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Slow-Tempo Music and Delirium/Coma-Free Days Among Older Adults Undergoing Mechanical Ventilation
A Randomized Clinical Trial

Babar A. Khan, MD, MS; Sikandar H. Khan, DO, MS; Anthony J. Perkins, MS; Annie Heiderscheit, PhD; Frederick W. Unverzagt, PhD; Sophia Wang, MD; J. Hunter Downs III, PhD; Sujuan Gao, PhD; Linda L. Chlan, PhD, RN

IMPORTANCE An estimated 70% to 80% of older adults develop delirium in the intensive care unit (ICU).

OBJECTIVE To determine if a slow-tempo music (60-80 beats/min) listening intervention decreases delirium duration, delirium severity, pain, or anxiety in older adults undergoing mechanical ventilation.

DESIGN, SETTING, AND PARTICIPANTS This multicenter randomized clinical trial with concealed outcomes assessments was conducted in older adults undergoing mechanical ventilation from February 2020 to December 2023. Patients were enrolled from the ICUs of 2 hospitals affiliated with the Indiana University School of Medicine and from the Mayo Clinic in Rochester, Minnesota.

INTERVENTION A music intervention comprising classical and contemporary tracks, delivered twice daily through noise-canceling headphones and tablets for up to 7 days, was compared to active control listening to a silence track delivered under identical conditions.

MAIN OUTCOMES AND MEASURES The primary outcome was delirium/coma-free days during the 7-day intervention period assessed by the Confusion Assessment Method for the ICU (CAM-ICU) and the Richmond Agitation-Sedation Scale. The secondary outcomes were delirium severity assessed by the CAM-ICU-7, pain assessed by the Critical Care Pain Observation Tool, and anxiety assessed by the visual analog scale for anxiety (VAS-A).

RESULTS A total of 158 patients were randomized (mean [SD] age, 68 (9.2) years; 72 [45.5%] female and 86 [54.4%] male). In an intention-to-treat analysis, no differences were found in the number of delirium/coma-free days in the music intervention group compared with control (median [IQR] days, 2.5 [0-5] vs 3 [0-5]; $P = .66$). There were also no statistically significant differences in the mean CAM-ICU-7 scores, mean pain scores, or mean VAS-A scores over the 7-day intervention period. By end of the 7-day period, both music intervention and control groups had similar mean (SD) CAM-ICU-7 scores (2.72 [2.80] vs 2.56 [2.72]), Critical Care Pain Observation Tool scores (0.20 [0.55] vs 0.61 [1.29]), and VAS-A scores (43.6 [24.7] vs 28.8 [38.4]).

CONCLUSIONS AND RELEVANCE In this randomized clinical trial among older adults undergoing mechanical ventilation, a slow-tempo music intervention did not demonstrate a statistically significant decrease in delirium duration, delirium severity, pain, or anxiety symptoms.

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Visual Abstract
Invited Commentary
Supplemental content

Author Affiliations: Indiana University School of Medicine, Indianapolis (B. A. Khan, S. H. Khan); Indiana University Center for Aging Research, Indianapolis (B. A. Khan, S. H. Khan); Regenstrief Institute, Indianapolis, Indiana (B. A. Khan, S. H. Khan); Department of Biostatistics and Health Data Science, Indiana University School of Medicine, Indianapolis (Perkins, Gao); Anglia Ruskin University, Cambridge, England, United Kingdom (Heiderscheit); Department of Psychiatry, Indiana University School of Medicine, Indianapolis (Unverzagt, Wang); Mayo Clinic, Rochester, Minnesota (Downs, Chlan); Area10 Labs, Rochester, Minnesota (Downs); Mayo Clinic College of Medicine and Science, Rochester, Minnesota (Chlan).

Corresponding Author: Babar A. Khan, MD, MS, Indiana University School of Medicine, 1101 W 10th St, Indianapolis, IN 46202 (bakhan@iu.edu).

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Each year, 2 million to 3 million critically ill adults in the US receive mechanical ventilation, and up to 80% of them develop intensive care unit (ICU) delirium,[1-6] associated with longer ICU and hospital stays, increased inpatient mortality, elevated costs of care, and long-term cognitive impairment.[6-12] Over the years, pharmacological strategies have failed to demonstrate efficacy in preventing or treating ICU delirium,[13-15] and receipt of certain anxiolytics and sedatives further predispose patients to delirium.[16] In the absence of safe and efficacious pharmacological options, nonpharmacological interventions that comanage pain and anxiety, potentially reducing exposure to harmful sedatives, hold promise in decreasing the burden of delirium.[17,18]

Music is one such intervention that could decrease ICU delirium by mitigating predisposing factors such as anxiety, stress, and pain.[19-22] Based on systematic reviews, relaxing slow-tempo music (60-80 beats/min) results in a reduction in inflammatory cytokines, decreases cortisol production, dampens sympathetic nervous system arousal, and promotes relaxation through entertainment, thereby acting on multiple pathways implicated in delirium.[23,24] A music intervention consisting of patient-directed slow-tempo music delivered during mechanical ventilator support demonstrated efficacy in reducing anxiety and sedative exposure.[25] We previously showed acceptability and feasibility of a music-listening intervention among patients undergoing mechanical ventilation in the ICU, testing 2 music interventions (patient preferred vs slow tempo) against an audiobook attention control.[26]

Building on our prior experience, along with consideration of music's neurobiological effects, we designed a multicenter, 2-arm, randomized clinical trial with concealed outcome assessments to assess the efficacy of a relaxing, slow-tempo (60-80 beats/min) music-listening intervention compared to a silence-only control in decreasing delirium among older adults undergoing mechanical ventilation in the ICU. We hypothesized that patients randomized to music would have a higher number of delirium/coma-free days (DCFDs), lower delirium severity, and improved pain and anxiety symptoms.

Key Points

Question Among critically ill, mechanically ventilated older adults in the intensive care unit, does a music-listening intervention reduce delirium, pain, or anxiety?

