICU admission. Length of ICU stay was recorded in days beginning with admission and ending with discharge from the unit or death. Days in the ICU prior to study enrollment was recorded in days beginning with admission and ending with the day the subject was enrolled in the study. Length of mechanical

ventilator support was recorded in days beginning when the subject was intubated and ending with extubation, tracheostomy dome greater than 24 hours, or death. Ventilator settings such as rate, mode, tidal volume, pressure support, PEEP, and FiO_2 were recorded daily.

Anxiety. Anxiety was measured daily using a visual analogue scale for anxiety (VAS-A). Subjects were asked to rate their anxiety on a 100-millimeter vertical line, which was anchored at the bottom by the statement, “not anxious at all” and anchored at the top by the statement, “the most anxious I have ever been”.

Music. Group assignment was determined using a computer-generated random numbers list, which allocated subjects into one of three groups: experimental group of PDM, and two control conditions of HPs and UC. To address the aims of this project, the PDM and HPs subjects were analyzed as separate groups, independent of each other. For the analyses, UC was considered the reference group.

Time to first weaning trial. Time to first weaning trial was defined as the time from study enrollment until the first weaning trial was attempted after study enrollment. Start and stop times for each trial were not available in the parent study’s electronic database. The day and time of the first weaning trial was abstracted by hand from paper records; only the day and time of the first recorded weaning trial after enrollment was abstracted. Time to first weaning trial

was defined as the time from study enrollment to the first recorded weaning trial during the study period.

Duration of weaning trials. Duration of weaning trials was defined as the length of time from the start of each weaning trial(s) to the end of each weaning trial(s) for every day of the study period***.*** Not all subjects experienced a weaning trial each study day. For those subjects who experienced a weaning trial at least once daily, weaning trial data were recorded including method of weaning, FiO_2, PEEP, pressure support and duration of each weaning trial in minutes, and the number of weaning trials for that day.

Additional detailed information about the variables and their measurement used can be found in Table 1 and Table 2.

Ethical Considerations

Approval for the use of human subjects in research for the parent study was obtained from the Institutional Review Boards (IRBs) at the University of Minnesota and from all participating sites in the parent study. Written, informed consent was obtained from all potential subjects for study participation and access to personal health information contained in the medical records (HIPAA). All written consents were obtained by trained research nurses. After the completion of the parent study, subject data were stored in a locked file cabinet with limited access and electronic databases were all password protected. IRB approval was obtained from the University of Minnesota for completion of this secondary data analysis (IRB Number 1410E54262).

Data Analysis Plan

Data analyses were accomplished using SPSS, v. 22 and SAS v 9.3. All data were analyzed descriptively via univariate statistics using independent samples t-tests and Chi-square tests. Means and standard deviations were provided for interval level data that were normally distributed. Medians and ranges were provided for non-normally distributed interval data. Frequencies and percentages were provided for categorical data. Results were considered significant *a priori* at $p < .05$.

Analysis by Specific Aims. The influence of music (assignment to PDM) on time to first weaning trial after study enrollment and the influence of anxiety on time to first weaning trial after study enrollment (Aims 1 and 2) were analyzed together using a Cox proportional hazards regression using group assignment (PDM, HP, and UC) as a fixed covariate.

The influence of music (assignment to PDM) on duration of weaning trials during the study period and the influence of anxiety on duration of weaning trials during the study period (Aims 3 and 4) were analyzed together using linear regression controlling for day in the study was accomplished by mixed modeling to account for repeated events and repeated covariates.

Results

Demographic and Clinical Characteristics

Table 3 summarizes the characteristics of the study sample (N=307); PDM (n=104), HPs (n=99), UC (n=104). Mean illness severity by APACHE III scores

was 62.9 (±21.6), median 61, range 15-133, reflecting a broad range of illness severity upon ICU admission. The majority of subjects were orally intubated [(n = 249) (81.1%)] for respiratory failure [(n =169 (55.0%)] or respiratory distress [(n = 79 (25.7%)]. Anxiety, sedation intensity score, and sedation frequency were not statistically different at study entry among groups. Of the 269 subjects that attempted at least one weaning trial during the study period, 130 (48.3%) required MV in a previous hospitalization, whereas, only 13 of the 38 (34.2%) subjects who did not attempt at least one weaning trial during the study period required MV in a previous hospitalization (p=.04). Subject status at discharge (dead vs. alive) was also significantly different between groups; 93% of subjects who attempted at least one weaning trial during the study period were alive at discharge compared to 79% of subjects who did not attempt to wean were alive at discharge (p=.01).

Aim 1 and Aim 2: The influence of music on time to first weaning trial after study enrollment, and the influence of anxiety on time to first weaning trial after study enrollment.

First, an exploratory survival analysis was graphed comparing the three groups and the general trends for time to the first weaning trial after study enrollment. Daily anxiety ratings were treated as a time dependent covariate. Other covariates, static and time dependent, were screened individually in the proportional hazards regression and introduced into the model if they were

significant at $p < .1$. Due to the almost collinear relationship between sedation frequency and sedation intensity, two models were created.

The first model estimates the time to first weaning trial after study enrollment by group assignment and anxiety, controlling for sedation frequency in addition to other covariates that may impact time to first weaning such as total days in ICU prior to enrollment, APACHE III, and history of MV during a prior hospitalization. This model indicated that group assignment and anxiety were not statistically significant predictors of time to first weaning trial after study enrollment for this subset of subjects (Table 4). Controlling for sedation frequency, subjects with higher severity of illness scores (APACHE III) were more likely to experience a shorter time to first weaning trial after study enrollment.

The second model estimates the time to first weaning trial after study enrollment by group assignment and anxiety, controlling for sedation intensity score in addition to other covariates such as total days in ICU prior to enrollment, APACHE III, and history of MV during a prior hospitalization. This model also indicated that group assignment and anxiety were not statistically significant predictors of time to first weaning trial after study enrollment (Table 5). Controlling for sedation intensity, subjects with higher severity of illness scores (APACHE III) were more likely to experience a shorter time to first weaning trial after study enrollment.

All covariates in the models showed various levels of significant correlations, weak to moderately strong (Table 6). Thus, it can be interpreted that the covariates shared much information and the results reflect that the shared information of these covariates influenced each other in relation to time to first weaning trial.

Aim 3 and Aim 4: The influence of music on duration of weaning trials during the study period, and the influence of anxiety on duration of weaning trials during the study period.

Linear regression with duration of weaning trial as the dependent variable in the context of mixed models was used to address the study aims. Mixed models were chosen as there could be multiple trials for a single subject and the related data had to be accounted for in the model. Covariates were screened individually in the linear regression and introduced into the model if they were significant at $p < .1$. Again, due to the almost collinear relationship between sedation frequency and sedation intensity, two models were created.

The first model estimates the influence of group assignment and anxiety on duration of weaning trials during the study period controlling sedation frequency in addition to other covariates including day, weaning trial number, age, days ventilated prior to enrollment, days in ICU prior to enrollment, FiO_2, and presence of a tracheostomy. In this model, group assignment and anxiety were not statistically significant predictors of duration of weaning trials during the study period (Table 7). For each day since study enrollment, weaning trials

increased by 8.4 minutes (p<.001). If a subject had a tracheostomy on the day of the weaning trial, weaning trials for that day increased by 53.6 minutes (p=.04).

The second model estimates the influence of group assignment and anxiety on duration of weaning trials during the study period controlling sedation intensity score in addition to other covariates including day, weaning trial number, age, days ventilated prior to enrollment, days in ICU prior to enrollment, FiO_2, and presence of a tracheostomy. This model also indicated that group assignment and anxiety were not statistically significant predictors of duration of weaning trials during the study period (Table 8). For each day since study enrollment, weaning trials increased by 8.6 minutes (p<.001). If a subject had a tracheostomy on the day of the weaning trial, weaning trials for that day increased by 54.6 minutes (p=.03).

As above, the covariates in the models were correlated and reflect the shared information of these covariates that influenced each other in relation to weaning trial time and duration (Table 9).

Discussion

The primary aims of the study were to determine if music (assignment to PDM) and anxiety influenced time to first weaning trial after study enrollment and duration of weaning trials during the study period in patients receiving mechanical ventilatory support. It was hypothesized that individuals who received PDM and those with lower anxiety scores would have shorter times to first weaning trial after study enrollment and weaning trials that were longer in

duration. Likewise, subjects who did not receive PDM and those who reported higher anxiety scores would have longer times to first weaning trial after study enrollment and weaning trials that were shorter in duration. The hypotheses were not supported; we determined that music (assignment to PDM) and anxiety were not statistically significant predictors of time to first weaning trial after enrollment nor were they statistically significant predictors of duration of weaning trials during the study period. However, important information regarding various factors that may impact weaning success can be gained from this analysis.

To our knowledge, this is the first-ever investigation of data from a large randomized clinical trial of acutely ill ICU subjects to examine music intervention (self-initiated, patient directed music listening) and anxiety on aspects of weaning from MV. Previous literature has demonstrated the positive impact of music intervention during MV (Bradt et al., 2010; Hetland et al., in press), but only one study could be identified that examined music intervention as an adjunctive treatment specifically during weaning from MV (Hunter et al., 2010). While this study reported that music intervention led to a more relaxed state during weaning, it had a small sample size and used historical controls (Hunter et al., 2010).

