Review Article

Meta-Analysis of Music Therapy Effects on Alzheimer's Disease

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ABSTRACT

Music therapy is beneficial for neurological diseases, especially in slowing down the progression of clinical symptoms in patients. However, it remains unclear to what extent can music therapy may affect patients with Alzheimer's disease (AD). Questions remain on whether music therapy can improve the quality of life (QOL) of AD patients, who are usually with poor QOL owing to the burden of the disease. A search that compared the effectiveness of music therapy to improve the QOL of AD patients was carried out. PubMed, Cochrane library clinical trial database, and WAN FANG database were searched to collect data from randomized controlled trials (RCTs). Two independent researchers extracted data from the selected eligible articles by using a collection form and RevMan5.3 statistical software and applied it for the meta-analysis. We included six RCTs in our meta-analysis. The results showed that compared to the control group, music intervention can significantly increase the score of the QOL-AD scale (MD=5.10, 95%CI: 2.95-7.24, *p<0.001*) and The World Health Organization QOL Rating Scale Short Form score (MD=5.76, 95%CI: 1.59-9.92, *p=0.007*). The results suggested that music therapy could improve the QOL for elderly patients with AD. Our findings indicated that music therapy might be considered a non-pharmaceutical therapy for patients with AD in the future.

Key-words Alzheimer's disease, Music therapy, Meta-analysis, Quality of life, World Health Organization

INTRODUCTION

Alzheimer's disease (AD) is a neurodegenerative disease which frequently occurs in the elderly population [1]. It accounts for most dementia cases (~60-70%) worldwide [2]. AD-related pathologies include abnormal deposition of β-amyloid (Aβ), formation of senile plaques and neurofibrillary tangles in the brain [3]. AD is characterized by severe defects in cognition, such as memory, sensory and motor functions [4-6]. Motor dysfunction is characterized by slow walking, great gait variability, impaired balance, and postural control, and deteriorated fine motor control in AD patients [7-9]. These symptoms have reduced the quality of life of AD patients.

So far there is no effective treatment for AD, however, it is urgently needed to develop effective treatment methods or prevention strategies to prolong the progression of AD [10]. The clinical situation of AD patient is one of the main factors affecting their quality of life. Combined with multiple complications and the progressive aggravation of AD, the patient's quality of life was commonly seriously getting worse, and the caregiver's quality of life was correlated and affected as well. The imperfections of current comprehensive nursing intervention even make the management of AD patients a heavy burden not only to the patient's family but also to the whole country.

QOL mainly refers to the assessment of the status of an individual's physical, psychological, and social functions [11]. The QOL of patients can also be used as an important indicator of the effectiveness of the health care services, they received [12]. Studies have proven that cognitive impairment in the elderly with chronic diseases is a key determinant of poor QOL [13]. The relationship between quality of life and mortality is time-dependent. Because a

decrease in quality of life may increase the risk of mortality, quality of life can be used as a predictor of mortality [14]. The QOL has been accepted as an indicator for the evaluation of AD treatment because it can indicate the processing of AD, activities of daily living and achievement under treatment [15]. Reduced QOL, may have serious impacts on the psychological, physical, behavioural, and social levels of an individual.

Music therapy is a systematic intervention process [16]. In the process, various types of music experiences and the therapeutic relationship developed during the therapy process were used by therapists to help patients [16-18]. Music therapy is a relatively safer strategy than many other therapies such as medication and surgery, and it is greatly valuable for further study [19]. Studies have demonstrated that listening to music can increase brain functional connectivity in AD patients, and can also increase memory and cognitive ability in AD patients by improving the neural structure and neurophysiological characteristics [20,21]. In summary, music therapy may potentially improve many aspects in patients with different degrees of dementia, including biological and physiological, behavioural, and psychological, QOL, memory failure, cognitive level and so on [22]. However, it remains unclear whether music therapy can improve the QOL in AD patients, and therefore promote the effect of treatment.