Findings In this randomized clinical trial of 158 mechanically ventilated older adults, a twice-daily music intervention delivered via noise-canceling headphones and tablets for up to 7 days did not demonstrate a statistically significant decrease in delirium duration, delirium severity, pain, or anxiety.

Meaning A music-listening intervention did not improve delirium, pain, or anxiety among critically ill older adults.

Methods

Study Setting and Eligibility

From February 2020 to December 2023, older adults admitted to the ICU services of 2 Indianapolis, Indiana, hospitals affiliated with the Indiana University School of Medicine and from the Mayo Clinic in Rochester, Minnesota, were enrolled. Inclusion criteria were (1) age of 50 years or older, (2) English speaking, (3) anticipated mechanical ventilation for at least 48 hours, and (4) presence of a legally authorized representative. Exclusion criteria were (1) history of neurodegenerative diseases such as Alzheimer disease or vascular dementia, (2) severe psychiatric illness, (3) alcohol withdrawal, (4) drug intoxication/overdose, (5) acute neurologic injury (traumatic brain injury, ischemic or hemorrhagic cerebrovascular accident, or undergoing neurosurgery), (6) uncorrected hearing or vision impairment, (7) incarcerated, (8) enrollment in another study that does not permit co-enrollment, (9) conditions precluding safe use of headphones (skin breakdown, burns, or facial or skull fractures), or (10) comfort care/hospice or imminent death.

The institutional review board at Indiana University approved the study, and patients' legally authorized representatives provided written informed consent. A detailed description of the trial protocol has been published previously (key details in Supplement 1).[27] We followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines for randomized clinical trials.[28]

Randomization

Research staff reviewed the electronic health records of patients in the ICU daily for eligibility. Eligible patients' legally authorized representatives were approached, and patients were enrolled within 72 hours of ICU admission. Randomization occurred in a 1:1 ratio between the intervention and control groups using a computer-generated allocation in random blocks of 2 and 4 stratified by enrollment site. Apart from the patient, all study personnel and clinical staff remained blinded to each patient's intervention assignment.

Music Intervention

Patients received twice daily 1-hour slow-tempo music-listening sessions initiated between 9 and 11 AM and from 12 to 4 PM. The intervention was delivered via study iPad tablets (Apple) loaded with Soundese, a music delivery application (app) developed by our team, and active noise-canceling headphones enabled by Bluetooth wireless technology. The app contained playlists (offering 408 classical and contemporary relaxing tracks without lyrics or spoken words) created by a board-certified music therapist (A.H.) at the trial's inception and used in our previous studies.[25,26,29] Each patient received identical playlists, which began with music at a frequency of 80 beats/min and transitioned down to pieces at 60 beats/min.[30]

Attention Control

During time windows identical to the music arm, control patients received twice-daily 1-hour sessions with a silence track delivered through the tablets and noise-canceling headphones. Music or control sessions were

discontinued after the 7-day intervention period or at ICU discharge, whichever occurred first. Patients received clinical care for delirium based on their primary team's discretion.

Process Measures

Research staff monitored listening sessions and recorded adherence data for each session (ie, start/stop times, missed or incomplete sessions). Detailed intervention and attention control adherence data were captured through the app, which delivered the assigned, blinded listening intervention (music or silence track) to each research subject and automatically collected usage data on music/silence tracks programmed into the device's playlists (eMethods in Supplement 2).[30]

Outcome Measures

DCFDs

DCFDs, defined as the number of days that a patient was alive and free of delirium and coma over the 7-day study period, comprised the primary outcome of the trial. DCFDs were computed similar to other delirium trials,[13,31] as detailed in the eMethods in Supplement 2. We used the Confusion Assessment Method for the ICU (CAM-ICU)[32] and the Richmond Agitation-Sedation Scale (RASS)[33] for assessment of delirium and coma, respectively. Patients with a RASS score of −4 or −5 with lack of response to verbal or physical stimuli were characterized as comatose and ineligible for CAM-ICU assessments. Patients with a RASS score of −3 to 4 were considered eligible for CAM-ICU assessments.

Delirium Severity

Delirium severity was assessed using the CAM-ICU-7, a scale from 0 to 7 derived from RASS and CAM-ICU, with higher scores indicating greater delirium severity.[34] For RASS scores of −4 or −5, a CAM-ICU-7 score of 7 was assigned, consistent with methodology used in the validation of CAM-ICU-7.[34]

Pain

Pain was assessed using the Critical Care Pain Observation Tool (CPOT), a valid and reliable instrument in critically ill patients with and without delirium.[35,36] Total CPOT scores range from 0 to 8, with higher scores indicating more pain.

Anxiety

Anxiety was collected using a 100-mm visual analog scale for anxiety (VAS-A).[37] The scale was presented vertically and anchored on the ends by 0, indicating not anxious at all, and 100, indicating most anxious ever.

Trained research staff blinded to patients' randomization status performed twice-daily RASS, CAM-ICU, CAM-ICU-7, CPOT, and VAS-A assessments immediately after each listening session (AM and PM) during the intervention period. For patients transferred out of the ICU prior to day 7 and no longer eligible for music or control doses, research staff continued to assess outcome measures twice daily (AM and PM) until study day 7 or withdrawal, death, or hospital discharge, whichever occurred first.

Other Data Collection

We assessed pre-ICU cognition using Informant Questionnaire on Cognitive Decline in the Elderly[38] and pre-ICU functional status using Katz and Lawton scales.[39,40] Demographics (including sex and race and ethnicity [Black or African American, Hispanic or Latino, Native Hawaiian or Other Pacific Islander, or White]) were obtained as self-reported in the electronic medical record. Comorbidities and ICU severity of illness were assessed using Charlson Comorbidity Index[41] and Acute Physiology and Chronic Health Evaluation,[42,43] respectively. Daily ICU variables including sedatives and clinical outcomes were collected as detailed in the eMethods in Supplement 2.

Safety

Adverse events were collected regularly and reviewed by an independent safety officer.