We found demographic characteristics to be comparable at study entry between subjects that attempted at least one weaning trial and subjects that did not attempt at least one weaning during the study period. There were no differences in anxiety level, sedation frequency, sedation intensity score, or

illness severity at study entry. However, subjects who did not attempt a weaning trial during the study period were more likely to die during the hospitalization (29% versus 8%, p=.01). In addition, we found that subjects with higher illness severity (APACHE III) were more likely to experience a shorter time to first weaning trial after study enrollment which is opposite of what would be clinically expected. These findings may be attributed to the manner in which illness severity was calculated in the parent study (Chlan et al., 2013). APACHE III scores were only measured once using variables from the day of ICU admission, thus we could not account for physiological changes over time (Knaus, et al., 1991). If a subject's physiological status improved or deteriorated in response to therapeutic treatments during the course of illness, measurements of illness severity would also be expected to fluctuate accordingly (Beck, Taylor, Millar, & Smith, 1997). With only one measurement taken on the day of ICU admission, we are unable to establish how sick patients were on the day of study admission and how illness severity fluctuated during the study period. Also, due to self-directed nature of the music intervention, the parent study required more "medically stable" critically ill subjects who were awake and alert enough to participate in the consent and self-administer the intervention as instructed.

It is recommended that weaning be considered as early as possible (Luetz, Goldmann, Weber-Carstens, & Spies, 2012). The majority of the subjects in this secondary data analysis project (n = 269) who attempted at least one weaning trial during the study protocol, did so within the first 24 hours of study

enrollment (68%). Also, in our subset of subjects, the duration of weaning trials increased progressively from the study enrollment day, which is an expected finding. The authors of the consensus report by the National Association for Medical Direction of Respiratory Care (NAMDRC) recommend progressively increasing the duration of weaning trials after a certain reduction of ventilator support has occurred (MacIntyre et al., 2005). We also found that after the influence of day was included in the models, the number of trials in each day did not influence duration of weaning trials. This is another expected finding, as previous research has shown no difference in outcome when comparing once daily weaning trials versus multiple daily weaning trials (Esteban et al., 1995).

Previous research has indicated that if a patient is expected to require prolonged MV, a tracheostomy should be considered early (Luetz, et al., 2012), but the definition for prolonged MV continues to evolve and the most ideal timing of tracheostomy placement remains unclear (Durbin, 2010). Tracheostomy placement may reduce the work of breathing, thus facilitating weaning and lessening the need for sedation and analgesia (Durbin, 2010). However, in another secondary analysis of this data set, subjects who underwent tracheostomy placement had no decrease in anxiety scores after controlling for time and gender (Breckenridge, Chlan, & Savik, 2014).

Our results demonstrated that subjects who had a tracheostomy tolerated significantly longer weaning trials, which may suggest “early” tracheostomy placement in individuals who are mostly likely to require ventilator support for a

significant period of time. These results could be due to our inclusion of weaning trials completed via a tracheostomy collar (dome). This method of weaning involves unassisted breathing with only supplemental oxygen. Patients who are able to tolerate breathing via a tracheostomy collar are often closer to achieving complete ventilator termination. Therefore, they may tolerate weaning trials that are longer in duration.

Given clinical similarities of illness severity at study enrollment, it is interesting to note approximately half of the subjects who had at least one weaning trial during the protocol had experienced MV during a previous hospitalization, compared to less than a third of subjects who never attempted a weaning trial. Further, subjects who had previously been mechanically ventilated during a prior hospitalization underwent their first weaning trial sooner after enrollment than those who had never been mechanically ventilated, suggesting that familiarity with the ventilator may positively influence weaning patterns.

Literature that specifically evaluates whether or not prior experience with MV influences weaning success is sparse, but studies have demonstrated that the weaning process elicits intense emotions of fear and anxiety due to a perceived lack of familiarity with and understanding of the weaning process (Rotondi et al., 2002; Wunderlich, Perry, Lavin, & Katz, 1999; Moody, Lowry, Yarandi, & Voss, 1997). These emotions may be lessened by frequent education regarding the weaning process. For example, in a qualitative study by Logan and Jenny (1997), ventilated, weaning patients reported feelings of fear and anxiety

in relation to being in a situation in which they had no preparation, prior experience, or understanding. One patient said, “Understanding what was going on really helps because you know where things are at, and you know how much more you have to get better or how far you have actually come.” (p. 144).

Limitations

There are a number of limitations associated with this secondary data analysis. The primary aims of this secondary analysis were not directly aligned to the specific aims of the parent study and the data collection measures used could not be amended (Smith et al., 2011). Thus, information to more accurately and thoroughly examine the aims for this study were not available for analysis such as whether or not PDM was being used at the time weaning trials were conducted, reasons why weaning trials were started and stopped, who initiated the weaning trial (physician, nurse, or respiratory therapist), sedative medication administration before, during, and after weaning trials, and overall environmental milieu that may have influenced each weaning trial. In addition, the observational nature of secondary data can make parameter estimates more difficult (Smith et al., 2011). Further, this secondary analysis project did not consider total minutes of PDM use each enrolled study day.

Limitations Specific to Study Aims

Study staff began recording weaning trials on the first day of study enrollment. It is unknown how many subjects in the analysis were already undergoing weaning trials and to what degree prior to study enrollment. Duration

of weaning trials was provided, but the exact start and stop times of each weaning trials after the first weaning trial were not available in the electronic data set; thus making it difficult to evaluate weaning patterns. The experimental PDM intervention was patient-initiated and not all subjects used the intervention twice daily as instructed. The variability in PDM use, timing and frequency could have impacted the ability to capture the group effect on study aims. Only one anxiety assessment was obtained daily and due to a variety of circumstances, some daily assessments were not completed for reasons such as “too sleepy” or “too sedated”. In addition, subjects were recruited from 12 ICUs, all of which employed a variety of weaning practices and protocols as well as sedative administration techniques. It is unknown to what degree this variability in practice influenced the colinearity observed in our models.

Conclusion

The purpose of this secondary data analysis was to examine the influence of music (assignment to PDM) and anxiety on time to first weaning trial after study enrollment and duration of weaning trials during the study period in a sample of subjects receiving mechanical ventilatory support. We found that PDM and anxiety were not significant predictors of time to first weaning trial or duration of weaning trials. However, subjects with higher illness severity (APACHE III) were more likely to experience a shorter time to first weaning trial after study enrollment. For each weaning trial a subject underwent per day, their weaning

trial increased in duration, and subjects with tracheostomies had weaning trials that were longer in duration than those who were orally intubated.

This study was the first in which a large randomized controlled trial data set was used to examine the influence of music intervention and anxiety on the physiological and psychological stressors that prolong weaning and delay extubation. Music may be a valuable non-pharmacological, adjunctive intervention to reduce burdensome symptoms that may prolong mechanical ventilator support and delay weaning. However, additional research with a prospective design and adequately powered sample sizes are needed to advance the science in this field.

