

# Music-based interventions in palliative cancer care: a review of quantitative studies and neurobiological literature

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## Abstract

**Purpose** This study aimed to review quantitative literature pertaining to studies of music-based interventions in palliative cancer care and to review the neurobiological literature that may bear relevance to the findings from these studies.

**Methods** A narrative review was performed, with particular emphasis on RCTs, meta-analyses, and systematic reviews. The Cochrane Library, Ovid, PubMed, CINAHL Plus, PsycINFO, and ProQuest were searched for the subject headings *music, music therapy, cancer, oncology, palliative care, pain, anxiety, depression, mood, quality of life, prevalence, neuroscience, functional imaging, endogenous opioids, GABA, 5HT, dopamine*, and permutations of these same search terms. Data for the review were comprised of articles published between 1970 and 2012. References of all the cited articles were also reviewed.

**Results** Available evidence suggests that music-based interventions may have a positive impact on pain, anxiety, mood disturbance, and quality of life in cancer patients. Advances in neurobiology may provide insight into the potential mechanisms by which music impacts these outcomes.

**Conclusions** More research is needed to determine what subpopulation of cancer patients is most likely to respond to music-based interventions, what interventions are most

effective for individual outcomes, and what measurement parameters best gauge their effectiveness.

**Keywords** Music · Cancer · Oncology · Palliative · Neurobiology

## Introduction

By alleviating the physical and psychological symptoms associated with malignancy, palliative care serves a vital role in the multidisciplinary care of cancer patients. Common symptoms such as pain, anxiety, and mood disturbance can be difficult to manage with standard pharmaceutical options and may significantly interfere with quality of life (QOL) [1, 2]. The search for complimentary interventions that are both cost effective and associated with few side effects has led to an increased interest in the therapeutic use of music for cancer patients within the field of palliative care [3–6]. This review summarizes findings from quantitative research literature. Furthermore, it discusses challenges and opportunities associated with this emerging area of research and provides practical suggestions for future investigation.

## Different music-based interventions defined

The interventions in this review are generally classified as either music medicine or music therapy. In “music medicine” interventions, patients listen to prerecorded music that is administered by healthcare staff and preselected by study investigators, who may or may not have any formal training in music therapy [7, 8]. In “music therapy” interventions, patients are offered prerecorded, live, and/or interactive music that is individualized by a trained music therapist [9, 10]. Hence, the crucial distinction between music medicine

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(MM) and music therapy (MT) is that the former involves only a stimulus and response, and the latter involves a *therapeutic relationship* based on individualized assessment, treatment, and evaluation [7].

### Specific clinical endpoints studied

#### Pain

Pain represents one of the most common symptoms affecting patients with advanced malignancy. One recent meta-analysis [11] pooled data from 52 studies (total  $N=19,985$ ) and estimated pain to occur in 33 % of patients who had completed treatment with curative intent, 59 % of patients undergoing anticancer therapy, and 64 % of patients with advanced/metastatic/terminal disease. A subsequent meta-analysis [12] pooled data from 64 studies (total  $N=95,159$ ), 34 of which reported pain prevalence in patients with all stages of cancer (including early disease), and 30 of which reported pain prevalence in patients with advanced cancer. The combined weighted mean prevalence of pain in the 14,961 patients with advanced cancer was estimated to be 75 %.

Multiple studies have demonstrated that music-based interventions may have a mild to moderate analgesic effect (Table 1). Five such randomized controlled trials (RCTs) (total  $N=391$ ) were analyzed in a 2011 Cochrane Review [13]. Pre-recorded music was provided perioperatively for 15 out of 30 breast cancer patients undergoing mastectomy [14], during bone marrow biopsy for 29 out of 59 hematologic malignancy patients [15], as a single 30-min session in 62 out of 126 adult patients with various malignancies [16], during lumbar puncture in 20 out of 40 pediatric leukemia patients [17], and as a single session with guided imagery in 65 out of 136 adult patients with various malignancies [18]. Based on the combined results of these five studies, the authors classified music's analgesic effect as *moderate*, with a standardized mean difference (SMD) of  $-0.59$ , (95 % CI from  $-0.92$  to  $-0.27$ ,  $P=0.0003$ ). All five of the above studies reported pain by self-reported measurement scales. An earlier Cochrane Review examined the effect of music on analgesic requirements during a painful procedure (five studies), during a 2-h postoperative period (three studies), or during a 24-h postoperative period (five studies) [19]. Although none of the included studies were limited to oncologic or palliative care settings, the 13 included studies ( $N=1016$ ) *did* show that exposure to music was associated with a decrease in opioid requirement, with a SMD of  $-1.29$  (95 % CI from  $-0.92$  to  $-0.27$ ,  $P=0.0062$ ). These results were consistent with those from a separate meta-analysis [20] which studied the use of music vs. standard care in adult patients undergoing colonoscopy. This meta-analysis

included three trials [21–23] in which music was provided to a total of 130 out of 261 patients. The patients who received music required 29.7 % less analgesia with meperidine, alfentanil, or pethidine ( $P=0.001$ ) and 15 % less sedation with midazolam or propofol ( $P=0.055$ ). Finally, a single-arm study from 2006 [5] found that in 126 palliative care patients with pain (90 % of whom had cancer), mean self-reported pain scores decreased from 2.7 to 2.1 on a five-point VAS after a single MT session ( $P<0.001$ ).

Overall, these data (derived exclusively from MM-based approaches except for [5]) support the use of music to decrease subjective pain and analgesic requirements in acute pain settings. However, more research is needed to investigate the analgesic efficacy of music for chronic pain, since cancer patients (particularly those in palliative care settings) frequently suffer from chronic pain (e.g., from bone metastases, visceral tumor growth, neuropathic pain associated with chemotherapy, etc.). In future studies investigating music-based interventions for chronic pain, careful consideration should be given to the frequency, duration, and type of interventions used (e.g., consideration of interventions not necessarily limited to MM).

