



DECREASING DELIRIUM THROUGH MUSIC: A RANDOMIZED PILOT TRIAL

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Background Management of delirium in intensive care units is challenging because effective therapies are lacking. Music is a promising nonpharmacological intervention.

Objectives To determine the feasibility and acceptability of personalized music (PM), slow-tempo music (STM), and attention control (AC) in patients receiving mechanical ventilation in an intensive care unit, and to estimate the effect of music on delirium.

Methods A randomized controlled trial was performed in an academic medical-surgical intensive care unit. After particular inclusion and exclusion criteria were applied, patients were randomized to groups listening to PM, relaxing STM, or an audiobook (AC group). Sessions lasted 1 hour and were given twice daily for up to 7 days. Patients wore noise-canceling headphones and used mp3 players to listen to their music/audiobook. Delirium and delirium severity were assessed twice daily by using the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) and the CAM-ICU-7, respectively.

Results Of the 1589 patients screened, 117 (7.4%) were eligible. Of those, 52 (44.4%) were randomized, with a recruitment rate of 5 patients per month. Adherence was higher in the groups listening to music (80% in the PM and STM groups vs 30% in the AC group; $P=.01$), and 80% of patients surveyed rated the music as enjoyable. The median number (interquartile range) of delirium/coma-free days by day 7 was 2 (1-6) for PM, 3 (1-6) for STM, and 2 (0-3) for AC ($P=.32$). Median delirium severity was 5.5 (1-7) for PM, 3.5 (0-7) for STM, and 4 (1-6.5) for AC ($P=.78$).

Conclusions Music delivery is acceptable to patients and is feasible in intensive care units. Further research testing use of this promising intervention to reduce delirium is warranted. (*American Journal of Critical Care*. 2020; 29:e31-e38)

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Patients receiving mechanical ventilation are at high risk for delirium, a syndrome of acute brain failure associated with prolonged stays in an intensive care unit (ICU), high health care costs, and high mortality.¹⁻⁶ An intubated patient also experiences pain, anxiety, and physiological stress, which are usually treated with sedatives—themselves risk factors for delirium. This creates a perpetuating cycle of pain, anxiety, sedation, and delirium.

Efforts to prevent and manage delirium in the ICU have had mixed results: pharmacological interventions have not changed delirium outcomes, whereas bundled protocols emphasizing judicious pain control, avoidance of oversedation, delirium monitoring, daily ventilator liberation trials, mobility,

Effective nonpharmacological interventions to prevent and treat delirium are needed.

and family involvement have reduced delirium.⁷⁻¹¹ These multicomponent protocols are limited by low adherence; greater adherence was associated with increased patient-reported pain.¹¹ Scalable,

low-burden, and effective interventions are clearly needed to manage patients' symptoms and reduce the burden of delirium.

Music may be an ideal nonpharmacological intervention that could begin to address this gap.

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In hospitals, listening to music has been associated with lower heart rates, blood pressures, and serum cortisol levels, and less anxiety, postoperative pain, and sedative exposure.¹²⁻¹⁹ Patients undergoing mechanical ventilation who listened to slow-tempo music (STM) in a patient-directed music intervention had less anxiety and received fewer doses of sedative than did patients receiving usual care.¹³ Despite these findings, few studies have examined the effect of music on delirium in the ICU. Furthermore, prior studies limited enrollment to alert, stable patients receiving spontaneous mechanical ventilation in order to obtain the patients' music preferences.

Providing a personalized music intervention for critically ill patients poses unique logistical challenges, but the comparative efficacy of nonpersonalized STM has not been tested. Therefore, we designed our study to test the feasibility of, adherence to, and acceptability of 2 types of music intervention and attention control in complex, critically ill patients, and to estimate the effect of music on delirium outcomes.