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Figure 1

Flow Diagram of Study Subjects

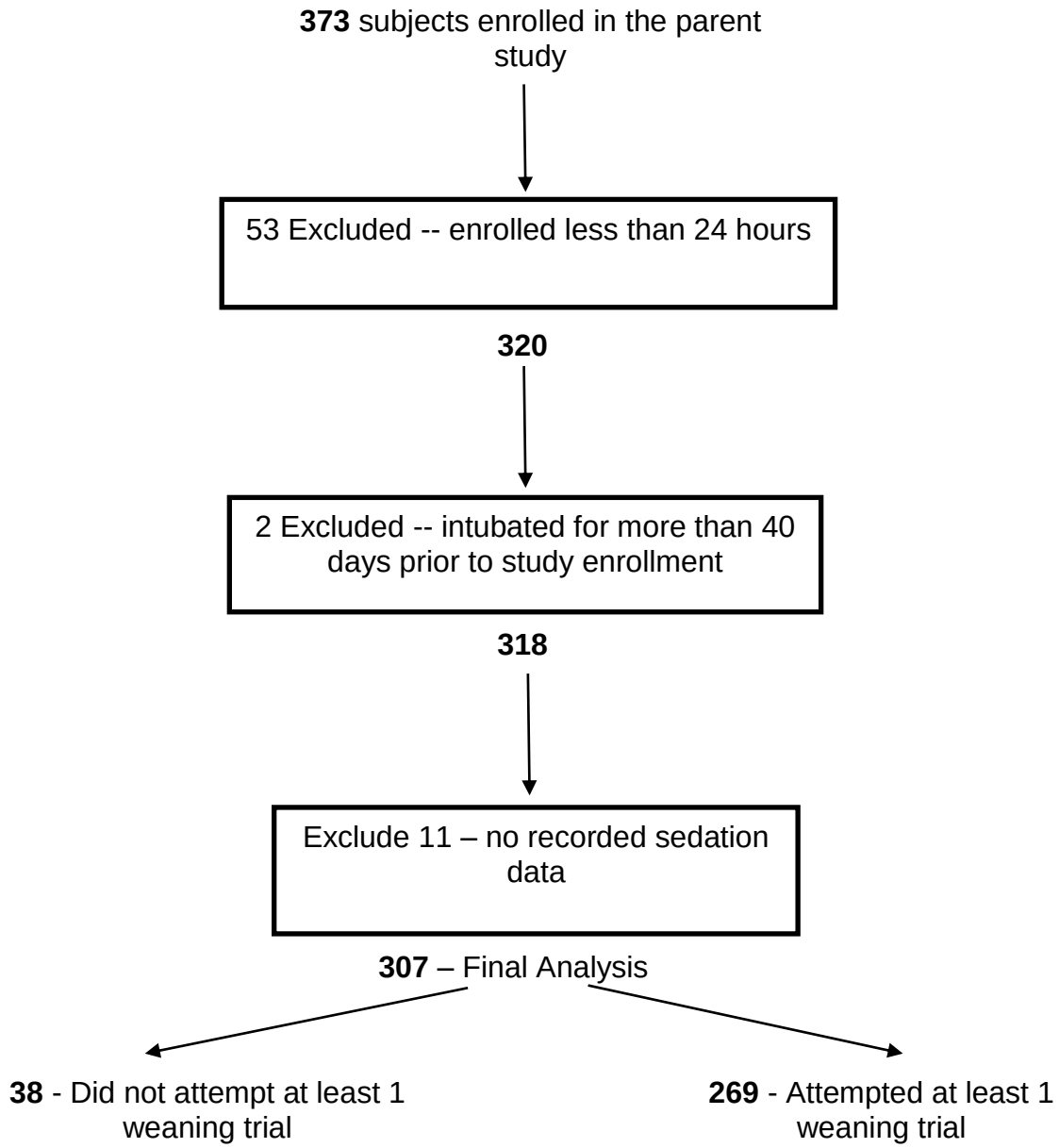

Figure 2

Influence of Music on the Stress Response and Outcomes in Mechanically Ventilated Patients

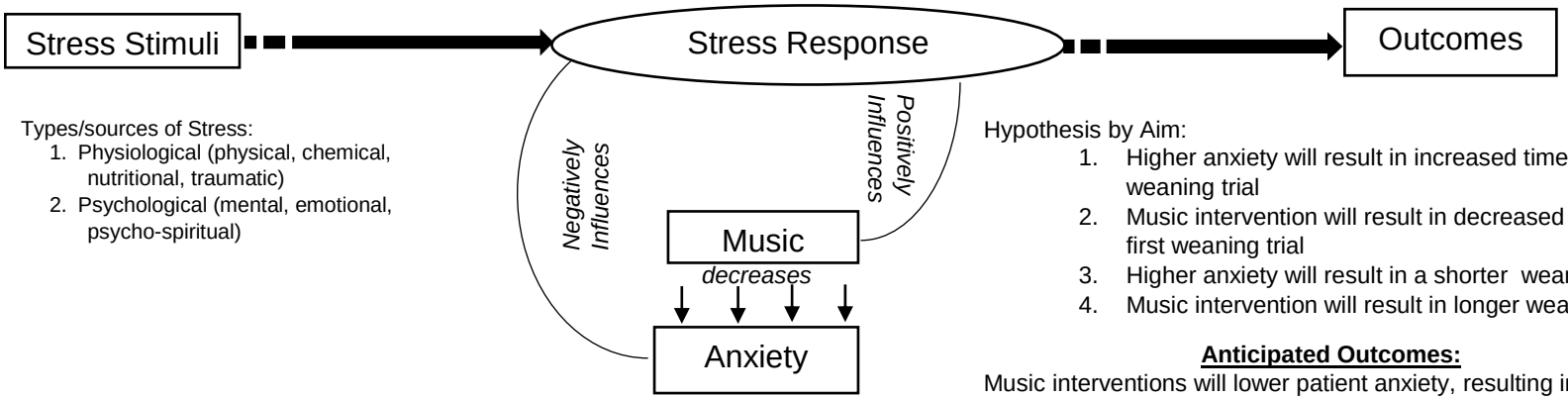

Table 1

Variables and Their Measurement

Demographic data	Baseline demographic data including age, gender, race, current medications, medical diagnosis, ventilator support history, and type of artificial airway
Severity of Illness	Severity of illness of each subject was obtained based on variables from the day of ICU admission via the Acute Physiology and Chronic Health Evaluation III (APACHE III) to establish comparability of illness severity among groups at baseline (Knaus et al, 1991). Scores range from 0-299 with higher scores indicating greater illness severity and correlating with increased incidence of in-hospital mortality (Knaus et al., 1991)
Visual Analog Scale – Anxiety (VAS-A)	Patients were asked to rate their current level of anxiety on the VAS-A in response to "How are you feeling right now?" A 100-millimeter vertical line was anchored on each end by statements "not anxious at all" to "the most anxious I have ever been."
Group Assignment	Group assignment was determined using a computer-generated random numbers list which allocated subjects into one of three groups: Patient Directed Music (PDM), Noise Canceling Headphones (HP), Usual ICU Care (UC)
Sedative Exposure	Amount of sedation (aggregate and dose frequency) and narcotics received over each 4-hour time block and the previous 12 hours. Data were quantified using two approaches: aggregate dose and frequency (Weinert & Calvin, 2007). Aggregate Dose. It is common for ICU patients to receive numerous sedative medications from different pharmalogical classes, and they may receive two medications within the same class. Therefore converting drug doses to equipotent amounts is problematic. An aggregate daily sedative dose score for each sedative medication that was weighted by its distribution within quartiles of all doses administered to the entire study sample was calculated. This method has been used in previous studies to assess sedative exposure (Chlan et al., 2013). Dose Frequency. For this approach, researchers divided the calendar day into six, 4-hour time blocks and aggregated the occurrences in which the drug was administered at least once during that interval.
Length of ICU stay	Length of ICU stay was recorded in days beginning with admission and ending with discharge from the unit or death.
Days in ICU prior to study enrolment	Length of ICU prior to study enrollment was recorded in days beginning with admission and ending with the day the subject was enrolled in the study.
Length of mechanical ventilator support	Length ventilator support was recorded in days beginning with intubation and ending with extubation or death.
Days ventilated prior to study enrollment	Length of ventilator support prior to study enrollment was recorded in days beginning with intubation and ending with the day the subject was enrolled in the study.
Ventilator settings	These values help determine the level of ventilator support required by the patient. They can indicate severity of respiratory illness as well as serve as predictors of weaning success/failure. Ventilator settings include: ventilation mode, ventilation rate, tidal volume, pressure support, fraction of inspired oxygen (FIO2), and positive end airway pressure (PEEP). Weaning variables were recorded for up to 5 weaning trials per day during the time the patient participated in the study. These variables include: time to first weaning trial, mode of oxygen support, FIO2, PEEP, pressure support, length of weaning trial in minutes.

	Time to first weaning trial after study enrollment. Recording of data began immediately after study enrollment and continued until the first weaning trial was attempted. Duration of weaning trials. Duration of weaning trials was defined as the length of time from the start of each weaning trial(s) to the end of each weaning trial(s) for every day of the study period. Not all subjects experienced a weaning trial each study day.

Table 2

Study Variables, Instruments, and Measurement Frequencies

Variable	Instrument/Source	Frequency of Measurement			
		ICU Admission	Study Entry	Daily During Study	During Each Weaning Trial
Demographic Data	Electronic Medical Record		X		
Severity of Illness	APACHE III	X			
Group Assignment	Computer generated random numbers list		X		
Anxiety	Visual Analog Scale for Anxiety (VAS-A)		X	X	
Sedative Exposure	Sedation Intensity Score			X[1]	
	Sedation Dose Frequency			X[1]	
Length of ICU Stay	Electronic Medical Record		Calculated from admission to transfer, discharge, or death		
Days in ICU prior to enrollment			Calculated from admission to study enrollment		
Length of Mechanical Ventilator Support	Electronic Medical Record		Calculated from intubation to extubation or death		
Ventilator Settings	Electronic Medical Record			X	
Weaning Variables	Electronic Medical Record				X

Notes: [1]Abstracted from medical record in four-hour blocks during mechanical ventilation; APACHE: Acute Physiology, Age, and Chronic Health Evaluation

