JCN Journal of Clinical Nursing

Journal of Clinical Nursing

ORIGINAL ARTICLE

A randomised controlled trial of the effect of music therapy and verbal relaxation on chemotherapy-induced anxiety

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Aims. To determine the effect of music therapy and verbal relaxation on state anxiety and anxiety-induced physiological manifestations among patients with cancer before and after chemotherapy.

Background. Cancer and its treatment provoke a series of changes in the emotional sphere of the patient's anxiety. Music therapy and verbal relaxation had reported the anxiety reduction effect on patients with cancer receiving chemotherapy. Few studies have been undertaken comparing music therapy and verbal relaxation in differentiating high–normal state anxiety subsample.

Design. A randomised controlled trial and permuted block design were used. Outpatient chemotherapy clinic operated by a University medical centre in southern Taiwan.

Methods. Ninety-eight patients were randomised into three groups: the music therapy group received one-hour single music session; the verbal relaxation group received 30 minutes of guided relaxation; the control group received usual care. Spielberger State-Trait Anxiety Instrument, Emotional Visual Analog Scale, three biobehavioural indicators: skin temperature, heart rate and consciousness level were measured during and after chemotherapy.

Result. Music therapy had a greater positive effect on postchemotherapy anxiety than verbal relaxation and control groups and a significantly increase in skin temperature. Patients with high state anxiety receiving music therapy had a greater drop in postchemotherapy anxiety than did the normal state anxiety subsample.

Conclusions. Both music and verbal relaxation therapy are effective in reducing chemotherapy-induced anxiety. Thirty minutes of intervention initiates anxiety reduction. Patients with high state anxiety receiving chemotherapy obtain the most benefit from music or verbal relaxation.

Relevance to clinical practice. Prior to chemotherapy, patients with high state anxiety must be sorted from all patients as they are more responsive to interventions. Oncology nurses can offer music and verbal relaxation as adjuvant interventions to reduce chemotherapy-induced anxiety and enhance the quality of care.

Key words: anxiety, cancer, chemotherapy, music therapy, nursing, verbal relaxation

Accepted for publication: 17 May 2010

Introduction

Cancer is a life-threatening disease across different populations. The World Health Organization (WHO) (2009) reported that 7·6 million people worldwide died from cancer in 2005. In the US, men have a one in two lifetime risk of developing cancer and, for women, the risk is one in three (American Cancer Society 2008). In Taiwan, a malignant

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doi: 10.1111/j.1365-2702.2010.03525.x

tumour is the leading cause of mortality (Department of Health, ROC 2009). The Taiwan Cancer Registration System (2009) reported a 4·52 increase ratio in the number of cancer cases from 12 950–58 499 between 1979–2000.

The undesirable side effects and the anticipation of problems during cancer chemotherapy increase the anxiety that is already present and related to the cancer diagnosis. Morasso (2002) reported that 15–40% of oncology patients suffer from psychological disorders related to anxiety and depression during chemotherapy. Cancer and its treatment provoke a series of changes in the emotional sphere of the patient that include anxiety, sense of guilt and low self-esteem.

Skills for managing negative emotional responses and distressful symptoms are critical to the quality of life of a patient with cancer. Creative interventions to alleviate patient symptoms, concerns and anxiety during medication regimens are needed. A variety of psychotherapeutic interventions, such as cognitive restructuring (Antoni *et al.* 2006), relaxation training (Yildirim & Fadiloglu 2006), guided imagery (Roffe *et al.* 2005) and music (Clark *et al.* 2006), have shown promise in decreasing psychological distress during cancer treatments. Music has been used for distraction and to enhance relaxation acting synergistically with pharmacological management (Lee *et al.* 2005) and helped patients with cancer in reducing anxiety (Smith *et al.* 2001).

Researchers have determined that imagery with music can be more beneficial than music alone. When used together, the imagery experience is regulated by the harmonic properties of the music (Thaut 2002) that increases the patient's involvement (Burns 2001). Additionally, music-assisted relaxation is highly effective in decreasing arousal for individuals under stress (Pelletier 2004). Therefore, cancer-related pain, discomfort and psychological distress may be reduced with music listening, guided imagery and relaxation.

Literature review

Chemotherapy

Patients with cancer experience overwhelming emotions and stress with the uncertainty of treatment and disease progression (Link *et al.* 2005). During chemotherapy, many physical and psychological problems are reported, such as fatigue (Jacobsen *et al.* 1999, Passik *et al.* 2001), depression (Williams *et al.* 2006) and anxiety (Iconomou *et al.* 2004). Many researchers have pointed out the role that anxiety plays in the incidence of pretherapy or post-therapy nausea and vomiting (Molassiotis *et al.* 2002). Arakawa (1997) found that a session of 25-minute taped, instructional, relaxation during chemotherapy decreased the intensity of nausea and vomiting symptoms after chemotherapy. In an early study, Benson *et al.* (1974) identified the association between anxiety state and autonomic arousal disorder, finding a decrease in sympathetic nervous system activity during relaxation. Decreasing muscle tension is one way to induce relaxation (Ferrell-Torry & Glick 1993).

Anxiety

Anxiety and distress during treatment are common reactions of oncology patients who are newly diagnosed. Cancer patients' distress may be especially acute during the initial oncology visit when prognosis and treatment options are discussed. Elevated anxiety levels activate the sympathetic nervous system, the release of adrenal-medullary hormones, noradrenaline and adrenaline, increased heart rate (HR), respiratory rate (RR) and blood pressure.

Music therapy and verbal relaxation

Music therapy (MT) was defined as 'using music to help achieve a specific change in behaviour, feeling, or physiology' (McCloskey & Bulechek 2000). During music listening, the amplitude and frequency of the vibratory stimuli evoke psycho-physiological responses (Watkins 1997); that used therapeutically to reduce anxiety (Brunges & Avigne 2003) by affecting the individual's physiological and psychological response to anxiety.

The mechanisms reducing the anxiety and the stress response by MT is postulated as the direct inhibition of the expression of stress-induced genes (Bittman *et al.* 2005) or an alteration in the opiate and cytokine processes (Stefano *et al.* 2004). Burns (2001) speculated that music coordinates activation of cortical association areas, which explains how vivid imagery experiences are spontaneously triggered by music.

Sound waves stimulate involuntary centres in the central nervous system, causing physiological reactions that are later involved in conscious thought. The waves may also be transmitted to higher levels of the brain, involved with emotion (Juslin & Västfjäll 2008). Bernardi *et al.* (2006) found a significant positive correlation between musical rhythm and RR indicating an unconscious coordination between music and respiratory patterns.