To our best knowledge, there is no work conducted by systematic review and meta-analyses on the improvement of QOL by music therapy in AD patients previously. To clarify whether music therapy intervention is an effective and positive intervention to improve the QOL of patients with AD. We employed a detailed search strategy to comprehensively summarize Chinese and internationally published literature, and the impact of music intervention on the QOL in AD patients was analyzed.

MATERIALS AND METHODS

Search strategy- PubMed, the Cochrane Library, and Wanfang Database, were systematically searched from January 1986 to March 2021. The search is performed parallel by authors Yingzhen Su and Chaochao Chen. Keywords including "cognitive impairment'', "mild cognitive impairment'', "Alzheimer's disease", "music therapy", "music listening", "musical instrument", "music performance", "musical rhythms", "randomized controlled trial", "clinical trial" and "clinical study" were

searched and an updated final repeat search was carried out on 24 March 2021.

Inclusion criteria- 1) A randomized controlled study on the impact of music intervention on the QOL of patients with AD; 2) The subject in this study is patients with AD; 3) There is no significant difference among age, gender, and education background in sorted groups before analysis which make these groups comparable. 4) All data were sorted into two groups: the music intervention group and the control group without any music intervention; 5) The indicators evaluated in the literature included the score of QOL-AD or WHOQOL-BERF scale, at least one of the two scales summarized in selected publications.

Exclusion criteria- 1) Non-RCTs; 2) Articles lacking original data; 3) Repeat published reports; 4) The subjects were not diagnosed with AD; 5) The outcome data was not expressed in the form of scales; 6) Full text could not be obtained.

Quality rating of studies- Cochrane's Risk of Bias tool was used to evaluate the quality of collected studies. A total of 7 domains were counted in these studies such as random sequence generation, allocation concealment, blinding of participants and personal, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases. These domains were classified as high, unclear, and low risk of bias. A low risk of bias means that it has little effect on the results of our study and a high degree of risk of bias indicates that it will greatly affect the results of this study. Unclear-bias risk implies potential risks.

Data extraction and synthesis- A standardized template was used to extract data by two independent reviewers to show the population characteristics (Diagnosis was made according to the National institute of neurological and communicative disorders and Stroke and the Alzheimer's disease and related disorders association (NINCDS-ADRDA) criteria, Diagnostic and Statistical Manual of Mental Disorders (DSM-V) criteria, International Classification of diseases (ICD-10) criteria and in combination with clinical symptoms, medical history, neurological physical examination, neuropsychological scale test results (CERAD) and pathological scoring scale (BEHAVE-AD); Participants were elderly between 55 and 97 years of age) and the

outcomes and the name of the first author, region, year of publication, clinical study design, study subjects, intervention modalities, intervention period, and outcome measurement were included. Meta-analysis was performed by using RevMan software (Version 5.3; Cochrane Collaboration, Oxford, England). A heterogeneity test was conducted for the filtration of collected studies and *p<0.05* was considered heterogeneous. There was no significant statistical heterogeneity if $I^2 \leq 50\%$ and the fixed effect model should be used; there was statistical heterogeneity among all studies if $I^2 > 50\%$ and the random effect model should be used.