#### Anxiety

For many patients, the diagnosis of cancer can result in significant anxiety, which can interfere with sleep [24], enjoyment of life [25], interpersonal relationships [26], and overall daily activities [27]. Six studies using survey instruments found self-reported anxiety symptoms to be present in 19–48 % of cancer patients [1, 24, 28–31]. In contrast, three studies using structured clinical interviews found DSM-IV-defined Anxiety Disorders (e.g., generalized anxiety disorder, panic disorder, and post-traumatic stress disorder) to be present in 7.6 to 18 % of cancer patients [24, 32, 33].

Several studies have demonstrated that music-based interventions may have a mild to moderate anxiolytic effect (Table 2). Seven such studies (six RCTs and one controlled clinical trial (CCT), total  $N=386$ ) using self-report outcomes were analyzed in the 2011 Cochrane Review [13]. Music was provided perioperatively for 15 out of 30 breast cancer patients undergoing mastectomy [14], during invasive procedures for 20 out of 39 pediatric cancer patients [34], directly prior to the administration of adjuvant chemotherapy for 30 out of 60 breast cancer patients [35], during bone marrow biopsy for 29 out of 59 adults with hematologic malignancy [15], during chemotherapy for 10 out of 20 adult cancer patients [36], during radiation therapy for 19 out of 42 adult cancer patients [37], and as a single 30-min session for 65 out of 136 adult cancer patients with pain [18]. Based on the combined results of these seven studies, the SMD on the 80-point State-Trait Anxiety Inventory Scale (STAI-S) was  $-11.20$  units (95 % CI  $-19.59$  to  $-2.82$ ,  $P=0.0088$ ). These results were consistent

**Table 1** Individual studies investigating the analgesic effect of music-based interventions in either oncologic or palliative care settings

Author, year, type of study	Study population	Music intervention	Control	N, music group	N, control group	Results
Binns-Turner, 2008, RCT <sup>a</sup> [14]	Breast cancer patients undergoing mastectomy	MM: single session of prerecorded music through headphones (continuously from preoperative through postoperative period). Patients could select from classical, easy listening, inspirational, or new age	iPod and headphones but no music or sounds	15	15	Significant reduction in self-reported postop pain level by VAS ( $P=0.007$ )
Danhauer et al., 2010, RCT <sup>a</sup> [15]	Hematologic malignancy patients undergoing lumbar puncture	MM: prerecorded music through headphones for duration of procedure. Patients could select from classical, harp, general instrumental, nature sounds, country, gospel, and jazz	Standard care	29	30	No significant reduction in self-reported intra-procedural pain level by VAS ( $P=0.771$ )
Huang, 2006, RCT <sup>a</sup> [16]	Adult inpatients with various malignancies	MM: single 30-min session of prerecorded music through headphones. Patients could select from Taiwanese folk, Buddhist, harp, and piano recordings	Bed rest	62	64	Significant reduction in self-reported pain level by VAS ( $P<0.001$ )
Nguyen et al., 2010, RCT <sup>a</sup> [17]	Pediatric leukemia patients undergoing lumbar puncture	MM: prerecorded music through headphones for duration of procedure. Patients could select from either traditional Vietnamese songs or children's songs	iPod and headphones but no music or sounds	20	20	Significant reduction in self-reported intra-procedural pain level by VAS ( $P<0.001$ )
Yonghui et al., 2009, RCT <sup>a</sup> [18]	Adult inpatients with various malignancies	MM: single 30-min session of unspecified music with unspecified guided imagery	Standard care	65	71	No significant reduction in self-reported pain detected by numeric rating scale ( $P>0.05$ )
Gallagher, 2006, single-arm study	Adults with a terminal illness <sup>b</sup> in an inpatient palliative care setting	MT: single session of varying length including live performance, listening to prerecorded music, and interactive techniques	None	126	0	Significant reduction in self-reported pain by VAS, from mean score of 2.7 before the session to mean score of 2.1 after the session ( $P<0.001$ )

MM music medicine, MT music therapy

<sup>a</sup> Included in 2011 Cochrane Review

<sup>b</sup> For 90 % of the patients in this study, the terminal illness was cancer

**Table 2** Individual studies investigating the anxiolytic effect of music-based interventions in either oncologic or palliative care settings