Sample-Size Calculation

Sample size was based on the pilot data, where the slow-tempo music intervention group had higher DCFDs than the control group, with estimated effect size of 0.52.[26] We estimated that 128 total patients with complete data were needed to detect an effect size of 0.5 SD or higher using 2-sample *t* test at $\alpha = .05$. Allowing an attrition rate of up to 20% by day 7, we aimed to enroll 160 total patients (80 per group). Details of the sample size and power calculations for the secondary aims were published previously and are provided in Supplement 1.[27]

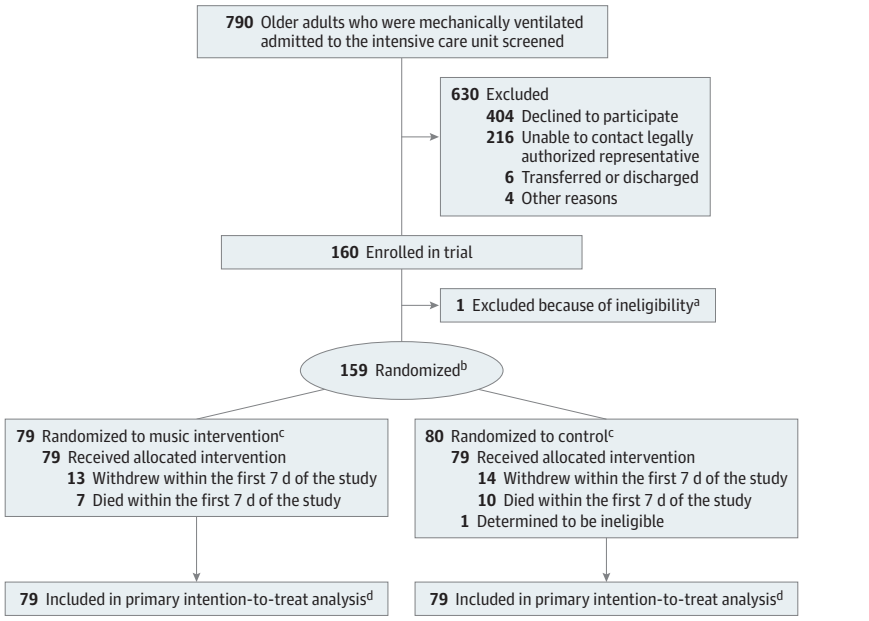
Statistical Analysis

We compared demographic characteristics (age, sex, race and ethnicity, and levels of education) and illness severity between the intervention and control groups using 2-sample *t* tests for continuous variables and χ^2 tests for categorical variables. We used an intention-to-treat approach in analyses. For the primary aim, DCFDs by day 7 postrandomization were compared using analysis of covariance models with log (DCFDs +1) as the dependent variable and group (intervention vs control) as the independent variable while adjusting for the randomization stratification variable (hospital site).

Mixed-effects models were used to compare delirium severity (CAM-ICU-7), pain (CPOT), and anxiety scores (VAS-A) measured twice daily from randomization to day 7, time of death, or discharge. Group, time, and group and time interactions were included as independent variables while adjusting for hospital site (stratification variable). Unstructured variance-covariance structures were used in the mixed-effects models to adjust for within-person correlations over time.

Analysis of covariance models were used to compare log-transformed duration of mechanical ventilation and length of stay, adjusting for site. Logistic regression models were used for comparing mortality rates and percentages of patients discharged home, adjusting for site. Per-protocol analyses were conducted in patients who had completed at least 7 sessions. Sensitivity analyses were conducted in subsets of patients who did not have coma on day 1 and in those who received benzodiazepines. In addition, we also conducted sensitivity analyses using mixed-effects models with CAM-ICU-7, CPOT, and

Figure 1. CONSORT Diagram



[a]Participant was found to be ineligible after enrollment/randomization.

[b]Randomization was stratified by enrollment (hospital) site.

[c]Participants in the music intervention group received slow-tempo music (60-80 beats/min), while participants in the control group received a silence track.

[d]All randomized patients were analyzed according to treatment group, with mixed-effects models.

VAS-A collected in the morning and afternoon, with time of the day as an additional independent variable. The mixed-effects models we used for secondary outcomes were unbiased under the missing-at-random assumption. We compared baseline characteristics between patients who withdrew before day 7 and those who completed study protocol to examine whether there were potential violations to the missing-at-random assumption.

All analyses were conducted using SAS, version 9.4 (SAS Institute). All statistical tests were 2-sided with $P < .05$ considered statistically significant.

Results

Patient Characteristics

A total of 790 older adults in the ICU were found eligible, and 160 were enrolled (**Figure 1**). One patient was found ineligible prior to randomization, thus 159 patients were randomized (79 to the music intervention vs 80 to control). One patient was found ineligible after randomization; therefore, 158 older adults (79 per arm) were included in the intention-to-treat analysis (Figure 1).

The mean (SD) age of the patients was 68 (9.2) years, 72 (45.5%) were female while 86 (54.4%) were male, and 30 (19.0%) were Black or African American, 1 (0.1%) was Hispanic or Latino, 1 (0.1%) was Native Hawaiian or Other Pacific Islander, and 121 (76.6%) were White. Patients had a median (IQR) Charlson Comorbidity Index of 3 (1-4). Both music and control groups had similar demographics, comorbidities, and pre-ICU cognitive and functional status (**Table 1**). Patients in both music and control groups had similar median (IQR) Acute Physiology and Chronic Health Evaluation scores (31 [26-36] vs 30 [25-35]), rates of shock requiring vasopressors (54 [68.4%] vs 54 [68.4%]), and severity of lung injury (median [IQR] PaO_2: FIO_2, 202 [132-205] vs 198 [128-287]), as shown in Table 1. Baseline clinical characteristics of enrolled patients by study site are shown in eTable 1 in Supplement 2.