RESULTS

Results of Literature Search- Our initial literature search yielded 298 unique recordings, 255 articles were extracted after duplicates were removed, and there were 32 records left after the screening of the titles and abstracts. There are 6 studies (396 patients) with full text that were identified as eligible and included in these meta-analyses [23-28]. The detailed screening process is shown in the flow chart in Fig. 1.
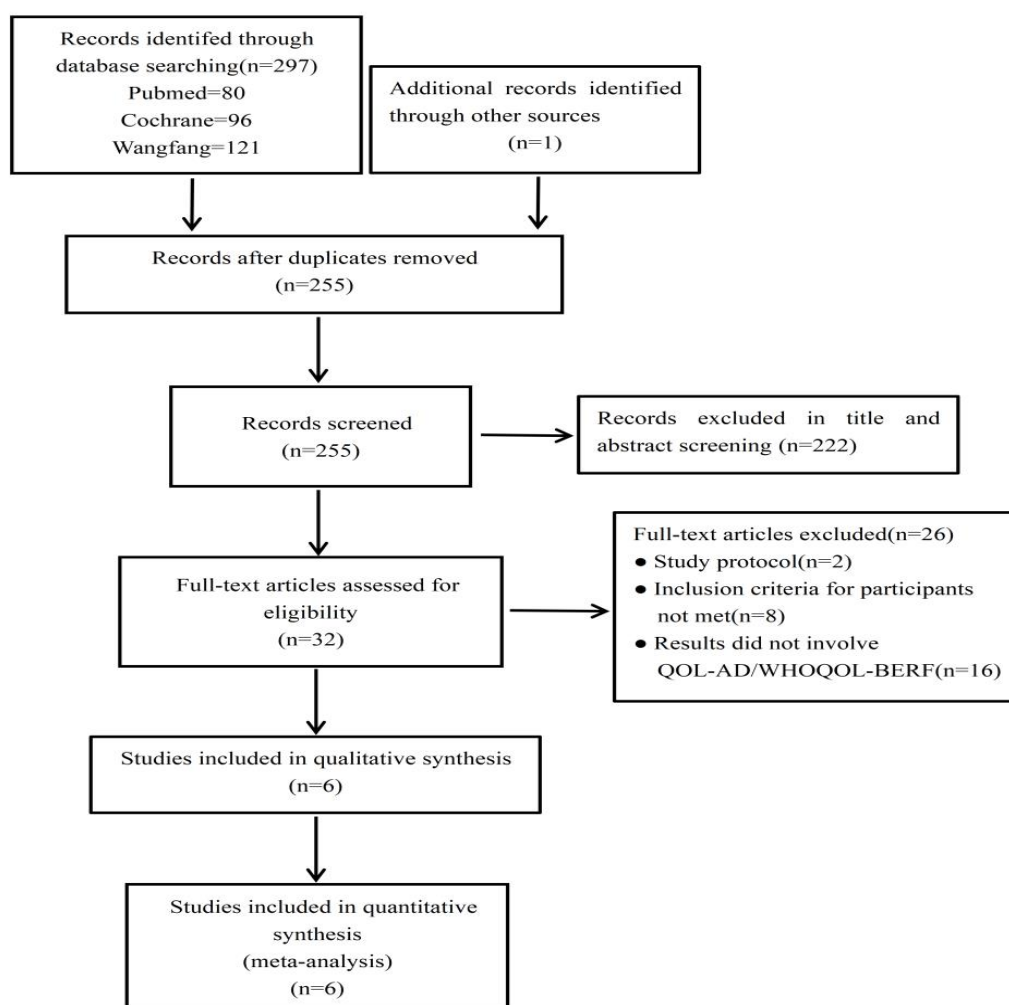

Fig. 1: Process of study selection- Flow chart of studies included and excluded

Characteristics of Included Studies- The sample size of the included RCTs ranged from 42 to 100 patients and the effect of music therapy on QOL in patients with AD was compared. The Study characteristics summarized the design of included RCTs focused on patient characteristics, the intervention methods, and the outcome assessment. Characterized studies are presented in Table 1.