Author, year, study type	Study population	Music intervention	Control	N, music group	N, control group	Results
Binns-Turner, 2008, RCT <sup>a</sup> [14]	Breast cancer patients undergoing mastectomy	MM: single session of prerecorded music through headphones (continuously from preoperative through postoperative period). Patients could select from classical, easy listening, inspirational, or new age MT: single 15-min session of music listening followed by interactive music making for the remainder of the invasive procedure (all during conscious sedation). For listening phase, patients could select from children's songs, folk, ethnic, and pop	iPod with headphones but no music or sounds	15	15	Significant reduction in anxiety detected ( $P<0.001$ ). Mean STAI in music group fell from 41.5 to 30.7, while mean STAI in control group rose from 41.9 to 49.7
Bufalini, 2009, CCT <sup>a,b</sup> [34]	Pediatric cancer patients undergoing invasive procedures (e.g., lumbar puncture, bone marrow biopsy, etc.)	MM: single 15-min session of prerecorded music through headphones while waiting for chemotherapy. Patients could select from new age, Celtic, classical, soundtracks, or nature music MM: single 20- to 60- min session of prerecorded music through headphones for duration of BM biopsy. Patients could select from classical, harp, instrumental, nature sounds, country, gospel, and jazz	Conscious sedation alone	20	19	Significant reduction in anxiety of patients in music group compared to control group at all times throughout procedure by modified Yale Preoperative Anxiety Scale ( $P<0.05$ ). STAI-S scores were only measured in the parents of the patients undergoing invasive procedures, in whom no significant difference was found
Bulfone et al., 2009, RCT <sup>a</sup> [35]	Breast cancer patients receiving adjuvant chemotherapy	MM: single 15-min session of prerecorded music through headphones	Standard care	30	30	Significant reduction in anxiety detected ( $P<0.001$ ). Mean STAI in music group fell from 46.2 to 36.3, while mean STAI in control group rose from 43.4 to 44.8
Danhauer et al., 2010, RCT <sup>a</sup> [15]	Hematologic malignancy patients undergoing bone marrow biopsy	MM: single 20- to 60- min session of prerecorded music through headphones	Standard care	29	30	No significant difference was found in the STAI-S scores between two groups ( $P=0.766$ ). However, "patient satisfaction with music was high; 66 % of the patients in the music group said that they very much preferred to listen to music with future biopsies"
Harper, 2001, RCT <sup>a</sup> [36]	Adult cancer patients receiving chemotherapy	MM: single 30-min session of prerecorded music through headphones during chemotherapy infusion. Patients were offered a new age recording published by Image Paths Inc., entitled, "Health Journeys: A Meditation To Help you with Chemotherapy"	Standard care	10	10	Borderline significant reduction in anxiety detected by STAI ( $P=0.05$ ). Mean STAI in music group fell from 42.9 to 28.5, while mean STAI in control group rose from 32.3 to 41.7. Although a significant reduction in anxiety was reportedly detected by the Beck Anxiety Inventory ( $P<0.01$ ), only BAI values after the intervention (not before) were specified
Smith et al., 2001, RCT <sup>a</sup> [37]	Adult cancer patients receiving radiation therapy	MM: multiple 30-min sessions of prerecorded music through headphones during simulation and daily treatments for the duration of therapy. Patients could select from rock and roll, big band, country and western, classical, easy listening, Spanish, or religious music	Standard care	19	23	No significant difference was found between two groups when mean STAI-S scores were compared. However, post hoc subgroup analysis showed that among patients with baseline state anxiety scores $>34$ , those "patients in the experimental group had a steeper decline [from before until after the intervention(s)] compared to the controls"

**Table 2** (continued)

Author, year, study type	Study population	Music intervention	Control	N, music group	N, control group	Results
Yonghui et al., 2009, RCT <sup>a,c</sup> [18]	Hospitalized adult cancer patients with pain	MM: Single 30-min session of prerecorded music with imagery during hospitalization	Standard care	65	71	Significant reduction in anxiety detected ( $P<0.05$ ). Mean STAI in music group fell from 57.9 to 33.8, but mean STAI in control group only fell from 58.6 to 55.9
Home-Thompson and Grocke, 2008, RCT [42]	Adults with a terminal illness in an inpatient palliative care setting (24 out of 25 of which had a diagnosis of cancer)	MT: single 20- to 40-min session conducted by a registered music therapist. Techniques included “playing live familiar music, singing, music and relaxation, music and imagery, improvisation, music-assisted counseling, reminiscence, and listening to recorded music”	Visit from volunteer that either read to, conversed with, or provided emotional support to the patient	13	12	Significant reduction of anxiety in music group compared to the control group by Mann–Whitney testing ( $P=0.005$ ). Eight patients in music group reported a decrease in anxiety of between 1 and 5 points on ESAS scale, while only 1 patient in control group reported a decrease in anxiety of 1 point. Three patients in control group reported increased anxiety after the study interval

MM music medicine, MT music therapy

<sup>a</sup> Included in 2011 Cochrane Review [13]

<sup>b</sup> Insufficient information regarding presence/absence/method of randomization led to the classification of the Bufalini 2009 study [34] as a controlled clinical trial by the authors of the 2011 Cochrane review [13]. Note that the Bufalini 2009 study [34] used mYPAS scores to measure anxiety in the patients, but only used STAI-S scores to measure anxiety in the parents. Since the STAI-S scores in the parents (unlike the mYPAS scores in the patients) showed no significant difference, its inclusion in the pooled analysis with the other six trials would have tended to underestimate the effect of music on anxiety. Furthermore, a sensitivity analysis, excluding the results of both the Bufalini 2009 [34] and Yonghui 2009 [18] studies (based on unclear randomization methods), resulted in a mean difference of  $-9.46$  (95 % CI  $-19.01$  to  $0.09$ ,  $P=0.05$ )

<sup>c</sup> Patients in the Yonghui 2009 study [18] were clearly randomized, hence its classification as an RCT by the authors of the 2011 Cochrane Review [13]. However, since its method of randomization was not entirely clear, it was excluded in the sensitivity analysis



with those from four other RCTs involving patients without cancer, in whom perioperative anxiety was significantly reduced by music-based interventions [38–41]. One small but well-designed RCT specifically examined the effectiveness of a single 20–40-min MT session in reducing anxiety for terminally ill patients [42]. Although cancer was not an inclusion criterion, 24 out of 25 patients in the study had cancer, and all study participants were inpatients receiving palliative care services. Based on the Edmonton Symptom Assessment Scale anxiety scores before and after the intervention, the Mann–Whitney test showed that anxiety was significantly reduced in the music group compared to the control group ( $P=0.005$ ).