Music therapy can act as a non-pharmacological nursing intervention to relieve pain and anxiety and increase comfort (McCaffrey & Freeman 2003). Lee *et al.* (2005) offered a single 30-minute preferred music to patients receiving mechanical ventilation ($n = 64$), indicating that the music group had greater relaxation than the control group as manifested by a decrease in RR and HR and an increase in resting behaviours. Interestingly, no statistical difference was found in state or trait anxiety of the subjects after the music intervention.

Music reduced anxiety in stressful medical conditions, such as breast biopsy (Haun *et al.* 2001) and chemotherapy (Sabo & Michael 1996). Haun *et al.* offered a 20-minute music to patients undergoing breast biopsy in the experimental group. No significant difference between groups was found in blood pressure and HR. Sabo's chemotherapy subjects received taped music and a message from their physicians to reduce anxiety in measuring anxiety before and after the fourth chemotherapy. A decreased anxiety level after the intervention was found.

For music to achieve a therapeutic effect, Chlan (2000) suggested that MT be approached scientifically by examining the resonance of body rhythms and the relaxation response. Bozcuk *et al.* (2006) used music for patients with breast cancer during chemotherapy ($n = 18$). The findings failed to identify any effect of the intervention on quality of life in listeners as a whole. However, the researchers postulated that a subgroup over 45 years old would benefit from a music intervention.

Burns *et al.* (2008) conducted eight music imagery sessions for adults with acute leukaemia ($n = 49$) and found significant improvements in anxiety over time in both music and control groups. There was no indication that the intervention was more beneficial than standard care. However, a subgroup of patients with low baseline negative affect, receiving the intervention, reported significantly less anxiety.

Research has consistently shown that relaxing music reduces subjective states of anxiety (Wong *et al.* 2001). MT has been widely used in clinical settings and has demonstrated benefits to various groups of patients in Western countries (Biley 2000, Evans 2002). Recent studies on the effect of music on Chinese patients have also shown a decreased level of anxiety (Yung *et al.* 2002, Mok & Wong 2003).

Hypnotic-like methods, involving relaxation, suggestion for distracting imagery, may help patients with cancer cope with the demands of a cancer experience (Redd *et al.* 2001). Verbal relaxation is a valuable auxiliary approach in the preparation of the patient to establish a state of deep relaxation, has been shown to reduce pain (Syrjala & Chapko 1995) and anxiety (McGrath & de Veber 1986), and has been shown to facilitate distraction (Zeltzer *et al.* 1991). Through use of audio-tape recording, the patient learns to focus on soothing images, to relax muscles and to breathe deeply. With practise, patients are taught to exert voluntary control over their anxiety and to go quickly into a state of deep relaxation.

León-Pizarro *et al.* (2007) studied relaxation among Spanish patients undergoing brachytherapy. Verbal-guided relaxation resulted in reduced anxiety, depression and body discomfort. Similar results were obtained from a meta-analysis conducted by Luebbert *et al.* (2001) on patients with cancer during chemotherapy. They concluded that relaxation training should be used routinely in the care of patients with cancer.

Conceptual framework

A psychophysiological model is used for the study, highlighting the reciprocal interplay of background psychological and physiological responses preceding anxiety. According to the model, heightened sensory awareness and self-attention, as well as physiological responses and accompanying elevated muscle tension, play a role in stress. Further, stress response to anxiety can activate hypothalamus–pituitary–adrenal (HPA) pathway and sympathetic nervous system. The release of corticotropin-releasing hormone (CRH) by the hippocampus in HPA stimulates the pituitary to secrete adrenocorticotropin (ACTH). ACTH regulates excretion of aldosterone from the adrenal cortex which increases blood volume and increases blood pressure (Herman *et al.* 2005). Peripheral nerve system can transmit the sensory signal to the area responsible for perception in thalamus. The signal information passes through thalamus and amygdala to reach to hypothalamus which regulate endocrine secretion and influence sympathetic system.

Based on the concepts from the psychophysiological model, researchers (Lai *et al.* 2006, Lai & Good 2005) have postulated that relaxation and distraction responses can be induced by music and result in reduced activity of the neuroendocrine and sympathetic nervous systems. Thus, a sedative music intervention was expected to increase temperature and decrease anxiety (Good *et al.* 2001), RR, HR and blood pressure (Lai & Good 2005).

Purpose

The purpose of this study was to determine the effects of MT and verbal relaxation (RX) on state anxiety and anxiety-induced physiological manifestations among patients with cancer before, during and after chemotherapy.

The following hypotheses were proposed:

1 Patients receiving MT during chemotherapy will have lower state anxiety, lower HR, increased skin temperature and increased resting behavioural state than patients receiving verbal instruction or no intervention.

2 Patients with high state anxiety (HSA) receiving MT during chemotherapy will show a greater decrease in poststate anxiety than patients with normal state anxiety (NSA).
3 If the positive effects of interventions on patients with HSA are supported, then one can expect that there will be a negative correlation between the magnitude of temperature change and magnitude of state anxiety change of patients in HSA exposed to interventions.

Method

Design

A randomised controlled trial (RCT) was conducted to determine the effect of MT on skin temperature, HR, behavioural state and self-reported anxiety in cancer patients receiving chemotherapy. Data were collected from January–December in 2007.

Sample

Adult patients with cancer requiring chemotherapy were recruited from a medical centre in southern Taiwan. Patients were included in the study if they were over 18 years old, receiving the first or second treatment of a chemotherapy protocol, the ability to hear using head phones and complete a written questionnaire in Chinese. Because Chinese cultural practices allow family members to determine if a patient is informed of a diagnosis or treatment, patients were excluded if they were not aware of their cancer or the purpose of chemotherapy.

To maintain good balance, a permuted block randomisation was used to randomise patients who met the inclusion criteria into experimental, comparison or control group. A random number sequence is generated. Each possible permuted block is assigned a number. Using each number in the random number sequence in turn selected the next block, determining the next participant allocations. The six block design contained equal proportions in each group with randomisation to remove sequence bias.

A previous pilot study (n = 42) determined that the effect size for anxiety reduction in a group of patients with cancer was 0·55. For the current study, a sample size of 15 per group was sufficient to achieve 80% power with α = 0·05.