Outcomes

There were no statistically significant differences between the music and control groups in the primary outcome of DCFDs (**Table 2** and **Figure 2**). The median (IQR) number of DCFDs were 2.5 (0-5) in the music group and 3 (0-5) in the control group (mean difference in log-transformed outcome, 0.00; 95% CI, −1.77 to 1.77; $P = .66$). There were also no statistically significant between-group differences in any of the secondary outcomes. Over the 7 days, no statistically significant differences in changes of delirium severity, pain, or anxiety were observed (Table 2 and Figure 2). By the end of the intervention, both music and control groups had similar mean (SD) CAM-ICU-7 scores (2.72 [2.80] vs 2.56 [2.72]; mean difference in change from baseline, −0.27; 95% CI, −1.39 to 0.84), CPOT scores (0.20 [0.55] vs 0.61 [1.29]; mean difference in change from baseline, 0.50; 95% CI, −0.17 to 1.16), and VAS-A scores (43.6 [24.7] vs 28.8 [38.4]; mean difference in change from baseline, −23.00; 95% CI, −69.29 to 23.29), as shown in Table 2. There was not a statistically significant difference in the duration of mechanical ventilation, ICU, and hospital days postrandomization; rates of discharge home; and in-hospital mortality between groups (Table 2).

Process Measures

The app delivered 281 tracks of contemporary (222 [79.0%]) and classical (59 [21.0%]) slow-tempo music in the intervention arm (see the eMethods in Supplement 2 for detail on the playlist design). The median (IQR) hours from ICU admission to first dose were similar in both music and control arms (42.4

Table 1. Patients' Baseline Characteristics

Characteristic	No. (%)	
	Music intervention (n = 79)[a]	Control (n = 79)[b]
Age, mean (SD), y	67.6 (9.1)	68.3 (9.3)
Sex		
Female	34 (43.0)	38 (48.1)
Male	45 (57.0)	41 (51.9)
Race		
Black or African American	15 (20.0)	15 (19.5)
Native Hawaiian or Other Pacific Islander	1 (1.3)	0
White	59 (78.7)	62 (80.5)
Ethnicity		
Hispanic or Latino	1 (1.3)	0
Not Hispanic or Latino	75 (98.7)	78 (100)
Years of education, mean (SD)	13.3 (2.6)	12.9 (2.7)
Charlson Comorbidity Index, median (IQR)	2 (1-4)	3 (2-5)
Pre-ICU cognitive and functional status		
IQCODE, mean (SD)	3.2 (0.3)	3.2 (0.5)
Activities of daily living, median (IQR)[c]	6 (6-6)	6 (5-6)
Instrumental activities of daily living, median (IQR)[d]	8 (6-8)	8 (6-8)
Insurance		
Medicare/private	17 (21.5)	13 (16.5)
Medicare	16 (20.2)	16 (20.2)
Medicaid/Medicare	10 (12.7)	11 (13.9)
Medicaid	8 (10.1)	10 (12.7)
Other (government, private, or none)	12 (15.2)	15 (18.9)
Severity of illness by APACHE II score, median (IQR)[e]	31 (26-36)	30 (25-35)
Primary admission diagnoses		
Acute respiratory failure	41 (51.9)	40 (50.6)
Sepsis or shock	12 (15.2)	16 (20.2)
Cardiac (including heart failure and cardiac arrest)	10 (12.7)	10 (12.7)
Postoperative or trauma	11 (13.9)	7 (10.1)
Other (gastrointestinal, metabolic, endocrine, or neurological)	5 (6.3)	6 (7.6)
Cause of respiratory failure		
Sepsis/shock	32 (40.5)	32 (40.5)
Cardiac	12 (15.2)	14 (17.7)
Surgical/postoperative or trauma	11 (13.9)	6 (7.6)
Primary pulmonary cause (ARDS, acute lung injury, exacerbation of chronic lung disease, or airway obstruction)	21 (26.6)	22 (27.8)
Other (including metabolic, endocrine, kidney failure, or neurological)	5 (6.3)	7 (8.9)
Shock requiring vasopressors	54 (68.4)	54 (68.4)
Invasive mechanical ventilation	79 (100)	79 (100)
Pao_2:FIO_2 ratio, median (IQR)	202 (132-205)	198 (128-287)
Primary service		
Medical ICU	57 (73.1)	62 (78.5)
Surgical ICU	21 (26.9)	17 (21.5)

Abbreviations: ARDS, acute respiratory distress syndrome; APACHE II, Acute Physiology and Chronic Health Evaluation II; ICU, intensive care unit; IQCODE, Informant Questionnaire on Cognitive Decline in the Elderly.

[a] Slow-tempo relaxing music (60-80 beats/min).

[b] Silence-track attention control.

[c] Assessed by Katz scale.

[d] Assessed by Lawton scale.

[e] Calculated using variables from admission to the ICU.

[29.1-65.5] vs 42.3 [25.2-62.7]; $P = .83$). A median (IQR) of 65.5% (50.0%-84.6%) of eligible sessions were delivered in the music arm vs 66.7% (33.3%-84.6%) of eligible sessions in the control arm. In the intervention arm, 78 patients (98.7%) received at least 1 music dose vs 76 (96.2%) in the control arm. eFigure 1 in Supplement 2 shows the number of patients receiving 0, 1, or 2 listening sessions each day over the 7-day study period (see eTable 2 in Supplement 2 for the number of patients receiving listening sessions each day along with reasons for attrition and missed sessions). A total of 441 (95.5%) morning listening sessions were initiated between 9 and 11 AM, and 436 (96.5%) afternoon listening sessions were initiated between 12 to 4 PM. The mean (SD) listening duration per patient was 312 (231) minutes over 3.6 (2.2) days in the interven-

Table 2. Comparison of Patient Outcomes by Study Groups During the 7-Day Intervention Period