Overall, these data (derived from six studies using MM and two studies using MT) support the use of music to reduce anxiety in situations such as before/during invasive procedures, chemotherapy, and radiation therapy. Relatively less is known about music's capacity to decrease the need for pharmacologic anxiolytics/sedatives/hypnotics. Although one study in 327 patients undergoing elective surgery showed a greater decrease in preoperative STAI-S scores with relaxing music than 0.05–0.1mg/kg of midazolam ( $P<0.001$ ) [43], the relevance of this finding to the oncologic and palliative care settings remains uncertain. Furthermore, more research is needed to investigate the anxiolytic efficacy of music beyond the acute/situational anxiety setting, particularly for cancer patients in whom the recognition of disease progression and impending death may be particularly anxiety inducing [44, 45].

### Mood disturbance

The period following diagnosis of cancer can be very emotional for many patients. Patients with frequent depressive symptoms may develop a sustained disturbance of mood and may eventually meet criteria for a DSM-IV-defined Affective Disorder (e.g., major depressive disorder or dysthymic disorder). Prevalence studies suggest that self-reported depressive symptoms in patients with cancer are common and perhaps more common in the terminal/advanced setting [46–49]. Four studies using survey instruments found depressive symptoms present in 53–74 % of cancer patients [46, 50–52]. A much more recent meta-analysis of 94 interview-based studies estimated the combined mean prevalence of major depressive disorder and dysthymic disorder in palliative and hematologic–oncologic settings [53]. From the 24 studies conducted in palliative care settings (total  $N=4,007$ ), the combined mean prevalence of these two disorders was found to be 24.6 %. From the 70 studies conducted in hematology–oncology settings (total  $N=10,071$ ), combined mean prevalence was found to be 20.7 %. To place these numbers in context, the NIMH estimates the combined prevalence of major depressive disorder and dysthymic disorder to be 8.2 % among US adults (two to three times lower than in cancer patients).

While multiple studies have found that music-based interventions may have a positive impact on mood (Table 3), this has not necessarily been the case for depression. Such a discrepancy may be at least partially explained by differences between methods used to assess mood disturbance versus those used to assess depression. For example, the commonly used Profile of Mood States (POMS) uses six domains to calculate a total mood disturbance score: depression–dejection, tension–anxiety, anger–hostility, fatigue–inertia, confusion–bewilderment, and vigor–activity. The first five domains are weighted positively and the last domain is weighted negatively, such that a higher score indicates a greater disturbance of mood. Henceforth, music could elicit improvement in mood via the five other domains but not in “depression/dejection.” This difference in outcomes was well illustrated in a 2011 Cochrane Review [13], which analyzed five trials examining the effect of music on depression (total  $N=468$  patients). Music was provided for 128 out of 182 adults with cancer receiving chemotherapy or radiation therapy [54], 34 out of 60 adults with hematologic malignancy admitted for autologous SCT [55], 27 out of 48 adults with cancer undergoing radiation therapy [56], 20 out of 42 women with metastatic breast cancer [57], and 65 out of 136 adult cancer patients with pain [18]. The pooled estimate from these five trials did *not* find a statistically significant effect of music on depression (SMD=−0.07, 95 % CI −0.40 to 0.27,  $P=0.69$ ). However, the same meta-analysis analyzed three trials examining the effect of music on mood (total  $N=105$ ), and the pooled estimate from these three studies *did* demonstrate a statistically significant effect (SMD=0.42, 95 % CI 0.03 to 0.81,  $P=0.03$ ). These three studies investigating the outcome of mood provided music to 8 out of 15 adults with cancer-related pain [58], 34 out of 60 adults with hematologic malignancy admitted for autologous SCT [55], and 15 out of 30 children with neoplasms needing chemotherapy [59]. That Cassileth's same study [55] showed no effect on depression, but *did* show an effect on mood, supports the idea that the difference between these two outcomes may be more than semantic. Among the 123 palliative care patients with mood disturbance in the single-arm study of Gallagher et al. in 2006 [5], mean self-reported mood disturbance scores improved from 1.8 to 0.7 on a five-point VAS after a single MT session ( $P<0.001$ ).

Overall, the limited data available regarding the outcome of mood (derived from three studies using MT and one study using MM) suggest that music may have a mild positive impact on the mood of cancer patients. Considering that the effects of music-based interventions on pain and anxiety have been most well demonstrated in acute settings, it may not be surprising that a single intervention (MM or MT based) may not show as much impact on mood disturbance, particularly chronically depressed mood. The availability of fast-acting pharmacologic analgesics and anxiolytics, versus

**Table 3** Individual studies investigating the effect of music-based interventions on mood disturbance in either oncologic or palliative care settings

Author, year, type of study	Study population	Music intervention	Control	N, music group	N, control group	Results
Beck, 1989, RCT <sup>a</sup> [58]	Adults with documented cancer-related pain (setting: patients' homes)	MM: three 45-min sessions of prerecorded music through headphones. Patients could select from classical, jazz, folk, rock, country and western, easy listening, and new age	Listening to 60-cycle hum through headphones	8	7	No significant difference detected in mean percent change of five-point VAS between groups ( $P=0.599$ ). However, "60 % of the subjects [in the music group] demonstrated at least some improvement in mood"
Cassileth et al., 2003, RCT <sup>a</sup> [55]	Adults with hematologic malignancy admitted for SCT	MT: median of five 20–30-min sessions (over median of 10 days). Live bedside music therapy was provided by trained music therapist	Standard care	36	33	Significant improvement in mood detected: Patients in the music therapy group scored 37 % lower on total POMS of mood disturbance ( $P=0.01$ ) and 28 % lower in the combined anxiety/depression domains ( $P=0.065$ )
Duocastella, 1999, RCT <sup>a</sup> [59]	Pediatric cancer patients receiving inpatient chemotherapy	MT: single 45-min individualized MT session. Sessions included singing, instrument playing, movement to music, and musical games	Single session of non-musical activities led by music therapist	15	15	No significant improvement in mood detected using five-point Likert scale
Gallagher et al., 2006, single-arm study <sup>b</sup> [5]	Adults with a terminal illness in an inpatient palliative care setting <sup>b</sup>	MT: single session of varying length including live performance, listening to prerecorded music, and interactive techniques	None	123	0	Significant improvement in mood detected: mean self-reported mood disturbance scores improved from 1.8 to 0.7 on a five-point VAS after a single music therapy session ( $P<0.001$ )

