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University of Southern Denmark

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Effects of live music during chemotherapy in lymphoma patients:  
A randomized, controlled, multi-centre trial

by

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## Abstract

**Purpose:** Chemotherapy is associated with both somatic and psychological side effects. Music might ease these problems. Several randomized controlled trials have investigated the effect of music, but the results are inconclusive. We aimed to examine whether live or pre-recorded music listening decrease anxiety during chemotherapy in newly diagnosed lymphoma patients.

**Methods:** A total of 143 patients with non-Hodgkin and Hodgkin lymphomas were randomly assigned into three groups receiving either 30 minutes of patient-preferred live music (n=47), 30 minutes of patient-preferred pre-recorded music (n=47) or standard care (n=49) during up to five outpatient chemotherapy sessions. The primary end-point was anxiety measured by the Spielberger's State Anxiety Inventory. Secondary end-points included blood pressure, pulse rate, nausea and vomiting, serum catecholamine levels pre- and post-intervention to measure arousal levels, and health-related quality of life. The Musical Ability Test was used to link musical ability to the primary endpoint.

**Results:** When adjusting for age, sex, diagnosis, number of sessions and baseline anxiety the linear mixed model, showed a borderline statistically significant reduction in the primary outcome anxiety in the live music group compared to standard care (7% (95% CI, -14% to 0%, p=0.05), while the effect of pre-recorded music was non-significant (5% (95% CI, -12% to +3%, p=0.18). No intervention effects were seen in secondary outcomes.

**Conclusion:** Our findings suggest that patient-preferred live music reduces anxiety among patients with malignant lymphomas undergoing chemotherapy. Musical ability among this group of cancer patients seems not to be a determining factor for effect of music intervention.

**Keywords:** Cancer, Hodgkin lymphoma, Non-Hodgkin lymphoma, chemotherapy, anxiety, music intervention, RCT

## Background

Lymphoma patients undergoing chemotherapy may experience severe somatic and psychological side effects-both during and after treatment [1-4]. The main psychological side effect is anxiety arising from paralyzing and fearful thoughts when informed of the cancer diagnosis and concerns about prognosis, somatic effects of the cancer, and side effects of the toxic chemotherapy [5, 6, 7]. In the search for ways of intervening towards anxiety, music has been suggested to relieve this problem [8-14].

In a recently published review and meta-analysis [14] we found that six out of nine randomized controlled trials (RCTs) [15-23] showed significantly improved effects when offering live (3/6) or pre-recorded (3/6) music and active participation (3/6) or passive listening (3/6) to patients during chemotherapy compared to controls. Both when anxiety was measured by the Spielberger State Anxiety Inventory Scale (STAI) [24] [16-22] and the Visual Analog Scale (VAS)[25] [19]. However, sample sizes were small, heterogeneity in diagnoses, type of given treatments and stages of disease were large, and information on the patient's musical background, ability, and preferences lacked across studies [8, 14]. Further, to our knowledge, no RCT has investigated the effectiveness of live vs pre-recorded music during chemotherapy compared standard treatment [14]. What are the musical needs of the patients? Is it either the musician's flexibility to adjust the tempo, repertoire and compliment the non-verbal moment-to-moment needs of the patient or a recorded musical experience to enhance inner dialogue and relaxation? Although Bailey LM 1983 found significant effects on tension-anxiety, vigour, mood, and physical comfort of 25 minutes of live music compared to taped guitar/voice music of the same material among 50 hospitalized cancer patients, lack of a control group, different

treatments and length of hospitalization does not provide basis for firm conclusions [26]. Music is related to activity in the brain's reward system, where it may induce emotions, moderate patients' mood and thereby decrease pain and anxiety levels [27, 28, 29]. Further, neurological research has shown that musical background and competence is linked to the brain's processing of music [30]. Especially, patient-preferred music has the potential to regulate arousal levels, to evoke cognitive, emotional, and physiological responses and to create pleasure, distraction and wellbeing [30, 31]. However, musical preference is only one aspect of music listening. To decrease emotional arousal, universal and cultural considerations are important to take into account, e.g., a slow tempo (60-80 beats per minute), volume, predictability in genre, rhythm, sound, musical structure, syntax, tonality and instrumentation [27, 30].