Table 1: Summary of study characteristics

	Studies	Hee-Jin Kim (2015)	Wang Zhao (2018)	Wang Xiao-Hong (2019)	FU Mei-Hua (2016)	Xiao Jie-Ping（2018）	Meng Shuang (2019)
Subj	Title	Effectiveness of a community-based multidomain cognitive intervention program in patients with Alzheimer's disease	Effect of multi-sensory stimulaᵗⁱon on excitatory agitation and quality of life in patients with Alzheimer's disease	Effect of music therapy on quality of life in patients with mild to moderate Alzheimer's disease	Effects of music therapy on sleep and life quality for patients with Alzheimer's disease	Effect of Music Therapy on Sleep Quality, Life Quality, Cognitive Function and Agitation Behavior in Patients with Alzheimer's Disease	Comparison of different types of music therapy for Alzheimer's disease
	Study design	RCT	RCT	RCT	RCT	T	RCT
	Participants (N)	N=53	N=100	N=60	N=91	N=50	N=42
	Participants type	Older adults	Older adults	Older adults	Older adults	Older adults	Older adults
Design	Patient's characteristics	All dementia with CDR=1, Probable AD, excluded (not meeting inclusion criteria; declined not to want to participate)	Patients with AD, BEHAVE-AD score ≥8 points	Meets DSM-V diagnostic criteria for mild to moderate Alzheimer's	patients with AD, BEHAVE-AD score ≥8 points	patients with AD, BEHAVE-AD score ≥8 points	patients with AD, BEHAVE-AD score ≥8 points
	Groups	N=53, music interventions (n =32) Non-music interventions (n = 21)	N=100, music interventions (n =50) Non-music interventions (n=50)	N=60, music interventions (n =30) Non-music interventions (n =30)	N=91, music interventions (n =45) Non-music interventions (n =46)	N=53, music interventions (n =25) Non-music interventions (n =25)	N=42, music intervention (n =21) Non-music intervention (n =21)
	Intervention; music type	Interactive (playing melodies and/or accompanying chords for popular songs and participants were encouraged to develop musical expression and/or imitate musical rhythms)	Interactive (Music Listening/Music Performance)	Interactive (Chorus/Music Appreciation/Musical instrument)	Passive (musical backgrounds)	Interactive (Music Listening/Music recollection/Music singing)	Passive (Music Listening)
	Intervention /control (minutes/per week/ weeks)	I: Music therapy (60/5/24) C: cognitive intervention and pharmacotherapy	I: Sic therapy (40~50/3/24) C: Conventional pharmacotherapy	I: Music therapy (60/5/48) C: Routine rehabilitation activities	I: Music therapy (30/3/4) C: pharmacotherapy	I: Music therapy (40/14/16) C: Cognitive training/ pharmacoth	I: Music therapy (30/14/8) C: pharmacotherapy
	Outcome assessment	QOL-AD	QOL-AD	QOL-AD	WHOQOL-BREF	WHOQOL-BREF	WHOQOL-BREF
	Conclusion	slightly improved quality of life	improved Quality of Life	improved Quality of Life	improved Quality of Life	improved Quality of Life	improved Quality of Life

I: Intervention group; C: Control group; RCTs: Randomized controlled trials

The evaluation of the studies included in the design is shown in Table 1. These studies were generally divided into a control group (non-musical intervention) and an experimental (musical intervention) group, except for one article due to it had 3 different types of musical intervention groups. Such studies commonly used interactive ways for musical interventions, which included music listening, chorus, music performance, musical instruments and so on. The duration of treatment varies from 4 to 48 weeks. QOL-AD or WHOQOL-BERF is a common parameter used for Outcome assessment by researchers, and the conclusions supported that music therapy improved the QOL in AD patients.

Risk of Bias Assessment- Cochrane's Risk of Bias tool was used to evaluate the quality of all selected studies and the 6-literatures included in this study had different degrees of bias, with moderate literature quality. All 6 papers were RCTs and concealment of allocation scheme was reported in 6 of them; the blind method on outcome measures was performed in four articles and all six papers contain complete data results without any publication bias. The risk of bias assessment in selected and results are summarized in Fig. 2 (high, low, and unclear risk of bias were marked with red, green, and yellow respectively).

Fig. 2: Risk of bias summary: review authors' judgments on the risk bias of included studies

Effects on cognitive function were shown by using different scales as outcome measurements following the intervention

QOL-AD score- There was 3 literature of all 6 papers performed music therapy as an intervention, and the QOL-AD score in patients was evaluated before and post-intervention [23-25].