Outcome	Music intervention		Control		Between-group differences (95% CI)	*P* value
	No.	Summary statistic	No.	Summary statistic		
Primary outcome[a]						
Delirium/coma-free days, median (IQR)[b]	78[c]	2.5 (0-5)	79	3 (0-5)	0.00 (−1.77 to 1.77)	.66
Secondary outcomes[a]						
Delirium severity by CAM-ICU-7, mean (SD)[d]						.99
Day 1	68[e]	5.43 (2.35)	67[e]	5.79 (2.16)	NA	NA
Day 2	67	4.77 (2.35)	67	5.51 (2.18)	0.11 (−0.53 to 0.74)	.75
Day 3	62	4.10 (2.55)	65	4.45 (2.61)	−0.06 (−0.91 to 0.78)	.78
Day 4	56	3.54 (2.75)	55	3.95 (2.72)	−0.11 (−1.14 to 0.92)	.84
Day 5	47	2.78 (2.70)	52	3.27 (2.83)	−0.13 (−1.19 to 0.92)	.80
Day 6	45	2.73 (2.73)	44	3.49 (2.94)	−0.13 (−1.19 to 0.94)	.81
Day 7	43	2.72 (2.80)	42	2.56 (2.72)	−0.27 (−1.39 to 0.84)	.63
Pain by CPOT, mean (SD)[f]						.67
Day 1	67[e]	0.42 (0.94)	66[e]	0.30 (0.72)	NA	NA
Day 2	67	0.34 (0.85)	62	0.34 (0.83)	0.12 (−0.18 to 0.41)	.43
Day 3	52	0.32 (0.82)	50	0.21 (0.47)	0.04 (−0.33 to 0.40)	.85
Day 4	44	0.51 (0.87)	43	0.31 (0.65)	−0.05 (−0.44 to 0.35)	.81
Day 5	31	0.44 (0.91)	32	0.31 (0.64)	−0.01 (−0.40 to 0.38)	.96
Day 6	24	0.17 (0.48)	26	0.25 (0.47)	0.20 (−0.16 to 0.55)	.28
Day 7	22	0.20 (0.55)	19	0.61 (1.29)	0.50 (−0.17 to 1.16)	.14
Anxiety by VAS-A, mean (SD)[g]						.33
Day 1	16	40.56 (34.41)	8	43.13 (33.77)	NA	NA
Day 2	25	38.40 (33.49)	17	38.82 (34.81)	−1.42 (−32.86 to 30.03)	.93
Day 3	25	39.38 (37.45)	19	35.39 (38.28)	−9.79 (−44.00 to 24.38)	.57
Day 4	21	37.86 (36.36)	15	39.50 (33.31)	−9.92 (−46.11 to 26.27)	.59
Day 5	16	25.72 (30.23)	13	53.50 (38.97)	21.58 (−16.44 to 59.60)	.26
Day 6	11	34.36 (35.40)	10	37.80 (44.57)	−2.77 (−43.72 to 38.18)	.89
Day 7	8	43.63 (24.67)	6	28.83 (38.40)	−23.00 (−69.29 to 23.29)	.33
Clinical outcomes[h]						
Duration of mechanical ventilation, median (IQR), h	66	95.4 (58.5 to 216.5)	63	105.3 (61.2 to 205.4)	−21.87 (−54.88 to 11.15)	.88
Length of ICU stay, median (IQR), d	66	7.0 (4.9 to 12.5)	63	7.2 (4.2 to 12.5)	0.40 (−1.90 to 2.70)	.98
Length of hospital stay, median (IQR), d	66	14.5 (9 to 25)	63	13 (9 to 23)	1.00 (−4.13 to 6.14)	.76
In-hospital mortality, No. (%)	66	14 (21.2)	63	18 (28.6)	0.65 (0.29 to 1.48)	.31
Discharged home, No. (%)	66	24 (36.4)	63	14 (22.2)	2.00 (0.90 to 4.43)	.09

Abbreviations: CAM-ICU-7, Confusion Assessment Method for the Intensive Care Unit 7-point scale; CPOT, Critical Care Pain Observation Tool; ICU, intensive care unit; NA, not applicable; VAS-A, visual analog scale for anxiety.

[a] Delirium/coma-free days by day 7 postrandomization was compared using an analysis of covariance model with log (delirium/coma-free days +1) as the dependent variable and group (intervention vs control) as the independent variable while adjusting for the randomization stratification variable (hospital site). Mixed-effects models were used to compare delirium severity (CAM-ICU-7), pain (CPOT), and anxiety scores (VAS-A) averaged daily from randomization to day 7 with group, time, and group and time interactions included as independent variables while adjusting for hospital site (stratification variable). For the longitudinal outcomes, between-group differences include the mean differences in change from day 1. For the variables reported using medians, between-group differences were calculated at the median point using quantile regression. For binary outcomes, between-group differences were calculated as odds ratios using logistic regression.

[b] Delirium/coma-free days were assessed twice daily postintervention by the CAM-ICU and the Richmond Agitation-Sedation Scale.

[c] Delirium and coma data were missing for 1 patient due to withdrawal prior to the first delirium assessment.

[d] CAM-ICU-7 scores were assessed twice daily postintervention and range from 0 to 7, with higher scores indicating higher severity of delirium.

[e] Number of patients providing assessments on day 1 reflects refusals, withdrawals, death, or discharge.

[f] CPOT, assessed twice daily postintervention, ranges from 0 to 8, with higher scores indicating greater pain.