The objective of this randomized controlled study was to evaluate the effectiveness of patient-preferred live music or CD music to lower anxiety among patients with lymphomas undergoing first-line chemotherapy taking the qualities and features of musical stimuli, musical background, preference and musical ability into account.

## **Methods**

### **Design**

We conducted a multi-centre, randomized, and controlled trial in newly diagnosed patients with Non-Hodgkin and Hodgkin lymphomas undergoing ambulatory chemotherapy at six hospital departments of haematology in Denmark. We used a three-armed design with two interventional arms consisting of either 30 minutes of patient-preferred live music listening or patient-preferred pre-recorded music listening vs standard care without music during chemotherapy.

### **Ethics**

Approval was obtained from the The Regional Committees on Health Research Ethics for Southern Denmark (File no. S-20120118) [32]. The study was reported to The Danish Data Protection Agency (File no. 2008-58-0035) [33] and registered at ClinicalTrials.Gov (NCT01870479) [34].

### **Participants**

The eligible patients were newly diagnosed with malignant lymphoma (Hodgkin or non-Hodgkin lymphoma), aged 18 or more, with planned ambulatory first-line intra-venous chemotherapy given intermittently every 2 to 3 weeks as 1-day administration. Non-Hodgkin lymphoma patients had most commonly diffuse, large B-cell lymphoma, and more rarely follicular lymphoma or marginal zone lymphoma. Typical treatment regimens were CHOP (Cyclophosphamide, Hydroxy-daunorubicin, Oncovin (Vincristine), Prednisolone), CVP (Cyclophosphamide, Vincristine, Prednisolone), or ABVD (Adriamycin, Bleomycin, Vinblastine, Dacarbazine), given every 2-3 weeks. To participate in the study, patients should have at least 3 chemotherapy sessions planned. We excluded patients with mental illness, deafness, or blindness.

### **Obtaining informed consent and randomization**

At the end of the first chemotherapy, a research nurse informed eligible candidates about the study and participant information was handed over. Patients who responded positively received further oral information and written informed consent was obtained by either the research nurse or the PI. Randomization was made by calling an independent

research unit, who had a computer-generated randomization list. The included patients were stratified by type of lymphoma [Hodgkin and Non-Hodgkin lymphoma], sex and age [Hodgkin: -/+35 years, Non-Hodgkin: -/+50 years] using the software program R.

#### **Power calculation and statistical analysis:**

Power calculation was based on a two-sided ANOVA test [35] on the mean reduction in the primary outcome anxiety measured by STAI-YI score in the three treatment groups. Assuming a within group variation similar to the between group variation, MIRECIF of 10%, significance level of 5%, and power of 90%, the number of participants needed was calculated to 25 in each group. Taking into account a maximal dropout rate of 30%, a total of 105 patients was planned to be included in the study. The initial dropout rate was higher than expected, and in an amendment we therefore increased the number of participants to 143 patients.

The patient characteristics at baseline were summarized by intervention group as mean and SD for continuous variables and n (%) for categorical variables.

The primary outcome was the level of anxiety as measured by the STAI-YI scale. A linear mixed model for all visits (baseline to chemo 6) was applied where the three intervention groups were assumed to be the same at baseline (as they were randomized) and after baseline different intervention effects at each visit were allowed. The observations from each individual were assumed to be correlated and this was considered using an unstructured covariance matrix. If possible, the model was simplified by testing for the same intervention effect at each visit.

The analyses were adjusted for the baseline factors sex, age group (-/+50) and lymphoma subtype (non-Hodgkin, Hodgkin). Assumptions underlying the model were checked using residual plots in case the data needed to be transformed (e.g. using a logarithm). The same analysis strategy was also used for the continuous secondary outcomes. Missing values were assumed to be "missing at random" as we assumed that the missing observations did not depend on the unobserved outcomes.

In order to measure the intervention effect size on primary outcome of the live music group vs control and the CD group vs control, Cohen's *d* was obtained by dividing the mean difference scores by the control group baseline standard deviation (SD=0.41 on the log-scale).