The results showed that there was statistical heterogeneity among the 3 literature (I^2= 81%, *p= 0.005*). A random-effects model was applied for the meta-analysis for selected results and showed that the QOL-AD scale score of the test group was higher than that of the control group (MD= 5.10, 95% CI: 2.95-7.24, *p<0.001*), as shown in Fig. 3.
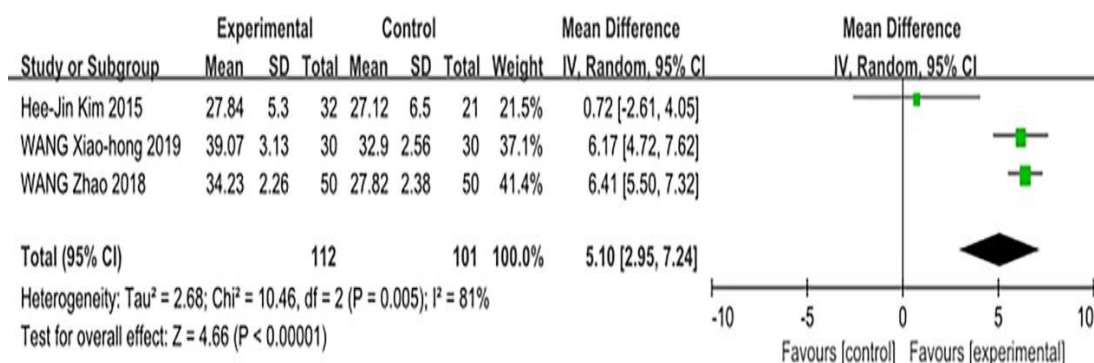
Fig. 3: Forest plot for meta-analysis of QOL-AD in patients with AD under music therapy intervention

WHOQOL-BERF score- There are three kinds of literature in which the WHOQOL-BERF score is used to evaluate whether the QOL of AD patients is improved under music interventions [26-28]. The results showed that there was heterogeneity among the 3 included literature (I^2= 85%, p=0.001) and the random-effects model was selected for meta-analysis. The results showed that the WHOQOL-BERF score of the test group was higher than that of the control group without music interventions (MD= 5.76, 95% CI: 1.59-9.92, p=0.007), as shown in Fig. 4.
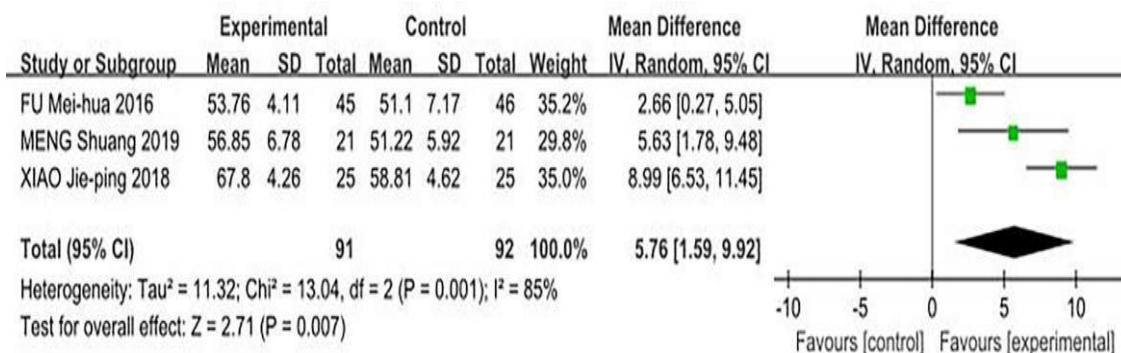

Fig. 4: Forest plot for meta-analysis of WHOQOL-BERF in patients with AD with music therapy intervention

Publication Bias- In this study, 6 articles were evaluated and the scales of QOL as outcome measurement parameters were observed for publication bias analysis. The funnel plot for the meta-analysis of the outcome is shown in Fig. 5. There are less than 10 kinds of literature included and this disadvantage might lead to publication bias potentially.