Table 3

Characteristics of Study Sample

Variable	Total (N=307)	Weaned (n=269)	Did Not Wean (n=38)	P value
Age, mean (SD), y	59.3 (14.4)	59.6 (14.4)	57.3 (14.4)	.36[a]
Female Sex No. (%)	161 (52.4)	140 (52.0)	21 (55.3)	.71[b]
Race No. (%)				.92[b]
White	264 (86.0)	232 (86.2)	32 (84.2)	
Asian	2 (0.7)	2 (0.7)	0	
American Indian	6 (2.0)	5 (1.9)	1 (2.6)	
Black	35 (11.4)	30 (11.2)	5 (13.2)	
Group, No. (%)				.91[b]
PDM	104 (33.9)	92 (34.2)	12 (31.6)	
HP	99 (32.2)	87 (32.3)	12 (31.6)	
UC	104 (33.9)	90 (33.5)	14 (36.8)	
APACHE III, mean (SD)	62.9 (21.6)	63.3 (21.4)	59.6 (23.0)	.32[a]
Required MV in past hospitalization, No. (%)	143 (46.6)	130 (48.3)	13 (34.2)	**.04[b]**
Median ICU days prior to study entry, (range)	7 (0-40)	5 (0-40)	2 (0-32)	.42[a]
Median ICU days total, (range)	18 (2-71)	14 (3-71)	7.5 (2-40)	.05[a]
Median ventilator days prior to study entry, (range)	6(0-38)	4 (0-38)	2 (0-32)	.35[a]
Median ventilator days total (range)	8 (1-52)	8 (1-53)	5 (1-40)	.07[a]
Airway Type at enrollment				.12[b]
ETT/Oral	249 (81.1)	216 (80.3)	33 (86.8)	
Nasal	2 (0.7)	1 (0.4)	1 (2.6)	
Tracheostomy	56 (18.2)	52 (19.3)	4 (10.5)	
Reason ventilator discontinued, No. (%)				.33[b]
Not off vent at study conclusion	123 (40.1)	107 (39.8)	16 (42.1)	
Extubated	145 (47.2)	125 (46.5)	20 (52.6)	
Trach dome ≥24 hours	39 (12.7)	37 (13.8)	2 (5.3)	
Primary Indication for Mechanical Ventilation, No. (%)				.86[b]
Respiratory Failure	169 (55)	145 (53.9)	24 (63.2)	
Respiratory Distress	79 (25.7)	71 (26.4)	8 (21.1)	
COPD	8 (2.6)	7 (2.6)	1 (1.0)	
Airway Protection	8 (2.6)	7 (2.6)	1 (1.0)	
Surgery	7 (2.3)	7 (2.6)	0	
Other	36 (11.7)	32 (11.9)	4 (10.5)	
Primary Medical Diagnosis, No. (%)				.57[b]
Pulmonary	182 (59.3)	162 (60.2)	20 (52.6)	
Cardiovascular	37 (12.1)	33 (12.3)	4 (10.5)	
GI	19 (6.2)	19 (7.1)	1 (2.6)	
Renal	3 (1.0)	3 (1.1)	0 (0.0)	
Oncology	10 (3.3)	7 (2.6)	3 (7.9)	
Neuro-neuromuscular	16 (5.2)	13 (4.8)	3 (7.9)	
Trauma	8 (2.6)	6 (2.2)	2 (5.3)	
Surgery	3 (1.0)	3 (1.1)	0 (0.0)	
Sepsis/Hypotension	22 (7.2)	18 (6.7)	4 (10.5)	
Other	6 (2.0)	5 (1.9)	1 (2.6)	
Types of Co-morbidities				
Cardiovascular	223 (72.6)	199 (74.0)	24 (63.2)	.23[b]
Pulmonary	210 (68.4)	186 (69.1)	24 (63.2)	.58[b]
Cancer	47 (15.3)	40 (14.9)	7 (18.4)	.53[b]
Renal	76 (24.8)	68 (25.3)	8 (21.1)	.62[b]

Obesity	46 (15.0)	41 (15.2)	5 (13.2)	.82[b]
Diabetes	91 (29.6)	83 (30.9)	8 (21.1)	.24[b]
Sepsis	36 (11.7)	31 (11.5)	5 (13.2)	.73[b]
Neurological	89 (29.0)	81 (30.1)	8 (21.1)	.28[b]
Psychological	69 (2.5)	60 (22.3)	9 (23.7)	.79[b]
[+]VAS-A at Study entry, mean (SD)	50.2 (31.1)	50.6 (30.5)	47.7 (35.2)	.60[a]
Sedation intensity at study entry, mean (SD)	4.2(2.6)	4.1(2.6)	4.7(2.5)	.73[a]
Sedation frequency at study entry, mean (SD)	6.4(4.0)	6.4(4.0)	6.2(4.1)	.17[a]
Subject status at discharge, alive, No. (%)	279 (90.9)	249 (92.6)	30 (78.9)	**.01[b]**

+ VAS-A at study entry was only available for 264/307 (86.0%) subjects.

Notes: Means and standard deviations are provided for interval level data that is normally distributed and frequencies are provided for categorical data. [a] Independent Samples T-Test, [b] Chi-Square

Table 4

Influence of Group Assignment and Anxiety on Time to First Weaning Trial after Study Enrollment, Controlling for Sedation Frequency and Other Covariates

Variable	Hazard Ratio (95% CI)	p-value
Patient Directed Music*	1.1 (.73, 1.6)	.72
Noise Canceling Headphones*	.98 (.66, 1.5)	.93
VAS	1.004 (.999, 1.007)	.16
Sedation frequency	.97 (.93, 1.007)	.11
Total days in ICU prior to enrollment	.995 (.981, 1.018)	.46
APACHE III	1.01 (1.003, 1.018)	**.004**
History of ventilation in prior hospitalization	1.3 (.95, 1.8)	.10

* Reference is Usual Care

Table 5

Influence of Group Assignment and Anxiety on Time to First Weaning Trial after Study Enrollment, Controlling for Sedation Intensity Score and Other Covariates

Variable	Hazard Ratio (95% CI)	p-value
Patient Directed Music*	1.06 (.73, 1.6)	.76
Noise Canceling Headphones*	.98 (.66, 1.5)	.92
VAS-A	1.004 (.998, 1.009)	.18
Sedation intensity score	.98 (.92, 1.03)	.42
Days in ICU prior to enrollment	.996 (.983, 1.018)	.59
APACHE III	1.01 (1.003, 1.018)	**.005**
History of ventilation in prior hospitalization	1.3 (.94, 1.8)	.11

* Reference is Usual Care

Table 6

Correlations among Covariates of Interest (Model Aims 1&2)

* p<.05; **p<.01

Variable	VAS-A	Sedation frequency	Sedation intensity score	Days in ICU prior to enrollment	APACHE III	History of ventilation in prior hospitalization
VAS-A	**---**	.09*	.09*	.01	.10*	.05
Sedation frequency	.09*	**---**	.83**	-.22**	-.04	-.08*
Sedation intensity score	.09*	.83**	**---**	-.19**	-.06	-.14**
Days in ICU prior to enrollment	.01	-.22**	-.19**	**---**	.05	-.03
APACHE III	.10*	-.04	-.06	.05	**---**	.06
History of ventilation in prior hospitalization	.05	-.08*	-.14**	-.03	.06	**---**

Table 7

Influence of Group Assignment and Anxiety on Duration of Weaning Trials during the Study Period, Controlling for Sedation Frequency and Other Covariates

Variable	**ß(se(ß)**	**p-value**
Patient Directed Music*	-44.6(30.9)	.15
Headphones*	-48.7(32.9)	.14
Study Day	8.4(2.3)	**<.001**
Weaning trial number	-10.7 (10.8)	.32
VAS-A	-.09(.30)	.77
Age	-.21(.94)	.82
Days ventilated prior to enrollment	4.1(3.0)	.17
Days in ICU prior to enrollment	-1.4(3.1)	.65
Sedation frequency	-1.8(2.8)	.52
FiO_2	1.8(1.0)	.08
Tracheostomy	53.6(25.7)	**.04**

* *Reference is Usual Care

Table 8

Influence of Group Assignment and Anxiety on Duration of Weaning Trials during the Study Period, Controlling for Sedation Intensity Score and Other Covariates

Variable	**ß(se(ß)**	**p-value**
Patient Directed Music*	-46.4(30.9)	.14
Headphones*	-48.9(32.9)	.14
Study Day	8.6(2.2)	**<.001**
Weaning trial number	-10.9 (10.8)	.31
VAS-A	-.09(.30)	.77
Age	-.17(.94)	.85
Days ventilated prior to enrollment	4.2(3.0)	.16
Days in ICU prior to enrollment	-1.4(3.0)	.65
Sedation intensity score	-1.7(3.9)	.66
FiO_2	1.7(1.0)	.08
Tracheostomy	54.6(25.7)	**.03**

*Reference is Usual Care

Table 9

Correlations among Covariates of Interest (Model Aims 3&4)

Variable	Study Day	Weaning Trial	VAS-A	Age	Days ventilated prior to study enrollment	Days in ICU prior to enrollment	Sedation frequency score	Sedation intensity score	FiO_2	Tracheostomy
Study Day	**---**	.02	-.03	-.04	-.06**	-.07**	-.18**	-.17**	-.11**	.45**
Weaning Trial	.02	**---**	-.02	.04	.06*	.09**	-.06*	-.10**	-.12**	-.10**
VAS-A	-.03	-.02	**---**	.13**	-.04	-.05	.08*	.08*	-.01	-.04
Age	-.04	.04	-.13**	**---**	-.19**	-.13**	-.10**	-.11**	-.06**	-.16**
Days ventilated prior to enrollment	-.06**	.06*	-.04	-.19**	---	.88**	-.15**	-.09**	-.10**	.38**
Days in ICU prior to enrollment	-.07**	.09**	-.046	-.13**	.88**	**---**	-.128**	-.04	-.15**	.41**
Sedation Frequency Score	-.18**	-.06*	.08*	.10**	-.15**	-.13**	**---**	.82**	.07*	-.30**
Sedation Intensity Score	-.17**	-.10**	.08*	-.11**	-.09**	-.04	.82**	**---**	.01	-.25**
FiO_2	-.11**	-.12**	-.01	-.06**	-.10**	-.15**	.07*	.01	**---**	-.12**
Tracheostomy	.45**	.10**	-.04	-.16**	.38**	-.41**	-.30**	-.25**	-.12**	**---**

* p<.05; **p<.01

CHAPTER 3 – SYNTHESIS

This chapter summarizes the major findings from both manuscripts in this dissertation. First, a synthesis of the findings and limitations from Manuscript 1 are presented. Second, a description of the conceptual framework is given. Then, an overview of the findings and limitations from Manuscript 2 are provided. Finally, the impact of this work on nursing practice is discussed and suggestions for future research are offered.