#### **Intervention:**

**Group I** (live music): Based on the patients oral and written feedback on musical preference, musical background, wishes for specific music pieces/genres and constellation of musicians (see appendix 1), the PI chose musicians for the first treatment. Subsequently, one to three musician(s) planned a suitable repertoire, and the sound level was considered. The planned chemotherapy and music intervention took place in a multi-bed room where participants in the control group and intervention group 2 could not hear the music. All preparations: venous puncture, oral information regarding the treatment, anti-emetic medication, were completed before the music started. The intervention itself consisted of the patient's favourite music genre, special pieces of music/songs (25-30 minutes) with an average tempo of 60-80 beats per minute. In order to make the two intervention groups comparable, the musicians and the patients were informed to limit the communication during the intervention. Numbers of planned treatments varied between patients, thus the musicians played from the 2nd and up to 3th-6th chemotherapy sessions. Any request for a new repertoire and

constellations of musicians was agreed between the PI and the patient immediately after or between each of the up to 5 music sessions.

**Musicians:** Twenty-one musical groups from the Danish National Academy of Music [36] participated; classical guitar solo/duo, classical singing/piano, classical piano soloist, classical violin/guitar, pop/rock singer/guitar, blues guitar/bas, pop/rock/folk singing/piano/contrabass, jazz trio. To ensure the intervention quality in group I, the musicians had attended SDMKG's [36] hospital project for at least 2 years. Thus, they had passed a 4-hour introductory course dealing with patient information, communication, music psychology, differentiated music communication, choice of repertoire and they had played at least 10 concerts at the ward in conjunction with supervision by PI on performance skills and choice of suitable repertoire. The PI informed all musicians about the project and a "musician guideline" was handed over, followed by confidentiality signatures required by hospital departments involved.

**Group II (CD music):** The same oral and written feedback from the patients as in group I, was used to plan the music interventions in group II, and any request for new repertoire was agreed between the PI and the patient immediately after or between each of the up to 5 music sessions. The patients brought their favourite music or the PI produced CDs through iTunes for those who did not have the opportunity to do so. The CDs were created from the same considerations regarding musical preference and tempo as in intervention group 1. The music was played on a music centre (Denon DCD-720AE CD Player) with headphones (Denon AH-D340 Headphones) for 25-30 minutes starting at the beginning of each chemotherapy treatment. The patients determined the volume. Care and human contact was the same as in group one and the control group, given by the staff at the department.

**Group III (control):** The patients in the control group were not allowed to listen to music during planned chemotherapy.

All three groups received standard supportive care including anti-emetics according to national recommendations, which also include anti-pyretic and steroids in ABVD treated patients. Chemotherapy treatments were given by the same staff and in similar rooms.

#### **End of intervention assessment:**

Two to four weeks after completion of the last protocolled chemotherapy with music intervention or control visits, the patients were called by telephone for an interview. Hodgkin lymphoma patients received up to 16 chemotherapy courses and therefore the "end of music intervention assessment" was conducted before the 7<sup>th</sup> chemotherapy.

#### **Measurements:**

Before randomization, all included participants completed the following validated questionnaires on outcome variables (STAI-YI [24], EORTC-QOL-30 [37] and GOLD-MSI [38])

At the second to the sixth chemotherapy treatment, the research nurse measured vital parameters (blood pressure, heart

rate) immediately before and after each chemotherapy.

At the same treatment session a peripheral venous catheter was inserted at least 30 minutes before chemotherapy was started. Blood samples were collected immediately before start of chemotherapy and repeated 5 minutes after stopping. Samples were analyzed for plasma catecholamine's (epinephrine and norepinephrine) [39].

The patients completed the self-administered questionnaires on anxiety (STAI-YI) immediately after each given chemotherapy and completed the health-related quality of life questionnaire EORTC-QLQ-C30 [34] after the 2<sup>nd</sup>, 4<sup>th</sup>, and 6<sup>th</sup> given chemotherapy. Furthermore, the patients filled out an in-house validated diary questionnaire for the assessment of nausea and vomiting between every chemotherapy treatment.

At the end of music intervention ~~treatment~~ assessment, they filled out the questionnaires STAI-YI and EORTC-QOL-30. In addition, the patients performed the Musical Ear Test (MET) [40].