Methods

We conducted a 3-arm, single-blind, randomized controlled clinical trial; details of the protocol have been published elsewhere.²⁰ The Indiana University institutional review board reviewed and approved the study. In brief, we included English-speaking adult patients (≥ 18 years old) admitted to the ICU and receiving mechanical ventilation for at least 24 hours but not more than 48 hours. We excluded patients who had been receiving mechanical ventilation for longer than 48 hours because delirium develops early during the ICU stay, and our intervention may have preventive and therapeutic effects. Patients were excluded if they had neurologic injury, chronic neurologic disease, or uncorrected hearing or vision impairments; were intoxicated by or in withdrawal from alcohol or drugs; were in a coma after cardiac arrest, pregnant or nursing, or incarcerated; or the primary team did not consider the patient appropriate for the study (eg, patient soon enrolling in comfort care). We obtained consent from the patient or, if

the patient was unable to provide consent, from their legally authorized representative (LAR). If initial consent was obtained from the LAR, the patient was approached for re-consent once they were able to communicate.²⁰ To randomize patients, we used permuted block randomization with various block sizes and computer-generated random numbers. Patients were assigned to 1 of 3 arms: (1) personalized music (PM) playlists incorporating patients' preferences based on information obtained from their LAR; (2) nonpersonalized relaxing, STM (60-80 beats per minute) consisting of piano, guitar, and classical music and Native American flute sounds (eg, *Lifescapes: Relaxing Piano*, by John Story, and *Watermark*, by Enya) preselected by a board-certified music therapist; and (3) audiobooks for attention control (AC).²⁰ Patients in the AC group were randomly assigned 1 of the following audiobooks: *Treasure Island*, by Robert Louis Stevenson; *Harry Potter and the Chamber of Secrets*, by J.K. Rowling; or Dr. Seuss's *Oh the Places You'll Go!*. These books were chosen for their readability, their broad appeal, the quality of the audiobook narration, and the high audiobook ratings (as reviewed on commercial websites).

All patients received two 1-hour sessions each day (between 9 and 11 AM, and between 2 and 4 PM) for up to 7 days. The music or audiobook was delivered through noise-canceling headphones attached to Apple iPod Shuffle mp3 players. These sessions continued until the patient was transferred out of the ICU, was discharged, or died. In-hospital follow-up to measure delirium, pain, anxiety, and clinical and mobility outcomes continued until discharge or day 28, whichever occurred first.

We evaluated 4 primary outcomes of the pilot study: (1) recruitment rate (enrollment of 5 patients per month; 60 patients in 12 months), (2) adherence to the prescribed intervention (80% of sessions delivered), (3) acceptability of the intervention (patient survey), and (4) feasibility (retention of 80% of participants). Secondary outcomes were the estimated effect of music on the number of delirium/coma-free days, delirium severity, anxiety, pain, physiological stress, and mobility. (See the published protocol for details.²⁰)

Data Collection

We collected demographic data, baseline cognitive and functional statuses, clinical data (including medications), and blinded outcome assessments, as described in the published protocol.²⁰ We obtained music preferences from all patients or their LARs at enrollment using a Music Assessment Tool.¹² Research assistants assessed patients' delirium and delirium