Fig. 5: Funnel plot for the meta-analysis of the mean difference of QOL change between the group's music intervention and control groups

DISCUSSION

This meta-analysis was evaluated the effectiveness of music interventions on QOL in AD patients. Six RCTs (three for QOL-AD and three for WHOQOL-BERF) were selected for narrative review and included in the meta-analysis. Music intervention as a non-pharmacological treatment for AD to improve the QOL of patients has been recognized and confirmed by many studies. There are several reasons why the QOL-AD and WHOQOL-BERF scales are used as outcome evaluation indicators in the study. First, both scales in questionnaires are widely used to measure the QOL and it is a good tool for clinical use; second, QOL-AD is a scale developed to measure the QOL of patients with dementia, which can more specifically reflect the QOL of patients with AD [29,30]. In conclusion, these two scales have some feasibility and effectiveness for the evaluation of the QOL of patients. This Meta-analysis included 6 studies: participants aged 61-90, and 55-66 were included in Wang Z and Fu's
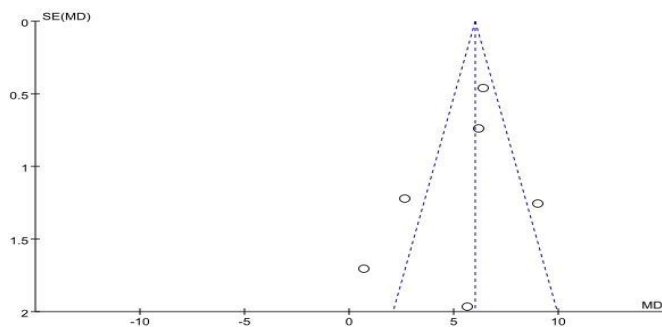
studies respectively, and they were all diagnosed with AD by ICD-10 as well as the presence of BPRS symptoms combined with BEHAVE-AD≥8 points [24,26]. The study subjects Xiao were 58-89 years old patients diagnosed with AD by clinical symptoms and BEHAVE-AD ≥8 points [27]. Subjects aged 61.5–71.5, 58–97, and ≥60 were studied in Meng, Wang Xiaohong, and Hee-Kin Jim's research, and the diagnostic methods used were the NINCDS-ADRDA criteria, DSM-V manual, and CERAD test, respectively [23,25,28]. The six articles selected in this meta-analysis have differences in the content and mode of music therapy including listening to music, music singing and instrument playing, and the main modes were interactive intervention, non-interactive intervention, short-term intervention, and long-term intervention [23]. The music therapy of all six articles included music listening, and for Meng's study, different types of music comparisons were performed indicating that Mozart and Liangzhu music could improve the quality of life of AD patients, while rock music had no significant effect. Music therapy such as music singing and instrument playing showed more effective intervention than therapy by just music listening. The interactive intervention showed more therapeutic effects than the non-interactive intervention. The long-term intervention gave a better intervention effect than the short-term according to Xiao's study [24-27]. In summary, different music types showed different effects on QOL; and the exposure of time length of music therapy interventions also has different levels of impact on the QOL in AD patients; as well as interactive interventions. A meta-analysis from six RCTs suggested that music therapies including either interactive interventions or passive interventions are effective in improving QOL in AD patients under clinical treatment. Several reasons motivated us to address the study on the effect of music therapy on cognitive status in patients with AD. Firstly, music therapy has been approved to counteract the development of dementia in recent days [31]. Meanwhile, the music intervention itself can improve cognitive function, autobiographic and memory capacity, as well as patient symptoms that occur substantial alterations, with improvements referred to agitation, apathy, depression, anxiety, mood state, and relational skills [28]. Secondly, music intervention presents significant therapeutic advantages in community situations, affecting QOL such as mood, cognition, social relations,

functional activities, energy level, and volition. The chronic diseases of older adults improved remarkably, which has the characteristics of low cost, high benefit, simplicity and easy to carry out. Most importantly, music therapy is safely combined with no obvious harmful side effects, and easier to be well integrated with health education. It also indicated that music therapy could be great and possibly be applied for AD patients' management and it is a potentially important intervention in the dynamic and continuous health management process of the elderly [29]. Due to ageing worldwide, dementia has become the fourth largest killer of geriatric diseases. The physical and mental health of the elderly should be widely concerned. Therefore, more recreational activities for the elderly should be advocated, and strategies should also be considered to avoid or reduce the occurrence of mild cognitive impairments [29-31].