Data collection

Physiological measures

Physiological responses were obtained using an eight-channel Data Acquisition Computer and ADInstrument Program (Power Lab System; AD Instruments Pty Ltd, Bella Vista, NSW, Australia). HR was measured as heart beats per minute by a three-lead ECG monitor (ML133, Power Lab 16SP; AD Instruments Pty Ltd). Skin temperature, in Centigrade, was monitored using a finger thermistor (ML309, Power Lab 16SP). Parameters are recorded continuously with a computer sampling rate of 100 time points per second (100/s). After data points are examined and artefact excluded the mean rate per minute is calculated. Data are aggregated in five-minute intervals.

Behaviour state

The behavioural state was measured by the Resting Behavioral State Scoring System (RBSS), modified by the researcher from the Behavioral State Scoring System (Anderson *et al.* 1990). The RBSS, three-dimension nominal scales: (1) facial expression, (2) motor activity and (3) wake–sleep status, was recorded in 10-minute intervals by a trained observer. Each item is rated on a Likert scale from 1–3. One equals alert with three being relaxed. Observer inter-rater reliability was established during a pilot study (α = 0·92).

Anxiety

Anxiety was measured using two instruments. The Chinese-STAI (C-STAI), based on the State-Trait Anxiety Inventory (STAI) of Spielberger *et al.* (1983) and translated by Shek (1993), was used to determine subject anxiety. Previously used in Chinese patients with breast cancer in Hong Kong (Efficace *et al.* 2006), the STAI has acceptable validity and reliability raging from 0·90–0·94 (Molassiotis *et al.* 2002). The C-STAI correlates significantly with other measures of psycho-psychological well-being (Shek 1993). The C-STAI is a 40-item self-report questionnaire, including 20 items in each of state anxiety and trait anxiety subscales. Respondents are asked to indicate their agreement on a four-point Likert scale with 1 (definitely agree)–4 (definitely disagree). State anxiety is defined as transient manifest feelings of insecurity while trait anxiety inhibits a relatively stable personality characteristic (Spielberger 1972, Spielberger *et al.* 1983).

Each subscale is summed for a possible score from 20–80. The higher the score, the greater the anxiety. A score above 40 differentiates HSA from and NSA (Spielberger *et al.* 1983, Wong *et al.* 2001). The C-STAI was administered prior to the application of physiological devices while the state anxiety subscale at the end of the intervention or chemotherapy.

The Emotional Visual Analog Scale (EVAS) was used as a simplified measure to evaluate immediate anxiety. The EVAS included six-item anxiety measure based on Diagnostic and Statistical Manual of Mental Disorders Fourth Edition, Text Revision (DSM-IV-TR) criteria (Chen 2003). Each item is placed on a magnetic board with dichotomous anchors (e.g. tension-relaxation). The subject moves the magnet along the continuum to describe their state measured in centimetres, with 0 being no anxiety and 20 being highest anxiety possible. The average mean score of the six items yields an EVAS score. Aitken *et al.* (2002) indicated that a Visual Analog Scale (VAS) might be more beneficial and sensitive than a Likert-type scale in measuring such subjective experiences as relaxation and anxiety. The EVAS was measured after completion of the pretherapy drugs and on initiation of chemotherapy infusion and at the end of the intervention or chemotherapy.

Procedure

After obtaining approval from the Human Subjects Review Board, physicians and nurse case managers identified patients receiving chemotherapy meeting research criteria. Patients were contacted by a research assistant who obtained written informed consent. After agreeing to participate, subjects were randomised to one of three groups: an intervention group to receive a 60-minute session of MT; a comparison group to receive a 30-minute verbal-guided relaxation session (RX); or the control group that received routine nursing care. After randomisation, subjects were interviewed for a pretherapy intake including distress symptoms, medical and family history, recent life stressors and music preferences.

On arrival for chemotherapy, all subjects completed the baseline C-STAI. Subjects were placed in a bed in private room and attached to an electrocardiogram (EKG) and skin temperature transducers. An IV was started and tropisetron hydrochloride, dexamethasone, diphenhydramine hydrochloride and metoclopramide hydrochloride were administrated as ordered to prevent chemotherapy related side effects.

After completion of the pretherapy drugs and on initiation of chemotherapy, the EVAS was administered. Head phones were then applied for the intervention and comparison groups. During the first 30 minutes of the chemotherapy protocol, the RBSS was recorded every 10 minutes and a five-minute mean score of each physiological parameter calculated. If the subject had fallen asleep, they were woken within 30 minutes after the chemotherapy was completed and completed the EVAS with the C-STAI for the music intervention and control groups. The relaxation comparison group completed the EVAS at the end of the 30-minute intervention.

Treatment condition

Chemotherapy treatment occurred in a private room in the oncology centre with an adjustable bed, a stereo compact disc (CD) player and head phones. For the intervention group, music played during the sessions registered between 55–70 db for playing soft music.

The music intervention group received a 60-minute MT according to the principles of guided imagery and music (GIM) (Laurie 2000). GIM, is a depth approach to MT used to generate a dynamic unfolding of inner experiences (Goldberg 1995), allowing for the emergence of all aspects of the human experiences: psychological, emotional, physical and spiritual (Goldberg 1995). The music intervention followed a 3-step GIM process (Mckinney 2002): a Preparation Period (10 min), Deep Relaxation Period (12 min) and Music Listening Period (38 min) provided by a trained practitioner. During the Preparation Period, *Songs of the Pacific (Ambient Moods-Whale Song)* including the sound of sea waves, seabirds and whales are played. During the Deep Relaxation Period, a meditation-relaxation with taped recorded verbal instructions guides the patient. In the Deep Relaxation Period, light music, *Forest Piano* with sounds of nature, such as wind, birds and piano are played. The music guides the patient to alter their consciousness to nature scenes, reaching physical and mental deep relaxation. The third step, the Music Listening Period, *Violin Rain, Aroma Lavender* are played.

The relaxation comparison group included a 10-min Preparation Period and a 20-minute Deep Relaxation Period directed by tape recorded verbal instructions. The Deep Relaxation Period for this group focused on abdominal breathing and guided imagery with light music background without music listening period. During the MT and RX protocol the subjects do not interact with nursing staff.

Data analysis

The means of HR and temperature were synchronised with the observation times of RBSS. Analysis of variance (ANOVA) compared group differences on continuous variables (e.g., age). The chi-squared test (χ^2) was used for categorical data (e.g., education and marital status). Outcomes were compared among groups using analysis of covariance (ANCOVA). The baseline C-STAI, EVAS, first five-minute mean of temperature and HR scores were included as covariates in analyses of postchemotherapy C-STAI, EVAS and physiological changes, respectively. Statistical significance was defined as $p < 0{\cdot}05$.