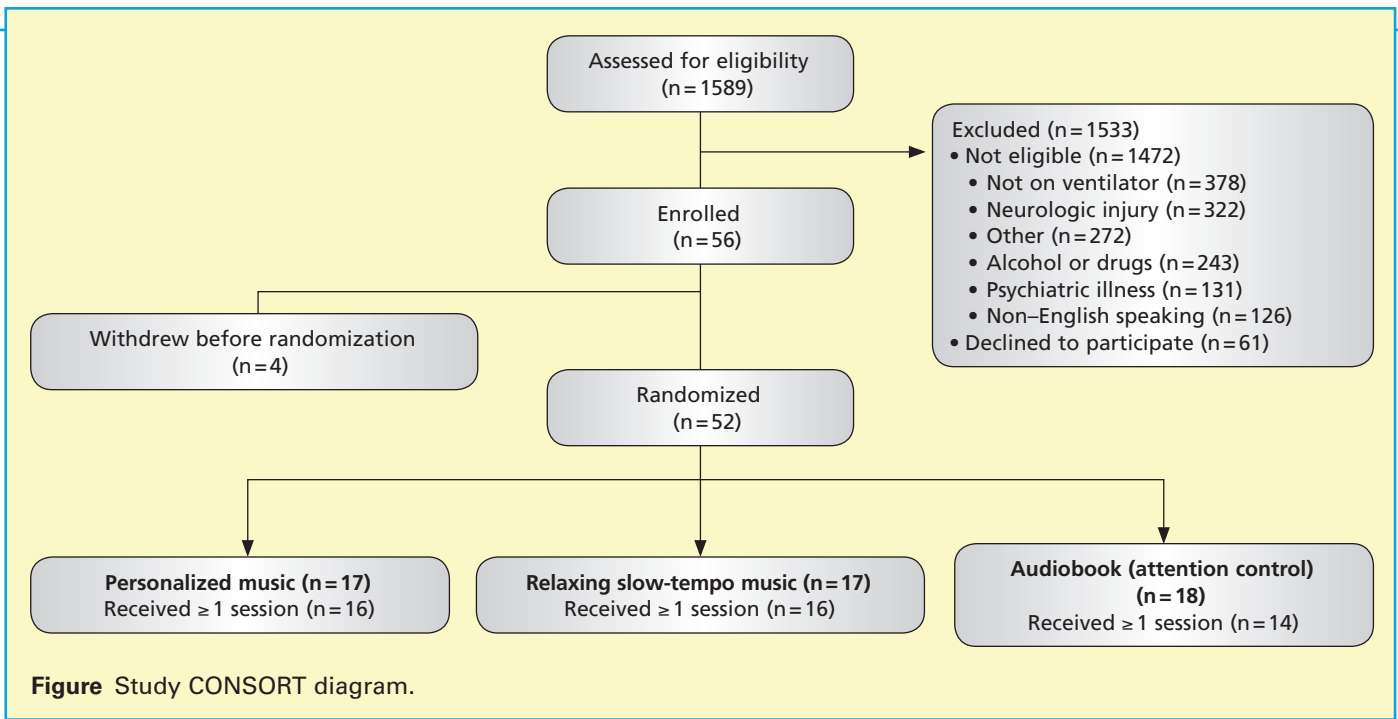
severity twice daily (after each intervention) using the Confusion Assessment Method for the ICU (CAM-ICU) and the CAM-ICU-7, respectively.^{2,21-23} They assessed patients' anxiety once daily (after the morning intervention) using a self-report visual analog scale (0, no distress; 4, very severe distress).^{24,25} Finally, the research assistants assessed patients' pain twice daily (after each intervention) using the Critical Care Pain Observation Tool.²⁶ To measure adherence, research staff, who were blinded to the type of intervention, recorded the duration of each music/audiobook session, including start and stop times, and reasons for any interruptions. Vital signs (heart rate, blood pressure, respiratory rate) were also recorded before and after each session. Staff obtained patients' mobility milestones from inpatient therapy notes. Patients were randomly surveyed by telephone after hospital discharge to assess the acceptability of the audio selections, the fit and comfort of the headphones, and whether they would enroll in the study again.

Statistical Analysis

We performed an intention-to-treat analysis. We compared baseline characteristics using the Fisher exact test and the Wilcoxon rank sum test. We considered adherence to the intervention as the percentage of sessions delivered, adjusted for the number of days the patient was eligible. We present delirium outcomes as delirium/coma-free days because delirium and coma fluctuate over hours or days, because delirium is difficult to assess when a patient is in a coma, and because death and discharge affect delirium/coma outcomes. We defined delirium/coma-free days as the number of days a patient was alive and free from coma or delirium; we compared delirium/coma-free days among the 3 groups using the Wilcoxon rank sum test. Delirium/coma-free days provide an estimate of the duration of normal brain function (free from coma and delirium), and hence they function as a surrogate of delirium duration not confounded by coma or death. Previous high-impact studies have used delirium/coma-free days as an outcome, and the variable accounts for confounding by death or discharge. For patients discharged from the hospital before day 7, the remaining days until day 7 were counted as delirium/coma-free.