Chapter 2 Findings

Manuscript 1, "The influence of music during mechanical ventilation and weaning from mechanical ventilation: A review". The purpose of this manuscript was to describe the state of the science on music as an integrative intervention during MV and ventilator weaning and to identify current gaps in knowledge regarding the use of music intervention for symptom management, specifically during ventilator weaning.

The narrative review, which followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Flowchart (Moher et al., 2009) and utilized the Matrix Method for data extraction consisted of 18 studies; 16 quantitative studies and two qualitative studies (Hetland et al., 2015). The quantitative studies included 10 randomized clinical trials, three case control trials, two pilot studies, and one feasibility study.

This review illustrated that the duration, frequency, and timing of music intervention varied greatly across studies. Consensus for the most effective appropriate means for implementing music intervention could not be determined from the literature.

The desired level of patient wakefulness deemed appropriate by investigators for study inclusion varied. While it is not known to what extent wakefulness impacts the physiological results of music intervention during MV and ventilator weaning, current guidelines (Barr et al., 2013) suggest patients should be kept as awake and alert as possible because increased wakefulness affords greater patient control and independence. It is not known if music intervention is more effective if the patient is more awake.

All studies implemented music styles that were considered “relaxing”, as previous research has demonstrated that familiar music consisting of 60-80 beats per minute with simple arrangements and no lyrics (Tracy & Chlan, 2011) is most effective for reducing anxiety. However, an assortment of music genres were used such as nature based sounds, classical, and easy listening. Two studies encouraged patients to self-select their preferred music styles, which is ideal and supports the goal for patients to maintain comfortable levels of alertness to promote control and independence over their care.

Music intervention was found to reduce the physiological signs of anxiety such as respiratory rate, heart rate, and blood pressure for patients undergoing MV as well as decrease the need for sedatives during MV. Some studies

evaluated anxiety by asking patients to complete various self-report measures. Results from these measures demonstrated music intervention to be effective in reducing self-reported anxiety during MV.

Some studies explored the influence of music on biomarkers of the stress response by testing blood and urine samples of mechanically ventilated patients. The connection between biomarkers and clinical observations of anxiety like increased heart rate and respiratory rate remains unclear.

Both patients and nurses expressed positive feelings towards music intervention. Nursing support is important to the success of the intervention because nurses are the individuals primarily responsible for promoting and implementing music intervention at the bedside.

To conclude, the results of the narrative review demonstrated music is an effective intervention for individuals undergoing MV by decreasing the physiological signs of anxiety. However, there is a remarkable lack of literature specific to the use of music intervention during weaning from MV, which was a major limitation to the review. Unfortunately, several articles related to the use of music specifically during ventilator weaning were identified, but these manuscripts were not presented in English. In addition, one major relevant study titled, “The effect of music intervention during daily weaning trials in patients on prolonged mechanical ventilation” (Liang et al., 2015) was published after the review was completed and therefore not included in the review.

Development of the Conceptual Framework. The narrative review in Manuscript 1 helped guide the development of the conceptual framework that, in turn, provided a strong foundation for the need and significance of the dissertation study presented in Manuscript 2. However, the aforementioned major limitation of the review pertains to the lack of literature specific to music intervention during ventilator weaning. Therefore, the development of the conceptual framework required application of clinical knowledge as well as frequent reference to the conceptual model that was used to guide the parent study from which the dissertation is derived.

The literature review suggests the potential value of incorporating music intervention during weaning from MV. Therefore, the study hypotheses presented in the conceptual framework are based on the perceived benefit of music intervention on the specific aims. The hypotheses were as follows: 1) higher anxiety would result in increased to time first weaning trial; 2) music intervention would result in decreased to time first weaning trial; 3) higher anxiety would result in weaning trials that are shorter in duration; and 4) music intervention would result in weaning trials that are longer in duration. The model refers to the sources of stress, both physiological and psychological that can elicit a negative stress response in the mechanically ventilated patient. The model suggests that music intervention can decrease the physiological signs of anxiety and promote a beneficial relaxation response. This relaxation response has the potential to

lower anxiety and facilitate ventilator weaning by hastening extubation, accelerating recovery and decreasing overall morbidity and mortality.

In addition to the conceptual framework, a figure illustrating the numerous available variables that might impact weaning was created to help guide the secondary data analysis presented in Manuscript 2. After IRB approval and gaining access to the parent study data set, extensive exploration of variables was completed. Given the vast data set, variables that were considered of most interest based on clinical knowledge were selected for further exploration in the secondary analysis. A "weaning continuum" was then created to help conceptualize the ways in which these individual variables would impact weaning.

Manuscript 2, "The influence of music and anxiety on weaning trials in patients undergoing mechanical ventilation". The specific aims of this secondary data analysis project were to determine the influence of music (1) and anxiety (2) on time to first weaning trial after study enrollment and to determine the influence of music (3) and anxiety (4) on the duration of weaning trials during the study period.

This study was based on a subset of individuals who participated in the parent randomized clinical trial (1RO1NR009295) from 2006 to 2011**.** The parent study, which included 373 subjects from 12 ICUs at five hospitals who underwent MV, used a three group experimental design with repeated measures to test whether listening to self-initiated, patient directed-music could reduce anxiety and

sedative exposure during ventilator support in critically ill patients. Subjects were randomized via a computer generated random numbers list into one of three conditions upon study enrollment: self-initiated, patient directed music (PDM), noise-canceling headphones (HPs), or usual ICU care (UC). Subjects remained in the study while mechanically ventilated for up to 30 days or until they were extubated, chose to withdraw, transferred from the unit, or died.

Subjects (N=307) from the parent study were included in this descriptive, correlational secondary analysis if they were enrolled in the parent study for at least 24 hours, they were intubated less than 40 days prior to study enrollment, and if they had recorded sedation data. The conceptual framework of the secondary data analysis was partially adapted from the conceptual model of the parent study and was guided by the results of Manuscript 1. Variables of interest for this analysis included: 1) demographic data such as age, gender, race, history of ventilator support, and type of artificial airway; 2) Length of MV and length of ICU stay 4) severity of illness, which was measured at study entry using the APACHE III; 5) sedative exposure which was measured by using a daily sedation intensity score and sedation frequency score; 6) group assignment; 7) anxiety, which was measured using a daily visual analogue scale that was completed by the subject; 8) ventilator settings; and 9) weaning settings. Statistical methods including descriptive statistics, survival analysis, Cox proportional hazards regression and linear regression with mixed modeling, were used to address the study aims.

The analysis of demographic variables showed that subjects who underwent at least one weaning trial during the study and subjects who did not undergo at least one weaning trial during the study had similar clinical characteristics at baseline. The only statistically significant differences noted between the two groups (those that weaned and those that did not) were the number of subjects who had required MV in a past hospitalization and subject status at study exit (alive versus dead). A higher percentage of individuals that had at least one weaning trial during the study required MV in a past hospitalization (130/269, 48.3%) compared to 13/38 or 34.2% of subjects who did not have at least one weaning trial during the study (p=.04). Additionally, subjects who had at least one weaning trial during the study were more likely to be alive at study exit (249/269, 92.6%) compared to subjects who did not have at least one weaning trial during the study (30/38, 78.9%) (p=.01).

Study aims one and two, the influence of music (1) and anxiety (2) on time to first weaning trial after study enrollment, were analyzed together. Due to the collinear relationship between the two measures of sedative exposure, sedation intensity and sedation frequency, two models were created. Both models controlled for the following covariates: group assignment, anxiety, total days in ICU prior to study enrollment, illness severity (APACHE III score), and history of MV during a prior hospitalization. Results of both models demonstrated that group assignment and anxiety were not statistically significant predictors of time to first weaning trial after study enrollment for this subset of subjects. Also, when

controlling for both sedation frequency and sedation intensity, subjects with greater severity of illness (APACHE III) were likely to experience a shorter time to first weaning trial after study enrollment.