Results

Demographic data

One hundred and twenty-three patients with cancer agreed to participate. Equipment malfunction occurring in 12 subjects resulted in incomplete data. Thirteen subjects

Table 1 Demographic characteristics of music therapy (MT), verbal relaxation (RX) and control (CO) groups (n = 98)

	MT (n = 34)	RX (n = 30)	CO (n = 34)
	$\bar{X}$ (SD)	$\bar{X}$ (SD)	$\bar{X}$ (SD)
Age (years)	50·2 (13·5)	54·3 (9·4)	54·3 (13·6)
Anxiety trait	42·0 (7·4)	45·0 (10·2)	42·0 (8·4)
	n (%)	n (%)	n (%)
Gender			
Female	21 (61·8)	21 (70·0)	23 (67·6)
Male	13 (38·2)	9 (30·0)	11 (32·4)
Education level			
Illiterate	3 (8·8)	2 (6·7)	7 (20·6)
Elementary	9 (26·5)	11 (36·7)	9 (26·5)
Junior high	3 (8·8)	5 (16·7)	3 (8·8)
Senior high	14 (41·2)	7 (23·3)	9 (26·5)
College and above	5 (14·7)	5 (16·7)	6 (17·6)
Marital status			
Married	27 (79·4)	26 (86·7)	25 (73·5)
Never married	5 (14·7)	2 (6·7)	8 (23·5)
Divorced/separated	2 (5·9)	2 (6·7)	1 (2·9)
Diagnosis			
Lung cancer	4 (11·8)	4 (13·3)	6 (17·6)
Breast cancer	12 (35·3)	13 (43·3)	15 (44·1)
Other	18 (52·9)	13 (43·3)	13 (38·2)
Cancer stage			
I	7 (20·6)	3 (10·0)	9 (26·5)
II	12 (35·3)	10 (33·3)	15 (44·1)
III	11 (32·4)	10 (33·3)	6 (17·6)
IV	4 (11·8)	7 (23·3)	4 (11·8)
Session of chemotherapy			
First	28 (82·4)	24 (80·0)	29 (85·3)
Second	6 (17·6)	6 (20·0)	5 (14·7)

withdrew during the study owing to complaints of music preference or personal needs (e.g. toileting). Ninety-eight subjects provided data for analysis. The mean age of subjects was 53 (SD 12·5) years old (Table 1). There was no difference among the groups on age, gender, education or marital status. The mean C-STAI trait anxiety score was 42·9 (SD 8·7) and ranged from 28–72. Over one-third scored above 45 indicated their propensity to develop anxiety. There was no difference among groups on mean trait anxiety score or the number of subjects scoring above 45. The majority of subjects had a stage 2 (37·8%) or 3 (27·6%) cancer diagnosis. Because the chemotherapy regimens differed among patients and diagnoses, each protocol was quantified according to drug category, pharmacokinetic toxicity and system effects. Eight-one (83%) subjects were undergoing their first chemotherapy session. Half of the subjects (n = 46) reported their music preference of light, popular or natural music.

Hypothesis 1

Hypothesis 1 was partially supported. Prior to chemotherapy, there was no difference in state anxiety or EVAS score among the groups. State anxiety before chemotherapy was significantly correlated ($r = 0{\cdot}54$, $p < 0{\cdot}001$, $n = 98$) with trait anxiety. State anxiety and EVAS score were also significantly correlated ($r = -0{\cdot}70$, $p < 0{\cdot}001$, $n = 98$). The difference between state anxiety scores and EVAS scores before and after treatment were examined by paired *t*-test and showed statistical differences (Table 2). The MT intervention, RX comparison and control groups all had significant declines in state anxiety and significant increases in EVAS score after 30 minutes. ANCOVA with pre-state anxiety or pre-EVAS as a covariate revealed that the MT intervention had a greater decrease in poststate anxiety ($F_{2,94} = 5{\cdot}580$, $p = 0{\cdot}005$, $\eta^2 = 0{\cdot}106$, power = 0·846) and greater increase in post-EVAS ($F_{2,94} = 7{\cdot}199$, $p = 0{\cdot}001$, $\eta^2 = 0{\cdot}133$, power = 0·972) than the RX comparison and control groups.

In addition, the magnitude of change ((Post-Pre/Pre) × 100) of both state anxiety and EVAS scores across the groups were significantly different over the 30-minute period ($p < 0{\cdot}05$).

Table 2 Changes in psychological effect of music therapy, verbal relaxation and control groups (n = 98)

Variable	Pretest $\bar{X}$ (SD)	Post-test $\bar{X}$ (SD)	Paired T	F
State anxiety (20–80)				
Music therapy	39·18 (12·26)	29·76 (8·76)	5·644***	5·580**
Verbal relaxation	41·07 (13·71)	31·63 (10·76)	5·363***	
Control	39·53 (13·10)	35·15 (10·96)	3·898***	
EVAS (0–20)				
Music therapy	12·79 (4·50)	17·08 (2·91)	−6·188***	7·197***
Verbal relaxation	11·53 (4·33)	15·73 (3·65)	−6·114***	
Control	12·76 (4·83)	14·69 (3·80)	−4·373***	

EVAS, Emotional Visual Analog Scale.
**$p < 0{\cdot}01$, ***$p < 0{\cdot}001$.

The pre to post difference of state anxiety ($F_{2,95}$ = 3·705, p = 0·028) and EVAS score ($F_{2,95}$ = 4·880, p = 0·01) revealed significant reduction among groups.

Prior to chemotherapy, there was no difference among the groups on HR or skin temperature. During and after the intervention, the three groups showed no significant differences on HR or skin temperature at any five-minute mean value. However, the temperature of 88·8 % (n = 87) of the subjects during the study period only varied within 1 °C. Despite the small variance, the changes in the temperatures before and after treatment among the three groups did differ. Both MT and RX groups showed a significant increase in skin temperature while the control group showed a decrease.

Prior, during and after chemotherapy, there was no difference among the groups in mean values of sleep-wake cycle, motor activity or facial expression. While more subjects in the music group fell asleep (n = 27, 27·6%) than in the relaxation group (n = 22, 22·4%) and control group (n = 25, 25·5%), only 24 subjects remained awake.