To provide a conservative estimate of the intervention's effects on delirium, and to be consistent

We conducted a 3-arm randomized controlled trial to test feasibility and acceptability of music in intensive care patients.



with methods applied in prior studies, for patients who died or withdrew before day 7, we counted their subsequent delirium/coma-free days as 0; this managed the conflicting effects of the intervention on delirium and survival.^{7,9,22} Similarly, to provide a conservative estimate of music’s or an audiobook’s effects on delirium severity, we imputed values missing from the CAM-ICU-7 on the basis of the patient’s worst coma/delirium status. We chose the patient’s

worst delirium severity score, rather than the group’s mean score, because of the small sample size in this feasibility trial. We present delirium severity during the intervention period as the median daily CAM-ICU-7 score for each patient. We report level of consciousness as the median of

the mean daily scores on the Richmond Agitation-Sedation Scale for each patient during the intervention period. We define ventilator-free days as the number of days the patient was alive and breathing without mechanical ventilation. We present medication exposure as the percentage of patients receiving at least 1 dose of medication during the intervention period. A mean daily dose was calculated from the total amount of a drug administered in 24 hours. We converted benzodiazepine doses to lorazepam equivalents and opioid doses to morphine intravenous equivalents.

Patients received music or an audio book through noise-canceling headphones and mp3 players for 1 hour twice daily for up to 7 days.

We analyzed changes in heart rate and blood pressure as mean differences before and after each intervention session, and we used fixed effects models to analyze changes in anxiety and pain scores over time. We used a Cox proportional hazards model to analyze time to ambulation. We calculated length of stay using dates of admission to and discharge from the ICU, date of death, or date of withdrawal from the study; we compared length of stay among the 3 groups by using the Wilcoxon rank sum test.

Results

From December 2016 to October 2017, we screened 1589 patients. Of the 117 eligible patients (7.4%), 56 (48%) consented to participate, and 52 (44%) were randomized (see Figure). We achieved a recruitment rate of 5 patients per month. Seventeen patients were randomized to PM, 17 to STM, and 18 to AC. The mean age was 57.4 years (SD, 14.2 years), and 40% of patients were African American. The mean Acute Physiology, Age, Chronic Health Evaluation II score was 21.7 (SD, 8.7). Characteristics did not differ significantly among the 3 groups at baseline (Table 1).

We randomized patients, developed playlists, and initiated the intervention within 24 hours of enrollment for all except 1 patient. Adherence to the intervention was higher in the 2 music arms than in the AC arm (Table 2). The PM and STM groups received 80% of their eligible sessions (interquartile range, 30%-90% [PM arm], 50%-90% [STM arm]), whereas those in the AC arm received only 30% of their sessions (interquartile

Table 1
Patient characteristics at baseline^a

Variable	All patients (n=52)	Personalized music (n=17)	Relaxing slow-tempo music (n=17)	Audiobook (attention control) (n=18)	P
Age, y					.97
18-49	12 (23)	3 (18)	4 (24)	5 (28)	
50-64	27 (52)	10 (59)	9 (53)	8 (44)	
≥65	13 (25)	4 (24)	4 (24)	5 (28)	
Race					.05
African American	20 (40)	9 (53)	8 (47)	3 (17)	
White	29 (56)	7 (41)	8 (47)	14 (78)	
Education					.58
High school/GED	22 (42)	7 (41)	6 (40)	9 (60)	
Female sex	27 (52)	10 (59)	8 (47)	9 (50)	.83
ADL index, ^b median (IQR)	6 (3-6)	6 (4-6)	5 (3-6)	6 (3-6)	.97
IADL score, ^c median (IQR)	8 (3-8)	8 (1-8)	8 (7-8)	7.5 (3-8)	.37
IQCODE, median (IQR)	3 (3.0-3.1)	3 (3.0-3.1)	3 (3.0-3.1)	3 (3.0-3.1)	.49
Charlson Comorbidity Index, median (IQR)	1 (0-3)	2 (1-3)	1 (0-4)	1 (0-3)	.64
Mechanical ventilation	52 (100)	17 (100)	17 (100)	18 (100)	NA
Inpatient characteristics					
APACHE II score, median (IQR)	20 (15-28)	20 (17-32)	19.5 (14.0-24.5)	19.5 (16-28)	.67
Primary diagnosis at admission					.53
Shock or sepsis	7 (13.5)	3 (17.6)	2 (12)	2 (11)	
Respiratory failure	20 (38.5)	5 (29.4)	6 (35)	9 (50)	
Surgery or trauma	14 (27.0)	5 (29.4)	6 (35)	3 (17)	
Cardiac	4 (7.7)	1 (5.9)	0 (0)	3 (17)	
Other	7 (13.5)	3 (17.6)	3 (18)	1 (6)	
Intensive care unit					.89
Medical	35 (68.6)	11 (68.8)	11 (65)	13 (72)	
Surgical	16 (31.4)	5 (31.2)	6 (35)	5 (28)	