MM music medicine, MT music therapy

<sup>a</sup> Included in 2011 Cochrane Review<sup>b</sup> Percentage of patients with cancer not specified

**Table 4** Individual studies investigating the effect of music-based interventions on QOL in either oncologic or palliative care settings

Author, year, type of study	Study population	Music intervention	Control	N music group	N control group	Results
Hanser, 2006, RCT <sup>a</sup> [57]	Metastatic breast cancer patients (outpatient setting)	MT: three 45-min sessions consisting of live music, improvisation, and songwriting	Standard care	20	22	No significant improvement in QOL detected using the 136-point FACT-G scale. Although the music group's mean score rose from 75.4 to 78.9, and the control group's mean score only rose from 82.2 to 83.1, $P>0.05$
Burns, 2001, RCT <sup>a</sup> [75]	Adult outpatients with cancer	MT: 10 weekly 90–120-min sessions of the Bonny Method of Guided Imagery and “specially sequenced Western Art” music	Wait-list group	4	4	No significant improvement in QOL detected using 100-point QOL-Cancer Scale. Although the music group's mean score rose from 75.40 to 91.77, and control group's mean score only rose from 76.02 to 77.85, $P>0.05$
Hilliard, 2003, RCT <sup>a</sup> [76]	Adults with terminal cancer (setting: home hospice)	MT: 2–13 weekly/biweekly MT sessions of varying lengths. Techniques included singing, lyric analysis, instrument playing, song parody, planning of funerals, song gifts	Standard care	40	40	Significant improvement in QOL detected using 280-point Hospice QOL Index-Revised scale ( $P<0.05$ ). Music group's mean score rose from 206.8 to 214.6, while control group's mean score fell from 188.5 to 177.9
Zhong and Gang, 2001, RCT <sup>a</sup> [77]	Adult cancer patients receiving chemotherapy	MM: twice daily 60-min sessions for 20 days	Standard care	124	136	Significant improvement in QOL detected using QOL Questionnaire for Chinese patients ( $P<0.01$ ). Music group's mean score fell slightly from 49.2 to 47.2, while control group's mean score fell from 49.9 to 34.5

MM music medicine, MT music therapy

<sup>a</sup> Included in 2011 Cochrane Review [13]



**Table 5** Individual studies and review articles investigating the neurobiology of music, pain, anxiety, and depression

Author, year	Description	Findings
Becerra et al., 2001 [79]	fMRI was used to examine changes in neural activation due to painful thermal stimuli (delivered to the skin of the left hand through a Peltier-based thermode at 46 °C) in 8 healthy male subjects, who rated their pain levels using a Visual Analog Scale	Two temporal phases of pain response were observed: early and late. During the early phase, increased signal was seen in reward regions such as the left anterior nucleus accumbens (NAc), the ventral tegmentum (VT), the periaqueductal gray (PAG), the subthalamic extended amygdala (SLEA) of the basal forebrain, and the orbital gyrus. In the late response, decreased signal was seen in the left posterior NAc, while increased signal was seen in classical pain regions such as the thalamus, S1, insula, and anterior cingulate gyrus
Blood et al., 1999 [110]	PET was used to examine changes in regional cerebral blood flow (rCBF) related to emotional responses to music. Ten musicians were exposed to 6 versions of a novel musical passage varying systematically in degree of dissonance	Subjective pleasantness and unpleasantness ratings were correlated with consonance and dissonance, respectively. Increasing consonance was correlated with increasing activity in the orbitofrontal cortex, frontal polar cortex, and the subcallosal cingulate gyrus. Increasing dissonance was correlated with increasing activity in the precuneus region and the right parahippocampal gyrus
Blood and Zatorre, 2001 [97]	PET was used to examine changes in rCBF related to “intensely pleasant emotional responses to music” manifesting as piloerect chills measured by electrodermal monitoring. Ten musicians were exposed to self-selected music, control music, amplitude-matched noise, and silence. rCBF values were extracted from individual scans and plotted against chill intensity	Increasing chill intensity was correlated with increasing activity in the left ventral striatum (including the NAc) and dorsomedial midbrain (including the PAG), and decreasing activity in the right amygdala, left hippocampus, and ventral medial prefrontal cortex
Engel et al., 2009 [82]	This article reviews findings from multiple neuroimaging studies using fMRI, PET, and radioligand binding experiments to investigate anxiety in healthy subjects as well as patients with panic disorder, generalized anxiety disorder, social anxiety disorder, and specific phobias	Enhancement of activity in the amygdala was a very common finding. Enhanced activity was also commonly found in the prefrontal cortex, insula, and the anterior cingulate cortex
Menon and Levitin, 2005 [98]	High-resolution fMRI was used to examine changes in neural activation due to “passive music listening.” Fourteen non-musicians were exposed to 10 intact samples of music and 10 scrambled samples for control stimuli. Hemodynamic changes were subject to statistical, functional connectivity, and effective connectivity analyses	Passive listening to music resulted in significant activation of multiple specific structures including the NAc, the VTA, and the hypothalamus. Functional connectivity analysis showed that responses in the NAc and the VTA were highly correlated, “suggesting an association between dopamine release and NAc response to pleasant music”
Nestler and Carlezon, 2005 [85]	This article reviews the mesolimbic dopamine reward circuit in depression. Data from animal studies and some human studies are discussed	The authors discuss how abnormalities in the VTA and NAc may be related to depressive symptoms such as anhedonia, reduced motivation, decreased energy level, etc. Roles of specific proteins, such as the transcription factor cAMP response element binding protein (CREB) and the endogenous kappa-opioid receptor agonist Dynorphin are reviewed
Pereira, 2011 [106]	fMRI was used to investigate blood oxygenation level dependence (BOLD) responses to musical stimuli that varied according to participant familiarity and preference. Fourteen non-musicians underwent a listening test which consisted of 15 s excerpts from 110 pop/rock songs which they rated by degree of familiarity and preference. During fMRI, the participants were then exposed to 48 excerpts, with 12 excerpts from each of the following categories based upon the listening test results: familiar liked, familiar disliked, unfamiliar liked, and unfamiliar disliked	Familiarity was found to have a greater impact than preference in triggering BOLD responses in the following emotion-related regions: putamen, amygdala, NAc, anterior cingulate cortex, and thalamus
Salimpoor et al., 2011 [100]	Ligand-based PET was used to estimate dopamine release in the striatum based on the competition between endogenous dopamine and [ <sup>11</sup> C] raclopride for binding to D2 dopamine receptors. Information about the dynamics of dopamine release over time was collected using fMRI. Eight participants were exposed to self-selected pleasurable musical excerpts versus neutral musical excerpts. Electrodermal skin conductance was used to measure piloerect chills while participants provided subjective feedback about degree of listening pleasure	Compared to neutral musical excerpts, pleasurable musical stimuli (concurrently measured by chill intensity and subjective participant ratings) resulted in distinct striatal responses detectable by PET and fMRI. Ligand-based PET data revealed increased endogenous dopamine transmission, as indicated by decreased [ <sup>11</sup> C] raclopride binding potential in the right NAc. fMRI showed increased BOLD response in the right NAc during peak pleasure experience epochs