Hypothesis 2

Hypothesis 2 was supported. The sample was divided by pre-state anxiety, score over 40 (HSA) and under 39 (NSA). There were 51 (52%) subjects in the HSA subsample, equally represented across the three interventions. Using ANCOVA the intervention effects were examined in the HSA and NSA subsamples, using pre-state anxiety or pre-EVAS as a covariate. The HSA subsample receiving MT showed a significant decrease in poststate anxiety score ($F_{2,47}$ = 4·364, p = 0·018, η^2 = 0·157, power = 0·728) or increase in post-EVAS score ($F_{2,47}$ = 8·148, p = 0·001, η^2 = 0·257, power = 0·948) compared to the RX and the control groups (Table 3). The HSA RX group also showed a significant positive effect. The NSA subsample showed no significant changes in state anxiety or EVAS before and after treatment across all interventions.

Using the first five-minute mean temperature value as a covariate and the sixth, or last, five-minute mean temperature value as the outcome, ANCOVA revealed that the RX intervention in the HSA subsample produced a greater increase compared to the MT group. The MT group had a greater increase in temperature than the control group. In the HSA subsample the difference in temperature change between RX and control groups was statistically significant (F = 3·503, p = 0·04) by Bonferroni test, a difference not found in the NSA subsample. The differences between the first five-minute mean and the sixth, or last, five-minute mean of HR showed no significant differences across interventions in the HSA or NSA subsample.

Table 3 Differences in psychological and physiological changes among groups in normal and high state anxiety subsamples (n = 98)

	Normal state anxiety (0–39) n = 47							High state anxiety (≥40) n = 51						
	Pretest			Post-test				Pretest			Post-test			
	MT	RX	CO	MT	RX	CO		MT	RX	CO	MT	RX	CO	
Variable	X̄ (SD)	X̄ (SD)	X̄ (SD)	X̄ (SD)	X̄ (SD)	X̄ (SD)	F	X̄ (SD)	X̄ (SD)	X̄ (SD)	X̄ (SD)	X̄ (SD)	X̄ (SD)	F
Anxiety (20–80)	27·94 (4·68)	31·13 (6·67)	27·27 (6·40)	24·00 (4·80)	26·56 (5·89)	26·27 (6·93)	0·985	49·17 (6·92)	52·43 (10·35)	49·21 (7·66)	34·89 (8·35)	37·43 (12·26)	42·16 (8·09)	4·364*
EVAS (0–20)	15·13 (3·55)	14·03 (3·90)	15·44 (4·50)	17·60 (3·13)	18·06 (1·27)	16·87 (3·44)	2·631	10·71 (4·30)	8·68 (2·80)	10·64 (4·05)	16·62 (2·70)	13·07 (3·68)	12·96 (3·18)	8·148***
Temperature (°C)	31·75 (2·60)	31·70 (2·32)	31·27 (2·30)	32·11 (2·60)	31·25 (2·60)	31·13 (2·45)	1·385	32·60 (2·15)	33·09 (2·29)	31·94 (2·48)	32·96 (2·19)	34·07 (2·08)	31·75 (2·72)	4·368*
HR (BPM)	73·82 (10·70)	70·42 (18·87)	75·14 (11·00)	76·35 (11·69)	70·89 (16·75)	73·71 (10·68)	1·830	76·34 (10·80)	69·75 (20·76)	79·49 (13·73)	76·20 (17·17)	66·95 (18·64)	80·68 (14·13)	1·127

MT, music therapy; RX, verbal relaxation; CO, control; BPM, beats per minute; EVAS, Emotional Visual Analog Scale; HR, heart rate.
*p < 0·05, ***p < 0·001.

Hypothesis 3

Hypothesis 3 was supported. The relationship between physiological and psychological outcomes across all interventions was examined using GraphPad Prism4 software (Zuluaga *et al.* 2009). In the HSA subsample, there was a negative correlation ($n = 51$, $r = -0{\cdot}413$, $p = 0{\cdot}0026$) between the magnitude of change in state anxiety and the magnitude of change in skin temperature. This finding indicates that in patients with HSA, there was a positive effect across all interventions in the reduction of state anxiety (Fig. 1). In contrast, there was no correlation between the magnitudes of change in physiological and psychological outcomes with NSA subsample (Fig. 2).

Discussion

While only one-third of the patients with cancer reported high trait anxiety (score >45) prior to chemotherapy, over half (52 %) reported HSA (score >39) prior to chemotherapy. This finding confirms the propensity of the impending chemotherapy to trigger anxiety. MT demonstrated the ability to reduce state anxiety in the MT and RX groups better than no music. This finding supports previous research of Ferrer (2007). Ferrer randomised 50 patients receiving chemotherapy to 20 minutes of live guitar and vocal intervention or control group, measuring anxiety with a visual analogue scale and anxiety questionnaire. While anxiety scores significantly decreased in the intervention group, the difference in trait anxiety between groups was not known. Ferrer's lack of standardised anxiety tool was overcome in the present study using the STAI and the EVAS. The findings in this study extend the work of Elliott (1994) in an early study of cardiac care patients. While Elliott found that MT and relaxation therapy had positive effects, no control group was included.

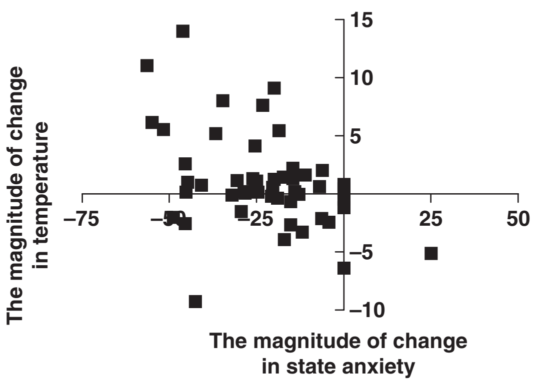

Figure 1 The correlation between the magnitude of change in physiological and psychological outcomes in high state anxiety subsample across all interventions ($n = 51$).

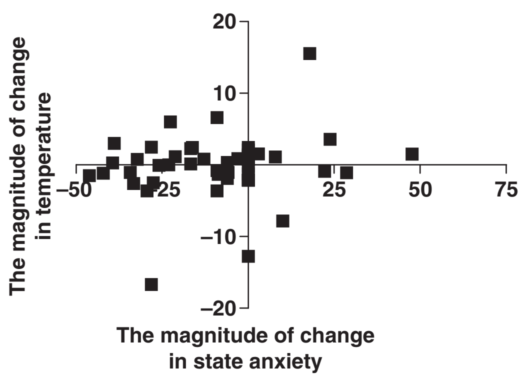

Figure 2 The correlation between the magnitude of change in physiological and psychological outcomes in normal state anxiety subsample across all interventions ($n = 47$).