Abbreviations: ADL, activities of daily living; APACHE II, Acute Physiology and Chronic Health Evaluation; GED, general education diploma; IADL, instrumental activities of daily living; IQCODE, Informant Questionnaire for Cognitive Dysfunction in the Elderly; IQR, interquartile range; NA, not applicable.

^a Data are presented as number (percentage) of patients unless otherwise specified.

^b Assessed with the Katz Index of Independence in ADL.

^c Assessed with the Lawton IADL Scale.

range, 10%-60%) ($P = .02$). More patients in the AC arm withdrew after 1 or more sessions ($n = 8$) than did so in the PM ($n = 3$) or the STM ($n = 3$) arms. Overall, 27% of patients withdrew after receiving at least 1 session (withdrawal was based on the patient's preference once they were clinically able to make decisions, on family member input, or both). Eight patients (15%) or their family members refused at least 1 intervention session during the study (1 [6%] in the PM arm, 2 [12%] in the STM arm, and 5 [28%] in the AC arm). Ten patients (4 in the PM arm, 3 in the STM arm, and 3 in the AC arm) completed an acceptability questionnaire after discharge. Among the patients, 80% rated the music enjoyable and the duration not too long, liked receiving sessions twice a day but would prefer to choose their own music, and would enroll in a similar study again. Among the surveyed patients, 90% rated the headphones comfortable and the volume appropriate. In comments, patients noted that music made them feel normal and calm. Patients rated the audiobooks poorly with regard to enjoyment and cited that as a

reason for withdrawal. Adherence and acceptability did not differ between audiobooks.

Patients in the STM group had more median delirium/coma-free days by day 7 than did patients in the PM and AC groups, but the difference was not statistically significant (Table 2). Similarly, the median delirium severity during the intervention period was lower in the STM group than in the other 2 groups, but again, the difference was not statistically significant (Table 2). The median Richmond Agitation-Sedation Scale scores were slightly (but not significantly) higher in the STM group than in the PM and AC groups (Table 2).

Patients in the STM group had significant increases in heart rate and diastolic blood pressure compared with patients in the PM and AC groups (Table 2).

We measured the effects of music on level of consciousness, delirium incidence and severity, anxiety, pain, and use of sedatives.

Table 2
Adherence, delirium, sedation, stress, anxiety, pain, and clinical outcomes by randomized groups

Variable	Personalized music (n = 17)	Relaxing slow-tempo music (n = 17)	Audiobook (attention control) (n = 18)	P
Adherence				
No. of sessions administered, median (IQR)	11.2 (4-13)	10.5 (7-13)	4.7 (2-8)	.02
Percentage of eligible sessions delivered, median (IQR)	80 (30-90)	80 (50-90)	30 (10-60)	.02
Delirium and sedation				
No. of delirium/coma-free days by day 7, median (IQR)	2 (1-6)	3 (1-6)	2 (0-3)	.32
Delirium severity ^a during intervention period, median (IQR)	5.5 (1-7)	3.5 (0-7)	4 (1-6.5)	.78
Level of sedation ^b during intervention period, median (IQR)	-1.8 (-3.5 to 0.2)	-0.8 (-3.6 to 0.0)	-1 (-1.8 to 0.5)	.64
Stress, anxiety, pain				
Change in heart rate, ^c mean (SD), beats per minute	-2.2 (3.7)	1.4 (3.7)	-3.7 (6.8)	.02
Change in systolic blood pressure, ^c mean (SD), mm Hg	-3.4 (9.2)	2.9 (8.9)	-3.5 (6.7)	.14
Change in diastolic blood pressure, ^c mean (SD), mm Hg	0.9 (5.8)	1.6 (3.3)	-4.5 (5.8)	.02
Change in anxiety score by day 7, ^d mean (SD)	0.103 (0.112)	-0.043 (0.155)	-0.162 (0.162)	.27
Change in pain score by day 7, ^d mean (SD)	0.001 (0.058)	-0.052 (0.084)	-0.096 (0.086)	.52
Mobility				
Achieving standing or greater, No. (%) of patients	5 (33)	9 (75)	8 (53)	.11
Duration of mechanical ventilation				
No. of ventilator-free days during intervention period, median (IQR)	1 (0-5)	3 (0-6)	2 (0-5)	.64
Mortality				
ICU mortality, No. (%) of patients	2 (12)	1 (6)	3 (17)	.86