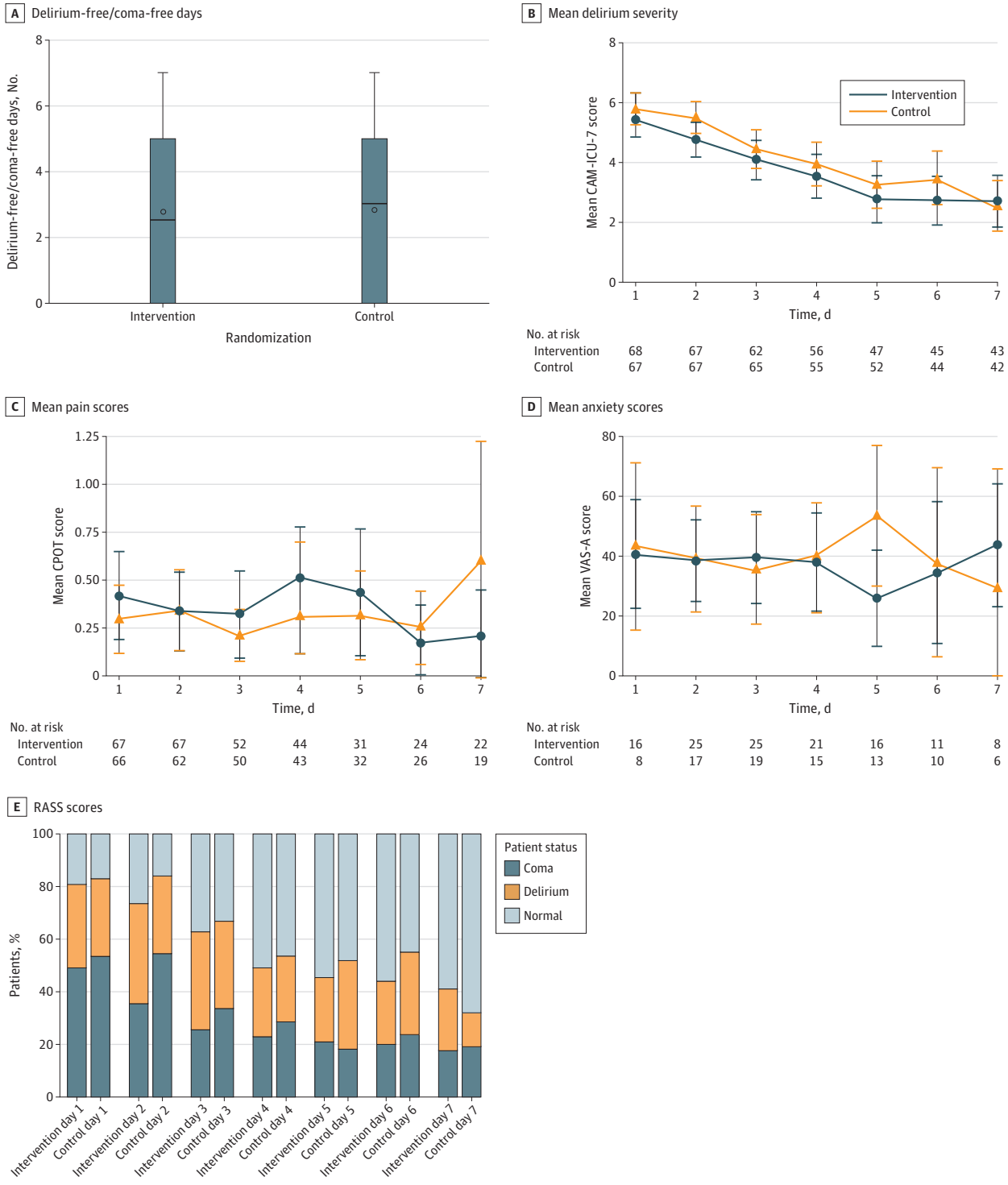
[g] VAS-A was obtained twice daily and ranges from 0 to 100 mm, presented to the patient on a vertical Likert scale like a thermometer. Higher VAS-A scores indicate greater anxiety state. VAS-A assessments were missing from participants who were unable to participate in the assessment.

[h] Clinical outcomes for ICU admission were censored at withdrawal, death or discharge, or 28-day follow-up in the hospital. Analysis of covariance models were used to compare log-transformed duration of mechanical ventilation and length of stay, adjusting for site. Logistic regression models were used for comparing mortality rates and percentages of patients discharged home, adjusting for site.

tion arm vs 279 (271) minutes over 3.1 (2.2) days in the control arm (P = .10).

Figure 2 provides the distribution of daily RASS scores per treatment group over the 7-day study period. eFigure 2 in

Figure 2. Primary and Secondary Outcomes Over the 7-Day Study Period



A, Coma and delirium were assessed twice daily using the Richmond Agitation-Sedation Scale (RASS) and Confusion Assessment Method for the Intensive Care Unit (CAM-ICU), respectively. Delirium/coma-free days were defined as duration alive and without coma or delirium. Bars indicate the median, error bars the IQR, and open circles the mean values. B, Delirium severity was assessed twice daily using CAM-ICU-7, in which scores range from 0 to 7, with higher scores indicating greater delirium severity. Error bars indicate 95% CIs. C, Scores for the Critical Pain Observation Tool (CPOT) range from 0 to 8, with higher scores indicating greater pain symptoms. Error bars indicate 95% CIs. D, The visual analog scale for anxiety (VAS-A) ranges from 0 to 100, with higher scores indicating greater anxiety symptoms. Error bars indicate 95% CIs. E, Patients were assigned a RASS category by computing the mean RASS for each day.

Supplement 2 shows the number of patients receiving 0, 1, or 2 RASS and CAM-ICU assessments each day over the 7-day study period. The number of patients assessed for RASS and CAM-ICU each day along with daily attrition is shown in eTable 3 in Supplement 2. Reasons for any missed assessments (RASS, CAM-ICU, CPOT, or VAS-A) are also shown in eTable 3 in Supplement 2. In patients randomized to music, there was a median (IQR) of 69.2% (50.0%-84.6%) of eligible RASS and CAM-ICU assessments for the 7-day study period, and a median (IQR) of 69.2% (50.0%-84.6%) of RASS and CAM-ICU assessments for patients randomized to control. A total of 436 (97.8%) morning CAM-ICU assessments were conducted between the hours of 9 and 11 AM, and 524 (96.7%) afternoon CAM-ICU assessments between 12 to 4 PM.

Exposure to opioids and sedatives was similar among patients in both the music and control groups postrandomization (opioids: 74 [93.7%] vs 78 [98.7%]; $P = .21$; benzodiazepines: 30 [38.0%] vs 38 [48.1%]; $P = .26$; propofol: 14 [17.7%] vs 13 [16.5%]; $P > .99$); dexmedetomidine: 39 [49.4%] vs 45 [57.0%]; $P = .42$; **Table 3**). The exposure to ketamine and antipsychotic medications was also similar (Table 3). Patients in both arms received similar components of the ABCDEF protocol each day over the 7-day period (eTable 4 in Supplement 2).

Adverse Events

Rates of serious adverse events did not differ between groups (eTable 5 in Supplement 2).