Although producing similar outcomes, the mechanisms of actions in MT and RX groups are different. Music allows subjects to relax by imagery (Burns 2001, Thaut 2002); RX provides guided instruction disrupting environmental stress to refocus concentration on breathing (Yildirim & Fadiloglu 2006). Our ANCOVA result showed a greater decreased anxiety in MT than in RX groups. Although small changes in temperature and resting behaviour did not achieve statistical significance, MT seemed to be more effective than RX and standard care. These indicators except HR have supported the hypothesis 1.

Further results which supported hypothesis 2 indicated that, in the subsample with HSA prechemotherapy, MT appears to be more effective than RX in decreasing anxiety; however, the NSA subsample showed no significant changes in state anxiety before and after treatment across all interventions. In a more recent study on patients with cancer receiving radiotherapy, Smith *et al.* (2001) also analysed patients with high and low state anxiety. They concluded that MT was more effective than standard care for the initial HSA subgroup, similar to the present study.

Previous research has determined that patients with HSA interact with the music to change their perception and body tension while RX is a more passive intervention. Using a RX intervention without music, Vasterling *et al.* (1993) found that patients with high anxiety reported significantly more postchemotherapy anxiety, depression and hostility than patients with low anxiety.

Because of the intervention-mediated relaxation and distraction, the HSA subsample showed a decrease in anxiety and an increase in skin temperature while the NSA subsample did not. The magnitude of change in state anxiety was found to be negatively correlated with that in temperature. This finding has supported our hypothesis 3.

The strong correlation between EVAS and state anxiety in the current study supports the validity of the EVAS in clinical practice (Aitken *et al.* 2002, Walworth *et al.* 2008). With only six items, clinical chemotherapy nurses can use the EVAS to assess pre- and post-treatment anxiety to determine appropriate interventions.

The lack of bio-behavioural changes found in this study may be related to the number of variables contributing to HR and skin temperature during chemotherapy. HR, expected to decrease during relaxation (Luebbert *et al.* 2001) and music (Evans 2002, Lee *et al.* 2005), may have been attenuated by prechemotherapy drugs, chemotherapy regimen and IV fluid administration. Individual differences in the ability to peripherally dilate and regulate cardiac output may explain the lack of variability. A large standard deviation in temperature negated any ability to identify differences. The inability to differentiate groups according to sleep-awake, motor activity and facial expression prior to the intervention was confounded as all but 15 subjects fell asleep. It is likely this behaviour was secondary to the administration of prechemo sedatives (Jordan *et al.* 2007).

Data demonstrate that in patients with HSA receiving chemotherapy, MT is most effective, though relaxation is also effective. HSA individuals may be more sensitive to environmental stimuli, such as the sights and sounds of the chemotherapy unit. Thus, when the environment is modified they readily respond by a decrease in anxiety after 30 minutes. A longer dose represented by the MT intervention further reduces anxiety.

Both music and RX showed positive effects at 30 minutes. At the end of the music intervention, the anxiety reduction increased. Because of the physiological consequences of prechemotherapy medications and intravenous fluid loading, MT can be interrupted by toileting. However, findings from this study indicate that even a 30-minute music or relaxation intervention is anxiety reducing.

Limitations

The long duration of music intervention when interrupted by patient toileting may underestimate the effect of music on physiological and psychological indicators. The current study did not attempt to provide the patient's preferred music and may be considered as a limitation. According to previous findings of Salamon *et al.* (2003), preferred music is more effective in reducing anxiety and stress than non-preferred music.

Conclusion

Music intervention during a 30-minute chemotherapy protocol possesses significant effects on reducing anxiety in those patients with prechemotherapy HSA. Physiological indicators are also significantly changed in patients with HSA as a result of MT. Furthermore, there is a negative correlation between psychological and physiological change. Behavioural measures to determine MT effectiveness require further investigation and specificity to measure effect size.

Thirty minutes of music or RX protocols are recommended for patients undergoing short-term chemotherapy protocols. Future research using the EEG to measure the consciousness level of patients during chemotherapy is indicated to differentiate the sleep status and intervention effect. Evaluation of state anxiety after repeated MT and RX intervention and booster interventions, for patients with HSA prechemotherapy in the clinical setting and at home is needed.

Relevance to clinical practice

Prior to chemotherapy, patients with HSA must be sorted from all patients as they are more responsive to music and RX interventions. Oncology nurses can offer music and RX as adjuvant interventions to reduce chemotherapy-induced anxiety and enhance the quality of care. MT or RX has several attractive features. It is safe and does not produce adverse effects or drug interactions. An additional benefit is that it can be generalised to other distressing circumstances. The patient who receives MT or RX for management of prechemotherapy HSA may be expected to have benefits for lessening or managing the distress of other side effects from chemotherapy. Moreover, the patient who receives MT or RX for anxiety control may achieve a sense of mastery over their anxiety that is additionally therapeutic.

Contributions

Study design: M-FL, M-CH; data collection and analysis: M-FL, Y-JH, Y-YH, M-CH and manuscript preparation: M-FL, Y-JH, SF.

Conflict of interest

No conflict of interest has been declared by the authors.

References

Aitken JC, Wilson S, Coury D & Moursi AM (2002) The effect of music distraction on pain, anxiety and behavior in pediatric dental patients. *Pediatric Dentistry* **24**, 114–118.

American Cancer Society (2008) Cancer facts & figures 2008. Available at: http://www.cancer.org/docroot/STT/content/STT_1x_Cancer_Facts_and_Figures_2008.asp?from=fast (accessed 29 April 2009).

Anderson GC, Behnke M, Gill NE, Colon M, Measel CP & McDonine TE (1990) Self-regulatory gavage-to-bottle feeding for preterm infants: effect on behavior state, energy expenditure and weight gain. In *Key Aspects of Recovery: Improving Nutrition, Rest and Mobility* (Funk SG, Tornquist EM, Champagne MT, Copp LA & Wiese RA eds). Springer, New York, pp. 83–97.

Antoni MH, Wimberly SR, Lechner SC, Kazi A, Sifre T, Urcuyo KR, Phillips K, Smith RG, Petronis VM, Guellati S, Wells KA, Blomberg B & Carver CS (2006) Reduction of cancer-specific thought intrusions and anxiety symptoms with a stress management intervention among women undergoing treatment for breast cancer. *The American Journal of Psychiatry* **163**, 1791–1797.

Arakawa S (1997) Relaxation to reduce nausea, vomiting and anxiety induced by chemotherapy in Japanese patients. *Cancer Nursing* **20**, 342–349.