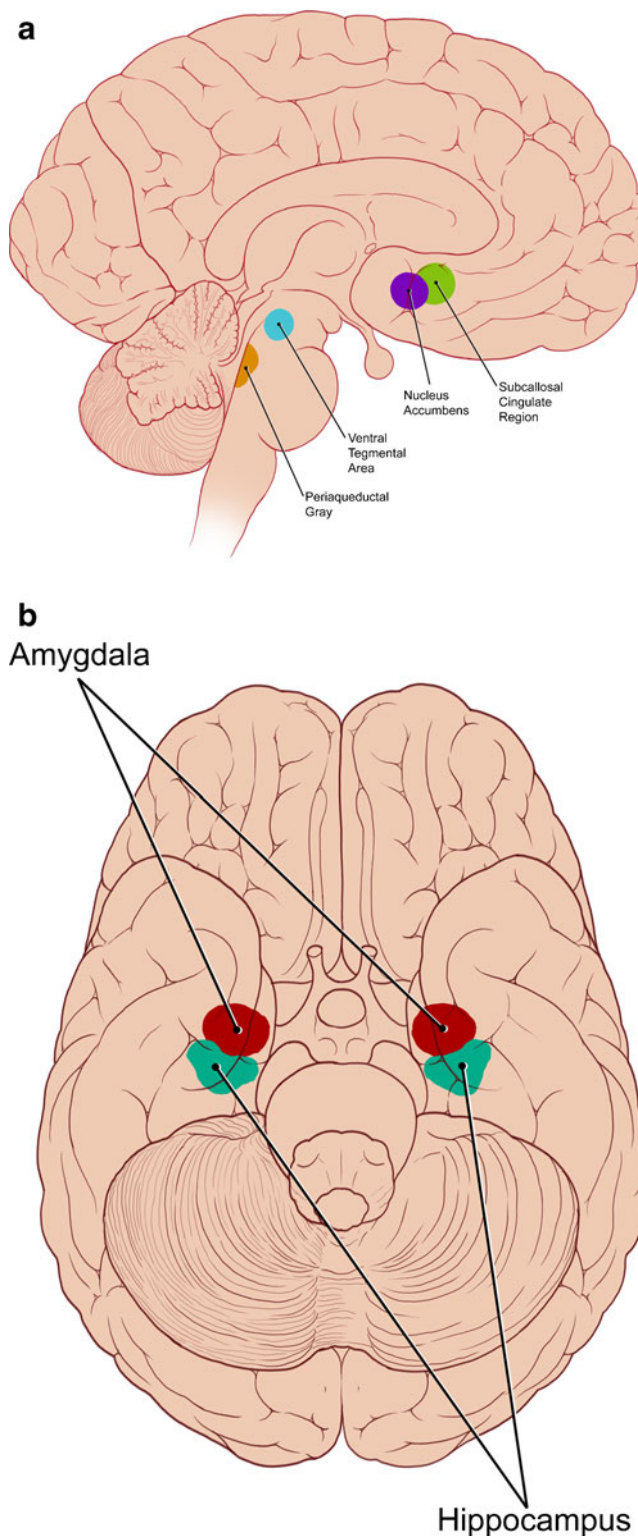
the unavailability of any fast-acting pharmacologic antidepressant, may point toward potentially important neurobiological differences underlying these symptoms. With this in mind, particular consideration should be given to the frequency and duration (as well as the type) of interventions in future studies investigating the impact of music on mood in cancer patients.

### Quality of life

Although there may be less prevalence data measuring overall QOL impairment in cancer patients (relative to pain, anxiety, and depression), the available data suggest that cancer is indeed associated with impaired QOL compared to the normal population [60–62]. This association could be expected for a number of reasons: first, because pain, anxiety, and depression are frequently incorporated into the tools used to measure HR-QOL in cancer patients; secondly, because all three of these symptoms have been shown to commonly affect patients with cancer [63]; and finally, because multiple studies in patients with multiple types of cancer have demonstrated independent associations between HR-QOL impairment and pain [64–68], anxiety [69–71], and depression [72–74].