## **Questionnaires**

### *Primary outcome*

We used STAI YI to measure anxiety. The Spielberger State-Trait Anxiety Instrument (STAI-YI) is a self-reported questionnaire [24]. It consists of 20 items in a four-point Likert format ranging from 1 (not at all) to 4 (very much so). The STAI-YI form reveals the anxiety level *right now*. According to Barnason, 20-39 points is considered as *low* anxiety, 40-59 points as *moderate* anxiety, and 60-80 points as *high* anxiety [41].

### *Secondary outcome*

The European Organization Research and Treatment of Cancer-Quality of Life Questionnaire (EORTC-QLQ-30) [37] measured health related quality of life.

### *Baseline measurements*

We measured the patients' musical competence and background by using the MET Test [40] and the Goldsmith Musical Sophistication Index [38], respectively. The Musical Ear Test distinguishes between groups of non-musicians, amateurs and professional musicians, and we used this test to form the basis for identifying whether the musical ability of the patients were important outcome measurements. The Goldsmith Musical Sophistication Index is a validated, self-reported inventory and test battery for individual differences in musical sophistication [38]. Further, we added three questions regarding musical wishes, preferences and hearing ability (see appendix).

## **Results**

Figure 1 shows the flowchart of the study. After exclusion of 34 (10 %) of the 344 patients initially eligible for the study, we obtained informed consent from 143/310 (46 %) consecutive patients. The main reason for eligible patients to decline inclusion was incapacity to oversee participation in the research project after the very recent cancer diagnosis. There were no imbalances between the three groups, when comparing baseline characteristics (Table 1).

**Primary outcome.** Baseline scores of anxiety were low across groups (live music: 33.4, recorded music: 35.6, controls: 33.1). When adjusting for age, sex, diagnosis, number of sessions and baseline anxiety, we found a borderline significant decrease in anxiety in the live music group with a 7 % reduction in STAI-YI from baseline (95% CI -14 % to 0 %) compared to standard care ( $p=0.05$ ) (Table 2). There was a non-significant decrease in anxiety when comparing the recorded music group with standard care (5% (95% CI, -12% to 3%,  $p=0.18$ ) and no statistically significant difference between the two music intervention groups. When calculating the Cohen's  $d$ , we found a modest effect size in the live music group ( $d=0.27$ ), whereas no effect was found in the recorded music group ( $d=0.18$ ) compared to controls.

### **Secondary outcomes**

There were no significant differences in secondary outcome measurements in either of the music intervention groups or when analyzing the overall effects of intervention. (Table 3)

Further, there were no statistically significant effects on nausea and vomiting observed in the patient diaries between groups. The number of patients with vomiting was very low, and at least 70% of the patients indicated no nausea on the different days. Reporting of nausea and vomiting were most frequent the first day after chemotherapy, and reported more in Hodgkin lymphoma patients than in non-Hodgkin lymphoma patients (not shown).

### **Data about the music provided**

The music provided ranged from patient-preferred classical, jazz, folk, rock to pop music. Across the 397 music interventions live- and pre-recorded music combined, contemporary music, e.g., jazz, folk, rock, pop, was the most frequently performed music style (73%) compared to classical music (27%), with an average tempo on 71 beats per minute and a percentage distribution in vocal/instrumental music (61/39%) and major/minor key 79/21%, respectively. Out of 198 live music interventions, classical guitarists and pop/rock singers/guitarists played during 125 chemotherapy treatments. The three intervention groups were similar as regard to their general musical sophistication [38] and musical ability [40] (Table 4). When adding the total MET score to the model for change in STAI-YI, we found no evidence that the intervention worked better for participants with a high compared to those with a low musical ability ( $p=0.79$ ).

### **Discussion**

In this large multi-centre clinical trial, we showed that patient-preferred live music with an average tempo of 60-80 beats per minute had a borderline significant effect on anxiety among lymphoma patients undergoing two to five ambulatory chemotherapy sessions compared to controls. A significant decline in anxiety was not observed in the CD group compared to controls. To our knowledge, this is the first live music listening study suggesting that the degree of anxiety relief among lymphomas undergoing chemotherapy seems not determined by musical ability, hence a possibility for many cancer patients.