Benson H, Beary JF & Carol MP (1974) The relaxation response. *Psychiatry* **37**, 37–46.

Bernardi L, Porta C & Sleight P (2006) Cardiovascular, cerebrovascular and respiratory changes induced by different types of music in musicians and non-musicians: the importance of silence. *Heart* **92**, 445–452.

Biley FC (2000) The effects on patient well-being of music listening as a nursing intervention: a review of the literature. *Journal of Clinical Nursing* **9**, 668–677.

Bittman B, Berk L, Shannon M, Sharaf M, Westengard J, Guegler KJ & Ruff DW (2005) Recreational music-making modulates the human stress response: a preliminary individualized gene expression strategy. *Medical Science Monitor: International Medical Journal of Experimental and Clinical Research* **11**, 31–40.

Bozcuk H, Artac M, Kara A, Ozdogan M, Sualp Y, Topcu Z, Karaagacli A, Yildiz M & Savas B (2006) Does music exposure during chemotherapy improve quality of life in early breast cancer patients? A pilot study. *Medical Science Monitor: International Medical Journal of Experimental and Clinical Research* **12**, 200–205.

Brunges MJ & Avigne G (2003) Music therapy for reducing surgical anxiety. *AORN Journal* **78**, 816–818.

Burns DS (2001) The effect of the bonny method of guided imagery and music on the mood and life quality of cancer patients. *Journal of Music Therapy* **38**, 51–65.

Burns DS, Azzouz F, Sledge R, Rutledge C, Hincher K, Monahan PO & Cripe LD (2008) Music imagery for adults with acute leukemia in protective environments: a feasibility study. *Supportive Care in Cancer* **16**, 507–513.

Chen YH (2003) Effects of Vivace-Allegro and Andante-Adagio music on stress responses in female college students. Unpublished thesis of National Cheng Kung University, Taiwan.

Chlan LL (2000) Music therapy as a nursing intervention for patients supported by mechanical ventilation. *American Association of Critical Care Nurses, Clinical Issues* **11**, 128–138.

Clark M, Isaacks-Downton G, Wells N, Redlin-Frazier S, Eck C, Hepworth JT & Chakravarthy B (2006) Use of preferred music to reduce emotional distress and symptom activity during radiation therapy. *Journal of Music Therapy* **43**, 247–265.

Department of Health, Taiwan, ROC (2009) *Mortality Statistics*. Available at: http://www.doh.gov.tw/CHT2006/DM/DM2_2.aspx?now_fod_list_no=10328&class_no=440&level_no=4 (accessed 29 April 2009).

Efficace F, Horneber M, Lejeune S, Van Dam F, Leering S, Rottmann M & Aaronson NK (2006) Methodological quality of patient-reported outcome research was low in complementary and alternative medicine in oncology. *Journal of Clinical Epidemiology* **59**, 1257–1265.

Elliott D (1994) The effects of music and muscle relaxation on patient anxiety in a coronary care unit. *Heart and Lung* **23**, 27–35.

Evans D (2002) The effectiveness of music as an intervention for hospital patients: a systematic review. *Journal of Advanced Nursing* **37**, 8–18.

Ferrell-Torry AT & Glick OJ (1993) The use of therapeutic massage as a nursing intervention to modify anxiety and the perception of cancer pain. *Cancer Nursing* **16**, 93–101.

Ferrer AJ (2007) The effect of live music on decreasing anxiety in patients undergoing chemotherapy treatment. *Journal of Music Therapy* **44**, 242–255.

Goldberg FS (1995) The Bonny method of guided imagery and music. In *The Art and Science of Music Therapy: A Hand Book* (Wigram T, Saperston B & West R eds). Harwood, Chur, Switzerland, pp. 112–128.

Good M, Stanton-Hicks M, Grass JA, Anderson GC, Lai HL, Roykulcharoen V & Adler PA (2001) Relaxation and music to reduce postsurgical pain. *Journal of Advanced Nursing* **33**, 208–215.

Haun M, Mainous RO & Looney SW (2001) Effect of music on anxiety of women awaiting breast biopsy. *Behavioral Medicine* **27**, 127–132.

Herman JP, Ostrander MM, Mueller NK & Figueiredo H (2005) Limbic system mechanisms of stress regulation: hypothalamo-pituitary- adrenocortical axis. *Progress in Neuro-psychopharmacology & Biological Psychiatry* **29**, 1201–1213.

Iconomou G, Mega V, Koutras A, Iconomou AV & Kalofonos HP (2004) Prospective assessment of emotional distress, cognitive function and quality of life in patients with cancer treated with chemotherapy. *Cancer* **101**, 404–411.

Jacobsen PB, Hann DM, Azzarello LM, Horton J, Balducci L & Lyman GH (1999) Fatigue in women receiving adjuvant chemotherapy for breast cancer: characteristics, course and correlates. *Journal of Pain and Symptom Management* **18**, 233–242.

Jordan K, Schmoll HJ & Aapro MS (2007) Comparative activity of antiemetic drugs. *Critical Reviews in Oncology/Hematology* **61**, 162–175.

Juslin PN & Västfjäll D (2008) Emotional responses to music: the need to consider underlying mechanisms. *The Behavioral and Brain Sciences* **31**, 559–575.

Lai HL & Good M (2005) Music improves sleep quality in older adults. *Journal of Advanced Nursing* **49**, 234–244.

Lai HL, Chen CJ, Peng TC, Chang FM, Chen ML, Huang HY & Chang SC (2006) Randomized controlled trial of music during kangaroo care on perinatal anxiety and preterm infants' responses. *International Journal of Nursing Studies* **43**, 139–146.

Laurie R (2000) Music as a vehicle for inner exploration: the Bonny method of guided imagery and music (GIM). *Guidance and Counseling* **15**, 23–28.

Lee OK, Chung YF, Chan MF & Chan WM (2005) Music and its effect on the physiological responses and anxiety levels of patients receiving mechanical ventilation: a pilot study. *Journal of Clinical Nursing* **14**, 609–620.

León-Pizarro C, Gich I, Barthe E, Rovirosa A, Farrús B, Casas F, Verger E, Biete A, Craven-Bartle J, Sierra J & Arcusa A (2007) A randomized trial of the effect of training in relaxation and guided imagery techniques in improving psychological and quality-of-life indices for gynecologic and breast brachytherapy patients. *Psycho-oncology* **16**, 971–979.

Link LB, Robbins L, Mancuso CA & Charlson ME (2005) How do cancer patients choose their coping strategies? A qualitative study. *Patient Education and Counseling* **58**, 96–103.