Abbreviations: ICU, intensive care unit; IQR, interquartile range.

^a Delirium severity was defined as the median of daily scores on the Confusion Assessment Method for the Intensive Care Unit-7 for each patient: 0-2, no delirium; 3-5, mild to moderate delirium; 6 or 7, severe delirium.

^b Level of sedation was defined as the median of the mean daily scores on the Richmond Agitation-Sedation Scale (RASS) for each patient (0, alert and calm); more negative RASS scores indicate deeper sedation, whereas more positive RASS scores indicate increased agitation.

^c Defined as the mean difference (value after the intervention minus the value before the intervention).

^d Analyzed by using mixed-effects models. Patients self-reported anxiety on a visual analog scale (0 = no distress to 4+ very severe distress). Pain scores were from the Critical Care Pain Observation Tool.

The changes in anxiety and pain scores by day 7 did not differ significantly among the 3 groups (Table 2). Other exploratory outcomes of mobility, duration of mechanical ventilation, and mortality are shown in Table 2.

Patients in the STM group received lower mean daily doses of haloperidol, opioids, propofol, and quetiapine by day 7 than did patients in the PM and AC groups, but the differences were not statistically significant (Table 3). Other medication exposures are also shown in Table 3. No adverse safety events occurred during the study.

Discussion

The Decreasing Delirium through Music trial demonstrates the feasibility and acceptability of an innovative, scalable music intervention among patients receiving mechanical ventilation in the ICU. In contrast to music interventions used in prior randomized controlled trials in this population, our intervention did not require the daily input of a board-certified music therapist or the participation of an awake and alert patient (music preferences could be obtained from LARs).

We found high acceptability of and adherence to both PM and STM, and we were able to deliver the intervention within 24 hours of enrollment, early during the course of mechanical ventilation. We chose to investigate preferred PM because of its familiarity, and relaxing STM (60-80 beats per minute) because of its sedative-sparing and anxiolytic effects. We chose to use audiobooks because they incorporate the spoken-word elements of PM, serving as behavioral and psychosocial controls.²⁷ In addition, in a pediatric study, audiobooks provided adequate distraction during radiology testing.²⁸ We learned, however, that audiobooks had poor acceptability and adherence among our patients, who completed only 30% of eligible sessions. This finding indicates that future study designs should avoid audiobooks as a control condition and consider noise-canceling headphones as an AC device.

Results of our secondary outcomes related to delirium, level of consciousness, exposure to sedatives and antipsychotics, and duration of mechanical ventilation may suggest a possible trend toward benefit in the STM group. Unlike the results of previous studies, heart rate and blood pressure significantly