Post Hoc Analyses

There were no statistically significant differences in daily distribution of RASS scores (eTable 6 in Supplement 2) or distribution of coma/delirium vs normal cognitive status between the 2 groups (eFigure 3 in Supplement 2), although patients in the music arm tended to have higher RASS scores and less experience of coma on day 3 of intervention. The median (IQR) daily RASS scores per arm among patients receiving a listening session on that study day are shown in eTable 7 in Supplement 2. The lowest median (IQR) RASS score in both arms was −3 (−5 to 1) and occurred only on study day 1 (eTable 7 in Supplement 2). In a sensitivity analysis restricted to patients who did not experience coma on study day 1, there was no statistically significant effect of the intervention vs control on median (IQR) DCFDs over 7 days (4 [1-6] days vs 4 [3-6] days; $P = .11$; eTable 8 in Supplement 2). Among patients who received benzodiazepines, those randomized to music had greater median (IQR) DCFDs compared to control, though this did not reach statistical significance (4 [0-6] vs 1 [0-4]; $P = .13$; eTable 9 in Supplement 2).

Delirium was present among 56 patients (78.9%) in the music arm and 55 (83.3%) in the control arm ($P = .52$). There were no statistically significant differences in duration of coma or duration of hypoactive or hyperactive delirium between the 2 groups (eTable 10 in Supplement 2). There were no statistically significant differences in mean CAM-ICU-7, CPOT, or VAS-A scores between the 2 groups over the intervention period (eTable 10 in Supplement 2).

There were no statistically significant differences in delirium severity, pain, or anxiety by study group between morning vs afternoon assessments during the intervention period (eTable 11 in Supplement 2). Patients who withdrew during the intervention period had characteristics similar to those who completed the study protocol (eTable 12 in Supplement 2). A per protocol analysis of patients receiving 7 or more listening sessions showed a trend toward higher median (IQR) of DCFDs in the music arm compared with control, though it was not statistically significant (2 [0-4] vs 0.5 [0-2]; $P = .08$; eTable 13 in Supplement 2).

Discussion

In this multicenter RCT with concealed outcomes assessments among older adults undergoing mechanical ventilation in the ICU, a slow-tempo music-listening intervention delivered through tablets and noise-canceling headphones did not result in a statistically significant improvement in the number of DCFDs or delirium severity compared to a silence-track listening control. These findings add to the existing negative literature of large, albeit pharmacological, trials to improve delirium in critically ill patients, showing no effect on days alive without delirium or coma.[13,14,44] Although a recent meta-analysis[45] reported lower rates of postoperative delirium in participants randomized to music,[46] this trial did not demonstrate improved delirium outcomes in critically ill older adults at high risk for delirium.

Music intervention in prior studies has been shown to reduce pain and anxiety, especially in perioperative settings,[20,47] effects presumed to be modulated through changes in circulating levels of β-endorphin.[48] A Cochrane review demonstrated that music has both analgesic and anxiolytic effects.[19] In a trial among adults undergoing mechanical ventilation, listening to patient-preferred slow-tempo music meaningfully reduced anxiety.[25] By managing pain and anxiety symptoms, we hypothesized that music may potentially reduce exposure to high amounts of opioids and sedatives, thereby ameliorating 2 risk factors directly implicated in delirium development.[49,50] The present trial did not show statistically significant effects of music on pain, anxiety, or medication exposure. Compared to postoperative settings where pain is the predominant actionable focus, patients in the ICU receive bundles of care and judicious analgesics/sedatives. Whether sedatives may dilute the effects of music intervention on delirium, pain, and anxiety needs further exploration. In the trial where a beneficial effect on anxiety was observed,[25] music intervention was delivered later in the ICU course once patients were awake and able to participate in self-initiated, individualized music intervention, guided by a board-certified music therapist. This contrasts with the present trial, where a preselected, prescribed music intervention was started within 72 hours of the ICU admission and delivered through headphones with minimal therapist interaction.

Delirium pathophysiology is not completely understood, but inflammation and disruption of brain functional networks have been implicated as inciting factors in its

Table 3. Exposure to Analgesics, Sedatives, and Antipsychotics During the 7-Day Intervention Period