Surprisingly, the baseline anxiety scores were low in our study, compared to three similar studies showing significant anxiety decrease measured by STAI, by offering recorded music during chemotherapy. These studies all reported moderate anxiety levels at baseline between 39 to 52 [16, 21, 22]. Due to optimizing inclusion rates, we, as the only study, included patients and collected baseline scores *after* the first chemotherapy, whereas for instance Li

collected baseline scores on the day before radical mastectomy and offered music at discharge and during the following two ambulatory chemotherapy treatments [21]. Anxiety may diminish considerably after the first chemotherapy, and possible therefore we had limited ability to register anxiety decrease above 7% (floor and ceiling effect). We might have found larger effect of intervention if we had done the baseline measurements before the first chemotherapy or we might have pre-selected participants based on evidence of high levels of anxiety in order to target the intervention to those with high needs. When calculating Cohen's *d* effect size, live vs control, we found a modest effect size [42]. Live music offers the flexibility for the musician(s) to personalize the music interventions. Rossetti points out that personalized and targeted music interventions should go hand in hand with personalized medicine [43]. However, awareness of the patient's role in the intervention is needed [14]. We conducted a *passive listening* approach in order to equalize groups by restricting the communication between the musician(s) and the patient.

It is noteworthy that patients in this study predominantly chose music in the major key. This differs from a "minor key"-trend in society, supported by The Billboard Magazine [44], saying that today American pop hits consist of 44% major key and the tendency is downward. This indicates that optimistic tunes may be preferred during chemotherapy.

According to our recent review [14], the complexity of conducting *multiple session* studies more often lead to non-significant results compared to *single session* design studies. Three multi-session RCT failed to reach significance on the primary outcome variable nausea [23], anxiety [15] and distress [18] applying passively listening (1/3) or active participation (2/3) during or after inpatient chemotherapy treatment. Delays in treatment, hospitalization, midway cancer status evaluation and thus the risk of altering the prognosis, as well as disease and treatment related problems are frequent and give rise to a persistent and prolonged mental strain among the patients. On the contrary, single session designs often imply increased levels before procedure and immediate relief afterwards. This may be the reason why we did not see an effect of music intervention on quality of life (EORTC-QOL-30). Andrade et al. argue that quality of life is difficult to measure among hematology/oncology patients undergoing chemotherapy due to individuality and multidimensionality [1].

Music is a multi-faceted, cultural and social phenomenon, difficult to simplify into measurable test parameters in the complexity of cancer treatment. Nevertheless, this study indicates that live music may provide some anxiety relief in a long-term course of chemotherapy treatment to lymphoma patients.

### **Clinical implications:**

Live music without any components from music therapy, performed by qualified, well-trained musicians in response to patient-preferred selections re: genre, artist, and song may be used for reduction of anxiety in patients with lymphomas undergoing chemotherapy, however low levels of inclusion and baseline anxiety prevent firm conclusions and call for more multisession studies targeting live music to the patient's phase of treatment and timing of intervention.

### **Strengths and limitations**

It is a strength of our study that we included a well-described and uniform group of lymphoma patients receiving first-line chemotherapy in a sequential one-day treatment schedule. We managed to overcome running of a multi-centre, multiple sessions study in very sick lymphoma patients and the logistic challenges among musicians with potential delays of treatment. Further, the guidelines for music-based interventions by Robb [45] were used to conduct the study, and the participants' musical backgrounds as well as musical abilities were obtained in order to adjust for these potential confounders.