Study aims three and four, the influence of music (3) and anxiety (4) on the duration of weaning trials during the study period, were analyzed together and again, two models were created. The first model created provides estimates of the influence of group assignment and anxiety on the duration of weaning trials while controlling for sedation frequency and other covariates including day, weaning trial number, age, days ventilated prior to enrollment, days in ICU prior to enrollment, FiO_2, and presence of a tracheostomy. Results indicate that group assignment and anxiety were not statistically significant predictors of duration of weaning trials during the study. However, after the initial weaning trial of any particular day, the overall duration of subsequent weaning trials increased by an average of 8.4 minutes per day ($p<.001$) and subjects with a tracheostomy were able to wean 53.6 minutes longer ($p=.04$).

The second model created provides estimates of the influence of group assignment and anxiety on the duration of weaning trials while controlling for sedation intensity score and other covariates including day, weaning trial number, age, days ventilated prior to enrollment, days in ICU prior to enrollment, FiO_2, and presence of a tracheostomy. Results indicate that group assignment and anxiety were not statistically significant predictors of duration of weaning trials during the study. However, after the initial weaning trial of any particular

day, the overall duration of subsequent weaning trials increased by an average of 8.6 minutes per day ($p<.001$) and subjects with a tracheostomy on the day of the weaning trial were able to wean 54.6 minutes longer ($p=.03$).

Covariates in all three models showed various levels of significant correlations, weak to moderately strong. Thus, much information was shared among the variables in the models and variables greatly influenced each other in regards to study aims.

As discussed in Manuscript 2, the study hypotheses were not supported. Music listening (PDM) and anxiety were not statistically significant predictors of time to first weaning trial after enrollment or duration of weaning trials during the study period. Nevertheless, important knowledge can be gained from this first-ever known investigation of data from a large randomized clinical trial of acutely ill mechanically ventilated patients. We found that subjects who did not attempt a weaning trial during the study were more likely to die during their hospitalization but subjects with higher illness severity were more likely to experience a shorter time to first weaning trial after study enrollment. This could be due to the fact that the APACHE III used to measure illness severity was only completed once using clinical variables from the first day of ICU admission; thus, we were unable to capture worsening or vacillating illness over time. Our results also show that individuals with a tracheostomy were able to tolerate longer weaning trials; however debate remains regarding the most ideal time to tracheostomy placement in patients receiving prolonged mechanical ventilatory support. In

addition, the results demonstrate that having a history of experiencing MV in a prior hospitalization indicates a subject was more likely to undergo a weaning trial. This result supports the hypothesis that familiarity with the ventilator may positively influence weaning patterns.

A number of limitations exist. Inherently, secondary data analyses are limited due to the fact that the primary aims are not aligned with the parent study, the investigator of the secondary analysis was not involved in the development and implementation of the parent study, and making accurate parameter estimates is more difficult with the observational nature of secondary data (Smith et al., 2011). In addition, this study had limitations related to the means in which data were recorded in the parent study. Exact start and stop times for weaning trials were not available in the electronic data set. Also, weaning data was recorded on the first day of the study; it is unknown if and for how long subjects were weaning before study enrollment making “time to first weaning trial” an arbitrary measurement. Anxiety was only measured once daily and completion times varied depending on the individual subjects. In addition, due to a variety of reasons, some anxiety assessments were not completed. The experimental PDM intervention was encouraged twice per day, but it is unknown to what degree subjects adopted the intervention. A variety of ICUs participated in this study (surgical, medical, teaching, and non-teaching, etc.). Therefore, it is not known to what extent individual ICU weaning and sedation protocols and practices influenced the outcomes.

Impact of Findings on Nursing Practice

As previously discussed, the findings from this dissertation research did not support the hypotheses, nor did they align well with previous research of music intervention during mechanical ventilation. The discussion in Manuscript 1 highlights the many benefits of music intervention, both physiological and psychological, that have been demonstrated in prior studies. The findings of this dissertation study do not support music as a significantly beneficial intervention in critically ill adults undergoing weaning from mechanical ventilation. However, it is important to share these findings with the scientific and nursing communities for a variety of reasons. This study had many limitations related to the study aims, it is critical that these results and limitations be disseminated to prevent future scientists from developing studies with similar limitations, thus wasting valuable time and resources. These results are also important in the discussion surrounding the theoretical backing of music interventions during mechanical ventilation. To date, no basic scientific theory or model has been developed to explain the mechanisms for how music impacts the stress response at both a cellular and physiological systems level. These results may lead to a paradigm shift in research practices in this area of nursing science. For example, it may be worthwhile to more closely examine objective outcomes such as biochemical markers as well as develop more appropriate measures of stress and anxiety in this population of patients instead of using traditional proxies.

As mentioned in Manuscript 1, nurses are the health care providers primarily responsible for managing distressful symptoms experienced by mechanically ventilated ICU patients. Symptom management is immensely challenging due to individual patient needs, severity of illness and rapidly changing health status of ICU patients, increased need for the inclusion of families and other health care providers in the care plan, difficulties in communicating with ventilated patients, and the physical demands required by the nurse to safely care for a critically ill patient. The most common approach to alleviating symptoms involves the administration of sedative and analgesic medications. While these medications may help lessen pain and anxiety, they put the patient at risk for dependence, over-sedation, and delirium, all of which can lead to significant delays in ventilator weaning.

The science regarding best practices of sedative administration and ventilator weaning continues to evolve. Current clinical practice recommendations (Barr et al., 2013) call for patients to receive as minimal sedation as possible to maintain comfort, to remain as awake and alert as possible while mechanically ventilated, and for providers to attempt daily weaning trials as soon as clinically possible in order to decrease the duration of MV and ultimately reduce morbidity and mortality in the critically ill. Further evaluation through primary studies is needed to determine if these recommendations are clinically feasible and lead to superior outcomes.

Unfortunately, pain and anxiety will continue to be an inherent part of MV and ICU care; therefore, it is critical that innovative non-pharmacological adjunctive treatments for symptom management are investigated and subsequently integrated into ICU practice in order to provide high quality care for mechanically ventilated patients. Music intervention is a viable, cost effective option that can be easily implemented and promoted at the bedside by nursing staff.

Recommendations for Future Research

The two manuscripts summarized above provide compelling evidence that future work is needed to examine the use of music intervention during weaning from MV in order to reduce anxiety and other harmful psychophysiological symptoms associated with weaning. The work summarized in the first manuscript demonstrates that music intervention is overall beneficial for this population, but additional studies must be done to gain a better understanding of the factors that influence weaning in order to determine the most effective and appropriate means for implementing music intervention to facilitate weaning. There is a great need for more prospective studies to be completed that evaluate the use of music intervention specifically during ventilator weaning.

A very recent study was completed by Liang and colleagues (2015), that used a prospective crossover pre-post repeated measures design to describe the effect of music intervention on physiological factors of blood pressure, heart rate, and respiratory rate as well as anxiety and dyspnea during ventilator weaning in

the long term acute care hospital (LTACH) setting. It was determined that music intervention significantly lowered heart rate, respiratory rate, anxiety and dyspnea during weaning. While the results found in Manuscript 2 were unable to demonstrate such a strong beneficial intervention influence on ventilator weaning trials, the study by Liang, et al. (2015) adds to the very limited body of knowledge that exists in this area of nursing science.

Future primary studies are warranted and should consider including physiological measures of anxiety such as heart rate, blood pressure, and respiratory rate, at times before, during, and after weaning trials. It would also be worthwhile to analyze various laboratory values such as arterial blood gasses or stress biomarkers that are less invasive than blood samples such as salivary cortisol, salivary alpha-amylase, heart rate variability, and Galvanic skin response (Centre for Studies on Human Stress, 2007; Sneed, Olson, Bubolz, & Finch, 2001; Harrison et al., 2006). Information specific to weaning trials such as reasons for why the trial was started and stopped and which provider initiated and/or stopped the trial (i.e. respiratory, nursing, or physician) would be valuable in order to understand what, if any, impact the immediate environment and health care personnel have on weaning patterns.

In this dissertation study, the use of the PDM music intervention was up to the individual subject's discretion. They could use the intervention as much or as little as desired and at any given time during the study period. Therefore, it was not paired directly with each weaning trial. In a recent study by Liang and

colleagues (2015), music intervention was applied specifically during the weaning trials in the LTACH setting, and the investigators had success with this method. It is not known if arranging music intervention with weaning trials in acutely critically ill patients would lead to more successful ventilator weaning. This dissertation study aimed to examine the “influence” of music intervention on ventilator weaning trials, but pairing the music intervention specifically with each weaning trial may more accurately capture the “effect” of music intervention on weaning trials. This should be considered as a possible future direction of the research. In addition, deriving a more thorough patient history regarding familiarity with the ventilator, previous intubations, as well as the patients’ knowledge of critical illness could help providers understand the impact of weaning knowledge and ventilator education on outcomes. Future studies should also include a record of activity during weaning trials such as presence of friends or family and overall milieu of the unit.