This study showed that music therapy can effectively improve the QOL for the elderly, and long-term treatment for the improvement of cognitive status is effective. The beneficial effects on the physical and mental health of music therapy were supported by previous studies [32]. Santivá Santivnguage> </record></Cite></EndNote>> relieved the pain and anxiety of AD patients [33]. Benedetto AR showed that music therapy improved mental health [34]. Further studies confirmed that music therapy did significantly improve cognitive function, ADL, and mood in patients with mild to moderate AD [35]. These beneficial effects could be due to that music therapy could positively tap into the emotion and reward systems in the brain [36]. Therefore, it is undoubted that music therapy is an efficient protective factor for AD. Meanwhile, to avoid the one-sidedness of outcomes caused by a single cognitive scale, two current mainstream scales for evaluating cognitive status were analyzed and studied. Results showed that no matter which scale was applied for the evaluation of QOL outcomes the intervention group performed better results than those in the control group without music interventions. This conclusion strongly supported that music therapy improves the QOL in AD patients.

The mechanisms by which music therapy improves the QOL in AD patients are far from known, and several hypothetic mechanisms is commonly accepted are listed: 1) listening to music stimulates neurological activities

and coordinate the brainstem reticular formation by enhancing the brainstem reticular formation; 2) listening to music ameliorates the electromyogram (EMG) level of patients so that the myocardium is in a relative relaxed statues, while playing hypnotic music before bedtime relieves the tension state of AD patients, so that patients quickly get into the sleep state deeply and obtain a good sleep quality [37-39]; 3) music therapy creates a good environment for AD patients, reduces the stress response of patients, achieves the effect of self-relaxation, promotes patient relaxation and relieves anxiety, reduces annoying disordered behavior, and improves the quality of life [40]; 4) music therapy stimulates the attention of AD patients, arouses the recall past experiences of patients, and promotes the recovery of patients' long-term memory; as well as the behaviors of AD patients are greatly and mildly enhanced under the music performance, which is conducive to the recovery of patients' orientation ability, enhances patients' language ability, and promotes self-expression and coordinated communication capability [41]; 5) music therapy does significantly improve the psycho-behavioral symptoms of AD patients, thereby effectively improving their agitation behavior [42].

CONCLUSIONS

This meta-analysis was distinctive because it aimed to compare the efficacy of music interventions on QOL in AD patients. Preliminary evidence suggested that certain music interventions are effective in improving QOL in AD patients. There are various forms of music therapy, and it is believed that each individual would find a suitable music mode for their characterized treatment and this patient management strategy might greatly possibly contribute to improving the QOL in AD patients. Although we confirmed that music therapy is beneficial to AD, there are still limitations in our study. Only published kinds of literature were included in this study and there was a lack of grey literature. There was a limited amount of literature using the QOL as the outcome assessment parameter. Thus, there might be publication bias caused by insufficient kinds of literature filtration and selection. Most studies included did not report the blind method, leading to selection bias and inaccuracy of the results.

The different trainers on the intervention measurement may affect the reliability of the results individually. There is a need to conduct studies with the rigorous design of large-sample, high-quality randomized controlled trials, which should be considered to provide a reliable basis for clinical practice.

CONTRIBUTION OF AUTHORS

Research concept- Jifang Shi
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Data collection- Hongyan Shuai
Literature search- Yingzhen Su
Writing article- Yingzhen Su
Critical review- Xin Yu
Article editing- Chaochao Chen
Final approval- Xin Yu

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