Although the impact of music-based interventions on QOL has not been as extensively studied as pain, anxiety, or mood disturbance, four RCTs analyzed in the 2011 Cochrane Review [13] compared the impact of music-based interventions to standard care on QOL scores (Table 4). Clearly, QOL represents a more complex and multi-faceted outcome than pain, anxiety, or depression, and the comparison of results from these four studies was made even more complex by the fact that they all used different QOL assessment tools. In one of the four studies [57], pretest differences were too large for the results to be included in the pooled estimate. Through the other three trials, music was offered to 4 of 8 adults with cancer [75], 40 out of 80 adults with terminal cancer [76], and 124 out of 260 cancer patients receiving chemotherapy [77]. When the results from these three trials were subject to meta-analysis, a heterogeneous, nonsignificant effect was found (SMD=2.01, 95 % CI -0.09 to 4.11,  $P=0.06$ ). Paradoxically, this nonsignificance actually resulted from a much larger beneficial effect reported in the study by Zhong [77] than that reported in the studies by Burns [75] and Hilliard [76]. When the results from the Burns and Hilliard studies were subject to meta-analysis ( $N=88$ ), this resulted in a homogenous and significant effect of MT on QOL (SMD=1.02, 95 % CI 0.58 to 1.47,  $P=0.00001$ ). One interesting aspect of the Hilliard study was that even as the physical health of the patients in the music group declined, QOL scores improved. This was not the case in the control group, in whom QOL scores worsened as their physical health declined [76].

Clearly, more research is needed to investigate the impact of music on QOL. Given the crucial importance of this



**Fig. 1** a Sagittal view of neuroanatomic regions affected by music (and implicated in the pathophysiology of pain, anxiety, and/or depression). b Inferior view of neuroanatomic regions affected by music (and implicated in the pathophysiology of pain, anxiety, and/or depression)

outcome to cancer patients in palliative care settings, future studies investigating the effect of music-based interventions on pain, anxiety, or mood disturbance in this patient population should incorporate QOL measurements into their outcome assessment.

### Relevant advances in neurobiology

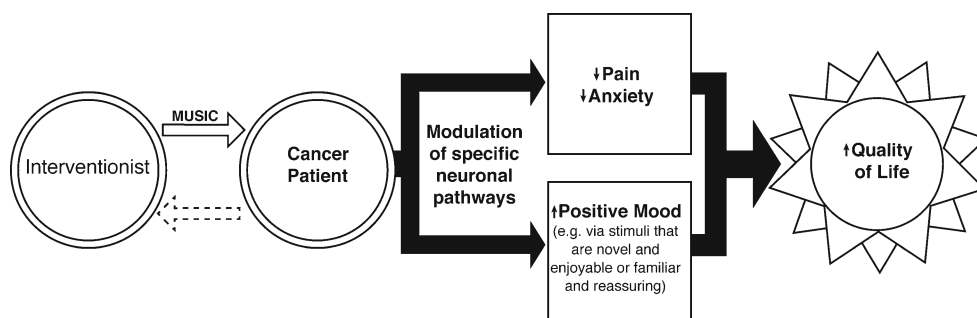
Previous speculations regarding the potential mechanisms of music-based interventions may have drastically oversimplified an extremely complex set of possible neurobiological processes [78]. Many investigators have proposed that music may compete with noxious stimuli and thereby close neurological gates of pain signal transmission, or that it may distract patients from threats that cause them to feel anxious, and/or that it may promote a sense of well-being in patients with an otherwise depressed mood. While these may all be valid theories, advances in neuroscience, and functional neuroimaging studies in particular, are providing dramatic new insights into the findings from clinical trials involving music-based interventions (Table 5).

Multiple studies have explored changes in activity within the brains of healthy, asymptomatic adults upon exposure to music. Broadly speaking, functional imaging data have shown that music modulates the activity of multiple limbic and paralimbic brain structures, but especially the ventral striatum (including the nucleus accumbens), the dorsomedial midbrain (including the ventral tegmental area and periaqueductal gray), the amygdala, and the hippocampus (Fig. 1a, b). This particular neuroanatomic distribution is striking for at least two reasons. The first is that functional abnormalities in these same structures are implicated in the pathophysiology of pain [79–81], anxiety [82–84], and depression [85–87]. The second is that these same structures are known to be densely populated by receptors of ligands associated with pain, anxiety, and depression—namely, endogenous opioids [88, 89], GABA [90, 91], and dopamine [92, 93].

Listening to music has long been known to evoke strong emotional responses which can sometimes be accompanied by physical manifestations, e.g., piloerection, more commonly known as “goosebumps” or “chills” [94, 95]. The suppression