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Appendix A. Notice of Grant Award

UNIVERSITY OF MINNESOTA

Notice of Grant or Contract Award

Sponsored Projects Administration

(Online Page Navigation: Main Menu > Grants >Awards > UM_NOGA Report)

Print Date: 7/3/2014
Page: 1 of 5
Award: CON000000044954
Primary Project: 00039108
PRF #: 765845

AWARD INFORMATION (Online Page Navigation: Main Menu > Grants > Awards >Award Profile)

Award Start Date:	07/01/2014	**Award End Date:**	12/31/2015
Funds Approved to Date:	$37,824.00		
Principal Investigator:	Closen,Breanna D	**Award Type:**	Grant
Primary Project Dept:	SoN Adult Gero Health Co-op	**Purpose:**	Research
Sponsor:	NIH NINR NATL INST OF NURSING		
Sponsor Award #:	1F31NR014591-01A1		
Award Title #:	Influence of Music on Anxiety in Weaning from Mechanical		

ASSOCIATED PROJECTS (Online Page Navigation: Main Menu > Grants >Awards > Award Profile – Funding Tab)

Project #:	00039108	**Department:** 11313 - SoN Adult Gero Health Co-op	
Project PI:	Hetland,Breanna Danielle	**Dates:** 07/01/2014 - 12/31/2015	**Project Title:** Influence of Music on Anxiety
F&A:	0.00 MTDC	**EFFDT:** 07/01/2014	

AWARD HISTORY (Online Page Navigation: Main Menu > Grants > Awards > Review Award Modifications)
(Displayed in action order ('Mod Issue Date' in descending order))

Reference Award#: 1F31NR014591-01A1 **Amount:** $37,824.00
Period: 1 **Begin Date:** 07/01/2014 **End Date:** 06/30/2015
Modification Seq: 1 **Modification Type:** Original **Mod Issue Date:** 07/03/2014
Comments:
This NOGA represents an Agreement in the amount of $37,824 for the budget period 07/01/2014 - 06/30/2015.

An Activation Notice (PHS416-5) must be submitted to the NIH awarding office as of the day the fellow begins training. See NOA for details.

Fellows are required to notify the awarding unit as soon as they are aware of any possible change in plans regarding their fellowship support.

In accordance with NIH Guide Notice NOT-OD-14-046, this award reflects the stipend level for pre-doctoral trainees, as published in the NIH Guide Notice, Ruth L. Kirschstein National Research Service Award (NRSA) Stipend and Other Budgetary Levels Effective for Fiscal Year 2014. (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-14-046.html).

PI & Department□s responsibility to comply with the terms and conditions within this award.

ESTIMATED FUTURE FUNDING / ACTIONS (Online Page Navigation: Main Menu > Grants > Awards > Review Award Modifications)
(Displayed by 'Period' and 'Modification Sequence' in ascending order)

Reference Award#: **Amount:** $20,574.00
Period: 2 **Begin Date:** 07/01/2015 **End Date:** 12/31/2015
Modification Seq: 2 **Modification Type:** Original **Mod Issue Date:**
Comments:

COMMENTS
Description: **Entered by:** FLETC070 **Date & Time:** 7/3/2014 11:24 AM
Date and Time Stamp indicates Proposal-to-Award Process

Description: **Entered by:** FLETC070 **Date & Time:** 7/3/2014 11:33 AM
Sponsor Contact:
Grants Specialist:
Lawrence R. Haller
hallerl@mail.nih.gov

12
6-12
115

UNIVERSITY OF MINNESOTA

Notice of Grant or Contract Award

Sponsored Projects Administration

(Online Page Navigation: Main Menu > Grants >Awards > UM_NOGA Report)

Print Date: 7/3/2014
Page: 2 of 5
Award: CON000000044954
Primary Project: 00039108
PRF #: 765845

P: 301-402-1878
F: 301-451-5652
Description: **Entered by:** FLETC070 **Date & Time:** 7/3/2014 11:33 AM
Sponsor Contact:
Program Official:
David Banks
banksdh@mail.nih.gov
P: 301-496-9558
F: 301480-8260

SPECIAL REVIEWS (Online Page Navigation: Main Menu > Grants >Awards > Award Profile – Certifications Tab)
Project #: 00039108

Description: Human Subjects
Approval Date: 01/01/1901 **Expiration Date:** 01/01/1901 **AssuranceNumber:**
Comments: No Human Subject expenses can be incurred on this grant until all approvals are in place with the IRB Committee

BUDGET INFORMATION (Online Page Navigation: Main Menu > Grants>Awards>Project Budget)
Please review online budget for valid account string combinations (ex. PCBU, Activity, Fund, Dept_Id, Project, Account)

Project #: 00039108 **Cost Share Budget Total:**
Project Start Date: 07/01/2014 **Project End Date:** 12/31/2015
ICR Sharing **Department:** SoN Adult Gero Health Co-op **Percentage:** 100.00

Period	Start Date	End Date	Direct Cost (Approved)	F & A Cost (Approved)	Direct Cost (Pending)	F & A Cost (Pending)	Total Period Cost
1	07/01/2014	06/30/2015	$37,824.00	$0.00	$0.00	$0.00	$37,824.00
2	07/01/2015	12/31/2015	$0.00	$0.00	$20,574.00	$0.00	$20,574.00
TOTAL			$37,824.00	$0.00	$20,574.00	$0.00	$58,398.00

Budget Detail (all periods)

Fund Code	DeptID	Program Code	Chartfield 1	Chartfield 2	Fin EmplID	Activity	Analysis Type	Account	Cost Share	Budget Item	Amount	Hold
3002	11313					1	BUD	720200		LABMED_SUPPLIES	$2,100.00	
3002	11313					1	BUD	800100		STUDENT_ASSIST	$11,148.00	
3002	11313					1	BUD	800600		OTHER_STU_ASST	$22,476.00	
3002	11313					1	BUD	810850		SPA_RESERVE_INT	$2,100.00	

COST SHARE/MATCH/IN-KIND
CSM - Cost Share, Matching and InKind

CSM05 - Departments must document all cost share/unpaid effort that is shown in the proposal.

PROGRAM INCOME INFORMATION
PIN - Program Income

PIN03 - Reportable Program Income must be deposited by the department into the Sponsored Program Income Unapplied Cash account.

TERMS & CONDITIONS (Online Page Navigation: Main Menu > Grants >Awards > Award Profile – Terms Tab)

APV - Additional Approval

APV03 - Prior sponsor approval required for no-cost extensions.

APV10 - Prior sponsor approval required for changes to work scope.

APV31 - Prior sponsor approval required for the addition of a foreign component.

EQP - Equipment

EQP04 - No equipment is allowed.

FIS - Fiscal

FIS08 - Deficits may not be carried forward.

IPR - IP Rights

IPR23 - Fellowships funded primarily for educational purposes are not subject to invention reporting requirements nor does NIH have any rights to inventions under those awards (as specified in 37 CFR part 401.1(b)).

PUB - Publications

PUB02 - U of M will place an acknowledgement of sponsor support and a disclaimer, as appropriate, on any publication generated by this award or reporting on the award results and/or activity.

PUB07 - Peer-reviewed articles must be submitted to NIH Pubmed Central (PMC) upon acceptance for publication and made publicly available within 12 months. Cite PMC ID number in progress reports/proposals.

REG - Regulatory

REG01 - 45 CFR Part 74 - Code of Federal Regulations as it pertains to institutions of higher education.

REG03 - OMB Circular A-21 (www.whitehouse.gov/omb/circulars/a021/a021.html)

REG04 - OMB Circular A-110 (www.whitehouse.gov/omb/circulars/a110/a110.html)

REG05 - OMB Circular A-133 (www.whitehouse.gov/omb/circulars/a133/a133.html)

REG16 - If applicable, no funds may be expended for human subject related activities until all appropriate human subject related approvals are in place

REG17 - If applicable, no funds may be expended for animal related activities until all appropriate animal related approvals are in place

REG18 - If applicable, any personnel involved in the design or conduct of human subject activity must satisfy the requirement for education on the protection of human subjects prior to participating in the study

REG19 - NIH Grants Policy Statement (http://grants.nih.gov/grants/policy/nihgps_2010/index.htm)

REG21 - If applicable, no funds may be expended for activities involving recombinant DNA, Infectious Agents or Biological Toxins until Institutional Biosafety Committee (IBC) approval has been obtained.

REG38 - Pilot Program for Enhancement of Employee Whistleblower Protection (41 U.S.C. 4712) - http://www.ospa.umn.edu/announcements/Whistleblower.html

TRN - Training

TRN04 - Established stipend levels may not be exceeded.

TRN06 - Unspent tuition funds revert at the end of each budget period.

TRN07 - Fellow must notify agency of any change of plans regarding fellowship.

TRN09 - A termination notice must be submitted to NIH at the conclusion of the fellowship.

TRN10 - Second half of Institutional Allowance will be released after fellow completes six months of training

TRN13 - All fellows are required to pursue their research training full time.

TRN14 - An Activation Notice must be submitted to the awarding IC as of the day the individual begins training. A Payback Agreement must also be completed and submitted for postdoctoral fellows in their first 12 months of Kirschstein-NRSA postdoctoral support.