Medication	Prerandomization[a]			Postrandomization[b]		
	Music intervention (n = 79)	Control (n = 79)	*P* value	Music intervention (n = 79)	Control (n = 79)	*P* value
Opioids[c]						
Patients received ≥1 dose, No. (%)	67 (84.8)	66 (83.5)	>.99	74 (93.7)	78 (98.7)	.21
Duration exposed, median (IQR), d	2 (1-2)	2 (1-3)	.53	4 (2-6)	4 (2-7)	.77
Median daily dose (IQR), μg[d]	236 (53-344)	221 (103-392)	.49	193 (51-345)	192 (49-301)	.88
Cumulative dose, median (IQR), μg[d]	325 (70-761)	386 (131-874)	.39	634 (195-1350)	603 (137-1681)	.85
Benzodiazepines[e]						
Patients received ≥1 dose, No. (%)	41 (51.9)	31 (39.2)	.15	30 (38.0)	38 (48.1)	.26
Duration exposed, median (IQR), d	1 (1-1)	1 (1-1)	.59	1.5 (1-3)	1.5 (1-2)	.43
Median daily dose (IQR), mg[d]	2 (1-3)	2 (1-4)	.35	2.2 (1-3)	1.7 (1-3)	.52
Cumulative dose, median (IQR), mg[d]	2 (1-3.5)	2.5 (1-4)	.41	4.5 (1-8.5)	3 (1-5)	.42
Propofol						
Patients received ≥1 dose, No. (%)	21 (26.6)	21 (26.6)	>.99	14 (17.7)	13 (16.5)	>.99
Duration exposed, median (IQR), d	1 (1-1)	1 (1-1)	>.99	1 (1-2)	1 (1-1)	.16
Median daily dose (IQR), mg[d]	60 (20-120)	80 (30-110)	.69	52 (20-100)	50 (30-110)	>.99
Cumulative dose, median (IQR), mg[d]	60 (20-120)	80 (30-110)	.63	65 (20-160)	50 (30-130)	.61
Dexmedetomidine						
Patients received ≥1 dose, No. (%)	21 (26.6)	21 (26.6)	>.99	39 (49.4)	45 (57.0)	.43
Duration exposed, median (IQR), d	1 (1-2)	1 (1-2)	>.99	2 (2-4)	2 (1-3)	.36
Median daily dose (IQR), μg[d]	304 (177-777)	475 (127-851)	.94	643 (287-940)	732 (433-945)	.65
Cumulative dose, median (IQR), μg[d]	361 (197-1327)	649 (127-1222)	.84	1432 (487-4370)	1665 (566-2831)	.64
Ketamine						
Patients received ≥1 dose, No. (%)	8 (10.1)	1 (1.3)	.03	7 (8.9)	7 (8.9)	>.99
Duration exposed, median (IQR), d	1 (1-1.5)	2 (2-2)	.36	2 (1-3)	2 (1-4)	.74
Median daily dose (IQR), mg[d]	3881 (388-4263)	1566 (1566-1566)	.85	1232 (379-6061)	1015 (415-4051)	>.99
Cumulative dose, median (IQR), mg[d]	3881 (388-4263)	3133 (3133-3133)[f]	.85	2013 (757-18 185)	4220 (1196-7780)	>.99
Quetiapine						
Patients received ≥1 dose, No. (%)	2 (2.5)	0	.497	6 (7.6)	5 (6.3)	>.99
Duration exposed, median (IQR), d	1.5 (1-2)	NA	NA	3 (3-4)	2 (2-3)	.35
Median daily dose (IQR), mg[d]	100 (100-100)	NA	NA	79.2 (66.7-141.7)	50 (50-50)	.19
Cumulative dose, median (IQR), mg[d]	150 (100-200)	NA	NA	275 (200-575)	100 (100-150)	.31
Haloperidol						
Patients received ≥1 dose, No. (%)	0	1 (1.3)	>.99	2 (2.5)	2 (2.5)	>.99
Duration exposed, median (IQR), d	NA	1 (1-1)	NA	1 (1-1)	1 (1-1)	>.99
Median daily dose (IQR), mg[d]	NA	1 (1-1)	NA	1.5 (1-2)	2.3 (2-2.5)	.41
Cumulative dose, median (IQR), mg[d]	NA	1 (1-1)	NA	1.5 (1-2)	2.3 (2-2.5)	.41
Olanzapine						
Patients received ≥1 dose, No. (%)	0	0	NA	4 (5.1)	4 (5.1)	>.99
Duration exposed, median (IQR), d	NA	NA	NA	1.5 (1-2)	2.5 (1-5.5)	.64
Median daily dose (IQR), mg[d]	NA	NA	NA	5 (3.8-5)	5.3 (5-9.6)	.14
Cumulative dose, median (IQR), mg[d]	NA	NA	NA	5 (5-7.5)	13.8 (5-58.8)	.41

Abbreviation: NA, not applicable.

[a] Prerandomization period includes data from intensive care unit admission to enrollment.

[b] Postrandomization period includes day of enrollment until end of intervention period or withdrawal, death, or discharge (if occurring within first 7 days of intervention period).

[c] Opioids data are presented as fentanyl equivalents.

[d] Data were collected from exposed participants. Comparisons were performed using Wilcoxon rank-sum tests.

[e] Benzodiazepines data are presented as lorazepam equivalents.

[f] One participant in the control arm received ketamine prerandomization.

development.[23,51,52] Music listening has shown to improve cognition through improved attention, restoring functional neural networks and mitigating network dysconnectivity, all of which are disrupted in delirium.[53-55] However, based on these trial results, beneficial effects of music at the doses tested herein may not be realized in the ICU. Future studies in elective preoperative and postoperative settings, incorporating electroencephalography or other biological measures, may better elucidate the biological effects of music on delirium. The present per-protocol results suggest that patients who re-

main in the ICU for longer periods and received at least 7 listening sessions trended toward greater DCFDs compared to controls, a finding that also needs further investigation.

Behavioral trials are usually critiqued for lack of rigor due to their rudimentary ability to capture granular data regarding the dose and delivery of intervention. Music intervention trials have been dependent on either direct observation of music intervention, which is resource intensive, or on patient recall that could introduce recall bias and prevent from capturing accurate dose of music. To capture intervention fidelity and process measures, our team developed a unique application, the Soundese app for iPad,[30] which automatically collected data on timing and content of the music intervention. This trial is, to our knowledge, the first music intervention trial where a specialized music delivery and data app were used and effectively implemented. Future avenues for similar apps can be envisioned for both clinical and research settings.

Limitations

This study has limitations. The intervention duration was only up to 7 days. It is possible that a longer intervention could have been efficacious. Due to early death, withdrawal, and patient-related factors (ie, weakness, inability to follow instructions, low RASS levels), we had a smaller number of observations for the secondary outcome of anxiety (measured by VAS-A), making it difficult to draw conclusions on the effect of slow-tempo music on anxiety in this patient population. Finally, incorporating patients' preferences for music, increasing the intervention duration, and testing music in patients with hyperactive delirium may have resulted in different findings. Strengths of this multicenter trial include blinded outcome assessments, collection of delirium severity, and capturing granular intervention data, which will enable future exploration of sedation's effects on the intervention.

Conclusions

In this randomized clinical trial, the dose and duration of slow-tempo music compared to listening to a silence track control did not result in statistically significant differences between groups on delirium/coma duration, delirium severity, pain, or anxiety symptoms in critically ill, older adults undergoing mechanical ventilation in the ICU. Future considerations include incorporating patients' music preferences, focusing on select patient populations, or administering the intervention in the post-ICU phase to improve long-term sequelae of critical illness.

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Concept and design: B. Khan, S. Khan, Heiderscheit, Downs, Gao, Chlan.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: B. Khan, S. Khan, Heiderscheit, Chlan.
Critical review of the manuscript for important intellectual content: All authors.
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