However, some limitations must be noted. First, the number of given chemotherapy courses varied across lymphoma subtypes; Hodgkin lymphoma patients usually went through 12-16 treatments, whereas non-Hodgkin lymphoma patients received between 3-6 treatments. Due to this heterogeneity, the end of assessment visit happened at some time-point after the end of the cancer treatment and not after the same time interval for everybody. For that reason, end of assessment data was not included in the main analysis. Second, the different numbers of chemotherapy sessions and hereby also music interventions across groups might have influenced the results. The fact that only 14 % of the patients in the CD group received less than 5 music interventions whereas this proportion was 27 %, and thereby significantly higher, in the live music group might have weakened the effect of live music, and the linear mixed model analysis chosen for this study cannot take this imbalance into account. Finally, only 42 % of the eligible patients were included in the study due to lack of mental and physical energy, and this will inevitably weaken the strengths of the results. Possibly, a pre-intervention assessment of the psychological needs might have ameliorated this problem

## **Conclusion**

We found a borderline significant decrease in anxiety by offering patient-preferred live music compared to standard care during first-line chemotherapy sessions in newly diagnosed lymphoma patients.

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## **Conflict of Interest**

The authors have no financial relationships to disclose. The corresponding author have full control of all data of this article and allow Supportive Care of Cancer to review the data, if requested

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**Figure 1: CONSORT flowchart of the patients' progress through the trial**

**Table 1: Baseline Demographic Data for Patients with Lymphomas reported by Intervention Group**

	Group I (Live)		Group II (CD)		Group III (Control)		Total	
<b>Total n</b>	47		47		49		143	(100)
<b>Sex n (%)</b>								
Male	23	(49)	28	(60)	29	(59)	80	(56)
Female	24	(51)	19	(40)	20	(41)	63	(44)
<b>Diagnosis n (%)</b>								
Hodgkin	16	(34)	10	(21)	16	(33)	42	(29)
Non-Hodgkin	31	(66)	37	(79)	33	(67)	101	(71)
<b>Type of chemotherapy n (%)</b>								
ABVD	16	(34)	9	(19)	16	(33)	41	(29)
CHOP	27	(57)	32	(68)	26	(53)	85	(59)
Other (eg. CVP)	4	(9)	6	(13)	7	(14)	17	(12)
<b>Age</b>								
Age<50 n (%)	11	(23)	8	(17)	13	(27)	32	(22)
Age 50+ n (%)	36	(77)	39	(83)	36	(74)	111	(78)
Age mean (SD)	59	(18)	61	(15)	59	(18)	60	(17)
<b>STAI-YI n</b>	45		45		44		134	
mean (SD) score	33	(12)	36	(13)	34	(10)	34	(12)
<b>EORTC QLQ-30 n</b>	46		45		43		134	
mean (SD) score	46		45		43		134	
Global Health Status	61	(21)	53	(24)	55	(21)	56	(22)

Abbreviations: ABVD, Adriamycin, Bleomycin, Vinblastine, and Dacarbazine; CHOP, Cyclophosphamide, Hydroxydaunorubicin, Oncovin (Vincristine), and Prednisolone; CVP, Cyclophosphamide, Vincristine, and Prednisolone, STAI, Spielberger's State Anxiety Inventory; EORTC-QLQ-30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; SD, standard deviation

**Table 2: Relative changes in the primary outcome STAI-YI compared to control group. Estimates from the main model using a linear model of the log-transformed scores with a random effect of participants. Sex, diagnosis, age group, number of sessions are covariates**

	Estimated effect	Lower 95% limit	Upper 95% limit	p
<b>Gender</b>				
Male	1.00	reference		.
Female	1.03	0.95	1.13	0.45
<b>Intervention group</b>				
Live	0.93	0.86	1.00	0.05
CD	0.95	0.88	1.03	0.18
Control	1.00	reference		.
<b>Diagnosis</b>				
Hodgkin	1.03	0.92	1.14	0.64
Non-Hodgkin	1.00	reference		
<b>Age group</b>				
Age<50	1.00	reference		.
Age 50+	0.83	0.74	0.93	0.002
<b>Visit number</b>				
Baseline	1.00	reference		
Chemo 2	0.90	0.84	0.95	0.0005
Chemo 3	0.92	0.86	0.98	0.01
Chemo 4	0.93	0.86	0.99	0.03
Chemo 5	0.92	0.85	0.98	0.02
Chemo 6	0.90	0.84	0.97	0.005
Intercept	36.99	32.54	42.05	

**Table 3: Absolute changes in the secondary outcomes compared to control group. Estimates from analyses using a linear mixed model on un-transformed outcomes. All analyses are adjusted for sex, diagnosis, age group and visit.**