TRN15 - Stipends and tuition/fees may not be charged until a fellow has actually activated and the appropriate paperwork submitted to the NIH.

TRN16 - Stipends must be expended using the stipend level provided in the award; no funds can be rebudgeted into the stipend category to accommodate a stipend level different from the established NIH level.

TRN17 - When tuition and fees is awarded, it is generally restricted and cannot be rebudgeted without prior written approval from the NIH awarding IC.

TRV - Travel Restrictions

TRV09 - Travel to scientific meetings is appropriate when it is necessary for the individual's training and when the costs are incurred within the period of grant-supported training.

TRV16 - Regulations implementing the Fly America Act provide that federal funds may be used to pay for air travel only on U.S. flag carriers, except in specified cases. 41 C.F.R. section 301-10.131, et. seq. For more about Fly America Act requirements and exceptions, see http://travel.umn.edu/flyamerica.php.

UMN - U of M Requirements

UMN03 - All U of M Policy and Guidelines relating to research must be followed and can be read in detail on the web at http://www.ospa.umn.edu/policiesandprocedures/index.htm

UMN04 - U of M Cost Transfer guidelines state transfers of non-salary expenses on accounts be clearly documented & made within 30 days after the end of the accounting period the charge was processed.

NON-FINANCIAL REPORTING (Online Page Navigation: Main Menu > Grants >Awards > Award Profile – Milestones Tab)
Type: Final Report **Description:** Other **Due Date:**
Comments: Termination notice due within 30 days of termination.

UNIVERSITY OF MINNESOTA

Notice of Grant or Contract Award

Sponsored Projects Administration

(Online Page Navigation: Main Menu > Grants >Awards > UM_NOGA Report)

Award: CON000000044954
Primary Project: 00039108
PRF #: 765845

Type: Final Report **Description:** Other **Due Date:**
Comments: Final Progress Report should be included with Termination Notice.
Type: Report **Description:** Other **Due Date:**
Comments: Annual report due 2 months before the beginning date of the next budget period.

INVOICE/BILLING INFORMATION

Basis of Payment: COST_REIMBURSE **Method of Payment:** Electronic Fund Transfer
Invoice Form: GPC - GM_LOC
Interim Invoice Deadline: 0 **Final Invoice Deadline:** 0

Contact Name:
Contact Phone:
Contact Fax:
Contact Email:
Contact Address:

FINANCIAL REPORTING

Report Form ID:
Interim Reporting Deadline: 90
Reporting Frequency: No Reporting Required
Final Reporting Deadline: 90

GENERAL PROVISIONS

This document is intended to provide guidance in managing this award, to the Principal Investigator, Academic Unit, and to those who are noted as receiving this document. Its intent is to provide general information regarding University and sponsor policies when given the award. In addition, it is intended to reference specific conditions related to this award. Specific questions should be addressed to the grant administrator from SPA noted below. By accepting this award, the Principal Investigator acknowledges and agrees to abide by all provisions of the sponsoring agency and the University of Minnesota policies related to sponsored projects management, including the Code of Conduct.

U OF M CONTACTS

Administrative questions to SPA staff member: Renee Frey 612/624-0810 renee@umn.edu
Billing and financial questions to SFR: Marjorie Nebo 612/624-6026 nebox001@umn.edu

Appendix B. University of Minnesota Notice of IRB Exemption Status

The IRB: Human Subjects Committee determined that the referenced study is exempt from review under federal guidelines 45 CFR Part 46.101(b) category #4 EXISTING DATA; RECORDS REVIEW; PATHOLOGICAL SPECIMENS.

Study Number: 1410E54262

Principal Investigator: Breanna Hetland

Title(s):
Influence of Auditory Stimulation on Anxiety in Weaning from Mechanical Ventilation

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This e-mail confirmation is your official University of Minnesota HRPP notification of exemption from full committee review. You will not receive a hard copy or letter. This secure electronic notification between password protected authentications has been deemed by the University of Minnesota to constitute a legal signature.

The study number above is assigned to your research. That number and the title of your study must be used in all communication with the IRB office.

If you requested a waiver of HIPAA Authorization and received this e-mail, the waiver was granted. Please note that under a waiver of the HIPAA Authorization, the HIPAA regulation [164.528] states that the subject has the right to request and receive an accounting of Disclosures of PHI made by the covered entity in the six years prior to the date on which the accounting is requested.

If you are accessing a limited Data Set and received this email, receipt of the Data Use Agreement is acknowledged.

This exemption is valid for five years from the date of this correspondence and will be filed inactive at that time. You will receive a notification prior to inactivation. If this research will extend beyond five years, you must submit a new application to the IRB before the study's expiration date.

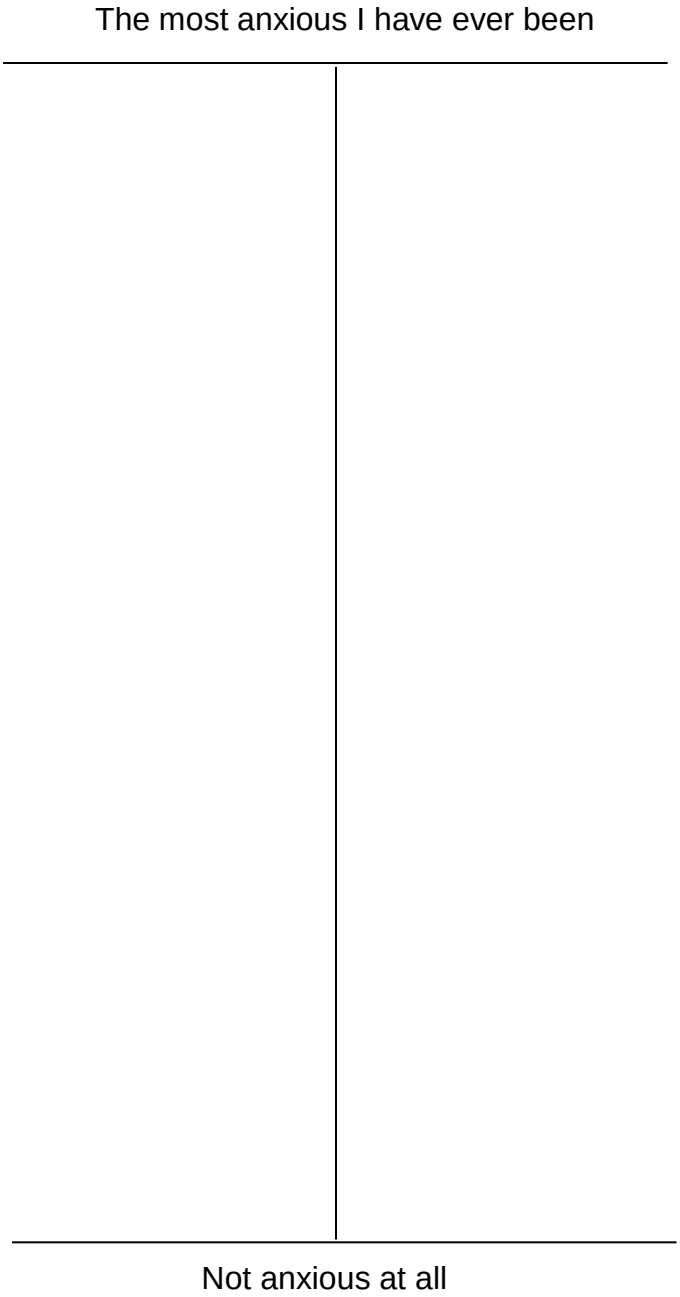
Upon receipt of this email, you may begin your research. If you have questions, please call the IRB office at (612) 626-5654.

You may go to the View Completed section of eResearch Central at http://eresearch.umn.edu/ to view further details on your study.

The IRB wishes you success with this research.

We value your feedback. We have created a short survey that will only take a couple of minutes to complete. The questions are basic, but your responses will provide us with insight regarding what we do well and areas that may need improvement. Thanks in advance for completing the survey. http://tinyurl.com/exempt-survey

Appendix C. Visual Analogue Scale for Anxiety (VAS-A)



Appendix D. Email from Elsevier Regarding Copyright Policies

As an Elsevier journal author, you retain various rights including Inclusion of the article in a thesis or dissertation (provided that this is not to be published commercially) whether in part or *in toto*; see http://www.elsevier.com/about/company-information/policies/copyright#Author%20rights for more information. As this is a retained right, no written permission is necessary provided that proper acknowledgement is given.

This extends to the online version of your dissertation and would include any version of the article including the final published version provided that it is not available as an individual download but only embedded within the dissertation itself.

If the article would be available as an individual download, only the preprint or (subject to the journal-specific embargo date) accepted manuscript version, but not the final published version, may be made available; see http://www.elsevier.com/journal-authors/sharing-your-article for more information. For embargo dates, see http://www.elsevier.com/__data/assets/pdf_file/0018/121293/external-embargo-list.pdf

If you need any additional assistance, please let us know.

Best Wishes,
Laura

Laura Stingelin
Permissions Helpdesk Associate
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F: (215) 239-3805
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