Table 3
Medication exposure during the first 7 days

Medication	Personalized music (n = 16)	Relaxing slow-tempo music (n = 16)	Audiobook (attention control) (n = 15)	<i>p</i> ^a
Benzodiazepines				
Patients, No. (%)	7 (44)	9 (56)	9 (60)	.63
Daily dose, ^b mean (SD)	2.6 (3.3)	10.7 (26.4)	13.9 (36.8)	.71
Dexmedetomidine				
Patients, No. (%)	1 (6)	2 (12)	1 (7)	>.99 ^c
Daily dose, mean (SD), mg	0.2 (0.0)	0.2 (0.2)	0.3 (0.0)	.90
Haloperidol				
Patients, No. (%)	2 (12)	1 (6)	3 (20)	.50 ^c
Daily dose, mean (SD), mg	1.2 (0.5)	0.7 (0.0)	2.1 (1.7)	.67
Ketamine				
Patients, No. (%)	1 (6)	3 (19)	3 (20)	.60 ^c
Daily dose, mean (SD), mg	1.4 (0.0)	413.3 (517.2)	3594.7 (3599.2)	.34
Opioids				
Patients, No. (%)	14 (88)	15 (94)	14 (93)	.78
Daily dose, ^d mean (SD)	116.9 (90.1)	85 (129.4)	111.4 (122.4)	.73
Propofol				
Patients, No. (%)	7 (44)	8 (50)	8 (53)	.86
Daily dose, mean (SD), mg	1383.9 (2178.7)	620.8 (697.8)	1157.7 (1375.0)	.61
Quetiapine				
Patients, No. (%)	3 (19)	0 (0)	3 (20)	.19 ^c
Daily dose, mean (SD), mg	111.9 (41.2)	0.0 (0.0)	42.9 (18.9)	.06

^a Unless otherwise indicated, mean (SD) values were compared using analysis of variance and No. (%) values were compared using χ^2 test.

^b Dose in lorazepam equivalents.

^c Fisher exact test.

^d Dose in morphine intravenous equivalents.

increased, and exposure to benzodiazepines was higher, in the STM group than in the PM group. These findings may be confounded by the use of inotropic and vasopressor agents and our study's small sample size (see the limitations described later). The findings also suggest that the beneficial effects of music on delirium may occur through a pathway other than physiological relaxation. Anxiety and pain scores decreased among patients in the STM and AC groups, whereas the opposite trend occurred in the PM arm. Our findings promote the need for further comparison of STM with an acceptable method of AC in the highly stimulating ICU setting.

Prior studies have suggested candidate pathways by which STM may be more effective against delirium than is PM or AC. Relaxing STM may reduce delirium by exerting a sedative-sparing effect, increasing cortical engagement and cognitive processing, and promoting entrainment of the nervous system.²⁹ In electroencephalographic studies, classical STM increased bihemispheric communication and neural connectivity.³⁰ Inability to focus or shift attention is a notable feature of delirium, and functional magnetic resonance imaging studies in patients listening to music have shown increased activity in areas of the brain involved with attention.³¹ Further mechanistic models are needed to explain the neurocognitive effects of music.

Our results also suggest that implementing an STM intervention may be logistically simpler than implementing a PM intervention, without loss of acceptability. Although we did not assess the dose-response effects of music, our findings suggest that 120 min/day may provide a trend toward improved delirium outcomes; we are not certain whether the potential benefits of music require twice-daily sessions or simply 120 continuous minutes of music. In a previous randomized controlled trial we performed, anxiolytic and sedative benefits occurred after patients listened to preferred, relaxing music for a mean of 79 min/day (divided among patient-initiated listening sessions).¹³ Further studies, including comparisons of continuous music versus more frequent but shorter sessions, as in our study, are needed.

Strengths of our study included the assessment process, in which research assistants were blinded to the patient's grouping; the innovative intervention design; and the prospectively collected clinical data. However, our study also has certain limitations. First, our analysis was limited by the small sample size. We nevertheless obtained valuable data regarding feasibility, acceptability, attrition, recruitment rates, and playlist design. Second, the intervention was not continued after a patient was transferred from the ICU, when they are likely to be able to interact

with their music devices. Third, we did not adjust data related to physiological stress for doses of vasopressors or inotropic agents, nor did we collect such data continuously. Finally, only those patients who survived the hospitalization and were able to be reached by telephone completed the acceptability questionnaire.

In this study, we found that both PM and STM (classical music) were acceptable to severely ill patients and feasibly delivered in the ICU, whereas audiobooks were not acceptable to patients. Further research is needed in order to test the efficacy of music and determine its mechanisms of action in managing delirium through the use of nonpharmacological means.

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