of this response with the mu-opioid receptor agonist naloxone provided early evidence that endogenous opioid activity might underlie pleasurable responses to music [96]. Positron emission tomography experiments subsequently showed that piloerection in response to music may be associated with increased regional cerebral blood flow to the ventral striatum and the dorsomedial midbrain but decreased regional cerebral blood flow (rCBF) to the hippocampus and amygdala [97]. Even in the absence of piloerective responses, fMRI evidence suggested that consonant musical excerpts may increase activity in the ventral striatum and the anterior insula [98, 99], while dissonant excerpts may increase activity in the amygdala and hippocampus [99]. Data collected from [ $^{11}\text{C}$ ] raclopride PET demonstrated that intensely pleasurable responses to music may be associated with dopamine release in the striatal system [100]. This dopaminergic activity in the NAc following exposure to music (and other pleasurable stimuli, e.g., sex, food, and drugs of abuse) may itself be modulated by endogenous opioids [101]. Furthermore, evidence from animal models suggests that opioid efferent projections from the NAc may directly mediate reward-related behavior [102]. Within the dorsomedial midbrain (which was found to receive increased rCBF during highly pleasurable musical experiences as shown in [97]), the substructure known as the periaqueductal gray has been shown to be densely populated with endogenous opioid receptors and may be involved in both opioid-mediated reward [103] and analgesia [79, 104]. Preliminary research suggests that the action of endogenous opioids in the PAG may be influenced by the hormone oxytocin [105]; the blood concentrations of which was found to be increased (along with subjective relaxation) in perioperative patients exposed to soothing music [106]. Although multiple functional imaging studies have shown music to modulate the activity of the amygdala [97, 107], and multiple functional imaging studies have demonstrated an association between anxiety and enhanced amygdalar activity [82, 83, 108, 109], no radioligand binding experiments have specifically investigated the effect of music on gamma amino-butyric acid activity in the brain. With regard to mood disturbance, it is worth noting that music has been shown to modulate the activity of the subcallosal cingulate region [107, 110], an area which has been shown to have

**Fig. 2** General conceptual model for the potentially therapeutic impact(s) of music-based interventions in cancer patients





decreased rCBF in patients with depression [111]. Furthermore, deep brain stimulation of the subcallosal cingulate region has been shown to be an effective treatment for severe depression [86]. Finally, platelet concentrations of serotonin, which may correlate with neuronal concentrations of serotonin [112, 113], were found to be increased in humans exposed to euphonic music, but decreased in humans exposed to cacophonous music [114].

Overall, these advances in neurobiology suggest that music may affect specific neuronal pathways that are implicated in the pathophysiology of pain, anxiety, and depression. Thus, future neurobiological studies may provide objective insight into the mechanisms by which music may affect these subjective symptoms that commonly afflict patients with cancer.

## Conclusions

In 2002, the WHO approved the following definition of palliative care: “An approach that improves the quality of life of patients and their families facing the problems associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual” [115]. In the future, music-based interventions may prove to become valuable tools in the “relief of suffering” of cancer patients. Specifically, music may help alleviate pain, anxiety, and mood disturbance, all of which commonly occur in cancer, and all of which may be associated with impaired QOL. The potential of music to reduce the need for analgesics and/or anxiolytics, even if only by a small amount, may still have major clinical implications, especially given the frequency with which advanced age and hepato-renal dysfunction co-exist in the palliative cancer care population (and hence their predisposition to pharmacologic toxicity). Furthermore, when the only pharmacologic agents available for mood disturbance take weeks to months to take effect, interventions that provide more immediate benefits, even if modest, may warrant further investigation.

It is not difficult to imagine how, for cancer patients unfamiliar with the standard inpatient healthcare environment, the hospital setting could be associated with unexpected pain (e.g., from repeated injections, blood draws, and other invasive procedures), anxiety (e.g., from loud equipment alarms and time-constrained conversations regarding prognosis often clouded by medical jargon), and even depression (e.g., related to the existential issues of having a life-threatening illness, limited social interaction, frequently interrupted sleep, etc.). The capacity of music to restore a sense of *familiarity*, and the therapeutic value of such a reassuring stimulus (regardless of where a patient may be in his or her disease trajectory), may be

underestimated. Such reassuring familiarity could be provided in the form of a playlist of favorite songs on a portable mp3 player with headphones or even through melodic arrangement by a live music therapist that actually incorporates tones from the surrounding environment [116]. It should not necessarily be assumed that the benefits of music are limited to the relief of symptoms; that is to say, that music merely counteracts the negative consequences of disease (Fig. 2). The need for beauty (and for some, spiritual solace) may be particularly great toward the end of life for many patients. In this respect, music may exceed where standard pharmacologic means fall short. Many qualitative studies support both the potential symptom-alleviating and wellness-promoting effects of music [3, 10, 117–125]. However, quantitative data in these areas still remain limited.

In the absence of more RCTs with larger sample sizes, meta-analyses [13, 20, 126] can provide useful quantitative assessments of impact. However, controlling for variation in study design, study population, specific intervention(s), and outcome assessment methods, presents enormous challenges. For example, different music therapists can introduce variability in outcomes, even when the same specific interventions are used [127]. The data presented in the individual trials and the meta-analyses discussed in this review should therefore be considered preliminary and interpreted with caution. The statistical quality of the data in question remains diminished by high risk of bias, which almost invariably arises from the inherent difficulties associated with conventional blinding in music-based intervention studies. Furthermore, without reliable biomarkers for pain, anxiety, and depression, defining the “gold standard” in quantitative assessment of these outcomes remains formidable. Fortunately, the cost of music-based interventions remains relatively low [128], and breakthroughs in the field of neurobiology continue to advance our understanding of the anatomical and biochemical basis of how music works in the brain, and why symptoms such as pain, anxiety, and mood disturbance might be influenced.

Further investigation is warranted to determine (1) if certain subpopulations of cancer patients are more likely to respond to music-based interventions than others, (2) what interventions are most effective for such responsive patients, and (3) what measurement parameters best gauge their effectiveness. Greater collaboration between the fields of music therapy and music neuroscience may accelerate the pursuit of these objectives. Finally, given the emerging evidence that earlier involvement of palliative care may improve outcomes in certain cancer patients [129], and that psychological stress may be linked to up-regulation of inflammatory processes that promote tumor growth and angiogenesis [130–133], it follows that research into the potential of music to specifically promote relaxation and reduce stress [134], perhaps earlier in cancer’s trajectory, may also be warranted.

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**Conflict of Interest** I have no financial relationships to disclose. I have full control over the content of this article. I submit the entirety of this manuscript for review by *Supportive Care in Cancer*.

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