Luebbert K, Dahme B & Hasenbring M (2001) The effectiveness of relaxation training in reducing treatment-related symptoms and improving emotional adjustment in acute non-surgical cancer treatment: a meta-analytical review. *Psycho-oncology* **10**, 490–502.

McCaffrey R & Freeman E (2003) Effect of music on chronic osteoarthritis pain in older people. *Journal of Advanced Nursing* **44**, 517–524.

McCloskey JC & Bulechek GM (2000) *Nursing Interventions Classification (NIC)*. Mosby, St. Louis, MO.

McGrath PA & de Veber LL (1986) The management of acute pain evoked by medical procedures in children with cancer. *Journal of Pain and Symptom Management* **1**, 145–150.

Mckinney C (2002) Quantitative research in guided imagery and music (GIM): a review. In *Guided Imagery and Music* (Bruscia KE & Grocke DE eds). Gilsom, Barcelona, pp. 449–450.

Mok E & Wong KY (2003) Effects of music on patient anxiety. *Association of perioperative Registered Nurses Journal* **77**, 396–397, 401–406, 409–410.

Molassiotis A, Yam BM, Yung H, Chan FY & Mok TS (2002) Pretreatment factors predicting the development of postchemotherapy nausea and vomiting in Chinese breast cancer patients. *Supportive Care in Cancer* **10**, 139–145.

Morasso G (2002) Distress psicologico e pazienti oncologici: uno studio negli IRCSS italiani. Available at: http://www.istge.it/clinica/servizi/Psicologia/italiano/ricerche2002-2004.htm (accessed 18 March 2007).

Passik SD, Kirsh KL, Rosenfeld B, McDonald MV & Theobald DE (2001) The changeable nature of patients' fears regarding chemotherapy: implications for palliative care. *Journal of Pain and Symptom Management* **21**, 113–120.

Pelletier CL (2004) The effect of music on decreasing arousal due to stress: a meta-analysis. *Journal of Music Therapy* **41**, 192–214.

Redd WH, Montgomery GH & DuHamel KN (2001) Behavioral intervention for cancer treatment side effects. *Journal of the National Cancer Institute* **93**, 810–823.

Roffe L, Schmidt K & Ernst E (2005) A systematic review of guided imagery as an adjuvant cancer therapy. *Psycho-oncology* **14**, 607–617.

Sabo CE & Michael SR (1996) The influence of personal message with music on anxiety and side effects associated with chemotherapy. *Cancer Nursing* **19**, 283–289.

Salamon E, Bernstein SR, Kim SA, Kim M & Stefano GB (2003) The effects of auditory perception and musical preference on anxiety in naive human subjects. *Medical Science Monitor: International Medical Journal of Experimental and Clinical Research* **9**, CR396–CR399.

Shek DT (1993) The Chinese version of the State-Trait Anxiety Inventory: its relationship to different measures of psychological well-being. *Journal of Clinical Psychology* **49**, 349–358.

Smith M, Casey L, Johnson D, Gwede C & Riggin OZ (2001) Music as a therapeutic intervention for anxiety in patients receiving radiation therapy. *Oncology Nursing Forum* **28**, 855–862.

Spielberger CD (1972) *Anxiety: Current Trends in Theory and Research*. Academic Press, New York.

Spielberger CD, Gorsuch RL, Lushene R, Vagg PR & Jacobs GA (1983) *Manual for the State-Trait Anxiety Inventory*. Consulting Psychologists Press, Palo Alto, CA.

Stefano GB, Zhu W, Cadet P, Salamon E & Mantione KJ (2004) Music alters constitutively expressed opiate and cytokine processes in listeners. *Medical Science Monitor: International Medical Journal of Experimental and Clinical Research* **10**, 18–27.

Syrjala KL & Chapko ME (1995) Evidence for a biopsychosocial model of cancer treatment-related pain. *Pain* **61**, 69–79.

Taiwan Cancer Registration System (2009) Taiwan Cancer Registry. Available at: http://crs.cph.ntu.edu.tw/main.php?Page=A5#t01 (accessed 29 April 2009).

Thaut MH (2002) Toward a cognition-affect model in neuropsychiatric music therapy. In *Music Therapy in the Treatment of Adults with Mental Disorders: Theoretical Bases and Clinical Interventions* (Unkefer RF & Thaut MH eds). MMB Music, St. Louis, pp. 86–103.

Vasterling J, Jenkins RA, Tope DM & Burish TG (1993) Cognitive distraction and relaxation training for the control of side effects due to cancer chemotherapy. *Journal of Behavioral Medicine* **16**, 65–80.

Walworth D, Rumana CS, Nguyen J & Jarred J (2008) Effects of live music therapy sessions on quality of life indicators, medications administered and hospital length of stay for patients undergoing elective surgical procedures for brain. *Journal of Music Therapy* **45**, 349–359.

Watkins GR (1997) Music therapy: proposed physiological mechanisms and clinical implications. *Clinical Nurse Specialist CNS* **11**, 43–50.

Williams PD, Piamjariyakul U, Ducey K, Badura J, Boltz KD, Olberding K, Wingate A & Williams AR (2006)

Cancer treatment, symptom monitoring and self-care in adults: pilot study. *Cancer Nursing* **29**, 347–355.

Wong HL, Lopez-Nahas V & Molassiotis A (2001) Effects of music therapy on anxiety in ventilator-dependent patients. *Heart and Lung* **30**, 376–387.

World Health Organization (2009) Cancer control: knowledge into action, WHO guide for effective programmes. Available at: http://www.who.int/cancer/publications/en/index.html (accessed 29 April 2009).

Yildirim YK & Fadiloglu C (2006) The effect of progressive muscle relaxation training on anxiety levels and quality of life in dialysis patients. *EDTNA/ERCA Journal* **32**, 86–88.

Yung PM, Chui-Kam S, French P & Chan TM (2002) A controlled trial of music and pre-operative anxiety in Chinese men undergoing transurethral resection of the prostate. *Journal of Advanced Nursing* **39**, 352–359.

Zeltzer LK, Dolgin MJ, LeBaron S & LeBaron C (1991) A randomized, controlled study of behavioral intervention for chemotherapy distress in children with cancer. *Pediatrics* **88**, 34–42.

Zuluaga AF, Agudelo M, Rodriguez CA & Vesga O (2009) Application of microbiological assay to determine pharmaceutical equivalence of generic intravenous antibiotics. *BMC Clinical Pharmacology* **9**, 1.