	Group I (Live)			p <sup>1</sup>	Group II (CD)			p <sup>1</sup>	Group III Control
	Estimated effect	Lower 95% limit	Upper 95% limit		Estimated effect	Lower 95% limit	Upper 95% limit		
EORTC-QOL Global Health Status <sup>2</sup>	2.0	-4.8	8.9	0.56	1.6	-5.2	8.3	0.65	0
Systolic blood pressure <sup>3</sup> (mmHg)	-0.7	-4.3	2.9	0.70	-0.9	-4.5	2.7	0.63	0
Diastolic blood pressure <sup>3</sup> (mmHg)	0.7	-2.2	3.5	0.63	-0.1	-2.9	2.8	0.96	0
Pulse <sup>3</sup> (pp/min)	-1.8	-3.9	0.2	0.08	-0.2	-2.2	1.9	0.87	0
P-Adrenaline <sup>3</sup> (nmol/L)	0.00	-0.01	0.02	0.51	0.01	-0.00	0.02	0.16	0
P-Noradrenaline <sup>3</sup> (nmol/L)	0.10	-0.08	0.29	0.27	0.08	-0.11	0.27	0.39	0

<sup>1</sup>Compared to the control group

<sup>2</sup>Model adjusted for baseline global health status

<sup>3</sup>Model adjusted for pre-treatment value

**Table 4: The patients' musical background, preferences and ability measured by The Goldsmith Sophistication Index (GOLD-MSI) and The Musical Ear Test (MET) reported by Intervention Group**

	Group I (Live)		Group II (CD)		Group III (Control)		Total	
<b>Total, n</b>	47		47		49		143	
<b>GOLD-MSI n</b>	42		43		37		122	
Overall GOLD-MSI, mean (SD)	53	(18)	58	(17)	60	(21)	57	(19)
Active Engagement, mean (SD)	26	(10)	29	(9)	30	(10)	28	(10)
Perceptual Abilities, mean (SD)	39	(10)	43	(9)	43	(9)	42	(9)
Musical Training, mean (SD)	15	(9)	15	(9)	16	(10)	15	(9)
Singing Abilities, mean (SD)	23	(8)	25	(9)	25	(10)	24	(9)
Musical Feeling, mean (SD)	26	(7)	26	(7)	27	(6)	26	(6)
Missing, n (%)	5	(11)	4	(9)	12	(24)	21	(15)
<b>Musical Preferences*</b>								
Classical, n (%)	17	(37)	23	(51)	15	(34)	55	(41)
Jazz, n (%)	12	(26)	12	(27)	9	(21)	33	(24)
Folk, n (%)	13	(28)	6	(13)	13	(30)	32	(24)
Pop, n (%)	23	(50)	26	(58)	16	(36)	65	(48)
Rock, n (%)	11	(24)	11	(24)	8	(18)	30	(22)
Other, n (%)	10	(22)	11	(24)	6	(14)	27	(20)
<b>Hearing test, n</b>	45		44		42		131	
Normal, n (%)	41	(9)	32	(26)	37	(10)	110	(15)
Hearing loss, n (%)	4	(87)	12	(68)	5	(76)	21	(77)
Missing, n (%)	2	(4)	3	(6)	7	(14)	12	(8)
<b>MET, n</b>	39		36		37		112	
MET-Total, mean (SD)	63	(8)	64	(11)	63	(9)	63	(10)
MET-Melody, mean (SD)	64	(9)	62	(12)	64	(12)	63	(11)
MET-Rhythm, mean (SD)	61	(10)	66	(11)	61	(9)	63	(10)
Missing, n (%)	8	(17)	11	(23)	12	(24)	31	(22)

GOLD-MSI, Goldsmith Musical Sophistication Index; \*Musical preference, patients were allowed to chose more than one favorite musical genre; MET, The Musical Ear Test

## **Appendix 1**

- 1) What is your favorite musical style(s) for the research project?
  - a. Classical, b. Jazz, c. Folk, d. Pop, e. Rock, f. Other
- 2) List the names of your favorite artists and/or favorite music pieces
- 3) Which constellation of musicians do you prefer?

