**Efficacy of music-based interventions in aphasia: a Systematic Review and Meta-analysis of Randomized Clinical Trials**

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**Introduction**

Aphasia is a disorder that results in the disruption of the process of speech, including the ability to understand, speak, read, write, pay attention, memorize, among other cognitive tasks (1). Currently, there is no data about the incidence of aphasia worldwide. However, cerebrovascular accidents (CVA) or strokes are one of the main etiologies of aphasia. In a prospective study conducted in Switzerland after 1 year of follow-up, 43 of 100 000 inhabitants developed aphasia as a complication of their first CVA (2). In addition, 1 of 7 individuals under the age of 65 experienced aphasia after their first episode of stroke, and this number increased three times in subjects older than 85 years of age (2).

Aphasia has a profound effect on a patient’s quality of life and is associated with a greater impairment (3). A study conducted in a long-term care hospital in Canada evaluated patient’s perception of quality of life, sixty disease diagnoses and health conditions were analyzed. Of these conditions, aphasia was found to have the largest negative relationship to the quality of life index (4). Further, patients with aphasia after a stroke had more severe disability compared to patients with stroke and without aphasia. These disabilities included limb weakness, loss of functionality, loss of intelligence quotient (IQ) and a lower degree of recovery of social activities (3). This also had a negative impact on people around them. For example, a study conducted in England showed that 27% of caregivers of post-stroke patients with aphasia had depression versus 19% of caregivers of post-stroke patients without aphasia (3).

Due to the burden of disease on patient's family and relatives, therapies such as music-based therapy has been used as a method for improving some of the aphasia related problems. Music therapy supports patient’s rehabilitation in different ways. To illustrate, in Parkinson's disease, a rhythm-based intervention facilitates movement, start and maintenance of a constant gait (5). Furthermore, music-based therapeutic interventions work by relieving pain and psychological symptoms in patients with terminal illnesses (6). Likewise, it showed a positive trend in pulmonary function in patients with long-term neurological conditions following singing or playing a wind instrument (7).

Music therapy seems to be an effective treatment in people with aphasia (PWA), neuroimaging studies focused on the voice found that left-hemisphere had a greater activation for speech tasks, meanwhile right-hemisphere activation was associated with singing (8–10). Additionally, it is well known that singing requires activation of several areas around the temporal lobe. The superior temporal gyrus (8–11), the anterior temporal gyrus and the contiguous region of the insula (9), and the premotor cortex (8) appear to be the most crucial components of this activation.

Music-based therapy could be an effective non-invasive intervention, with a significant cost reduction and easy implementation in aphasic patients. Melodic intonation therapy, is one of the most popular music-based therapies among aphasic patients, it consists on exaggerating and transforming the natural prosody of the spoken phrase into a melodic pattern. This therapy uses two basic elements: melodic intonation and rhythm for each syllable, the patients are asked to tap the rhythm with their left hand while singing the target phrase (12).

Two systematic reviews support the effectiveness of music therapy for speech production: naming and repeating (13); as well as in reproducing specific sung phrases (14). However, both studies included aphasia due to acute brain injury or CVA, they did not include those patients with aphasia related to neurodegenerative diseases. There are only few studies targeting this population. Also, both reviews had a quite small sample size, 67 individuals in the Magee study (13) and 16 individuals in the Pierce study (14). Both included quasi-experimental studies and randomized controlled trials. Another limitation in these meta-analyses was the broad inclusion criteria (that established limitations in language, onset time in aphasia and exclusion of rhythm-based therapy without melodic component).

The aim of the present study was to evaluate the effects of music-based therapy on speech improvement, understanding, mood and emotions, social skills and quality of life in aphasic patients.

**Methods**

The study protocol manuscript is available at Universidad Peruana Cayetano Heredia (UPCH). Ethical approval was obtained from the Institutional Ethics Committee of UPCH. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist was adopted to evaluate reporting of this study. (15).

**Eligibility Criteria**

The following inclusion criteria was considered for article selection: 1) Types of participants: Studies including fluent and non-fluent aphasic population (eg Broca aphasia, Wernicke aphasia, global aphasia, driving aphasia, aphasia transcortical motor, sensory transcortical aphasia, mixed transcortical aphasia and anomic aphasia). Patients with musical experience or comorbidity were not excluded and no restrictions about etiology of the disease were made (eg stroke, neurodegenerative disease, etc.). Patients with bilateral brain lesions were excluded, because the path of recovery may be related to the recruitment of perilesional cells or via homologous regions in the right hemisphere (12,16,17). Patients with severe hearing impairment, as well as mental illness or psychiatric disorders, were also excluded. 2)Types of intervention: The intervention must meet the definition as either music-based therapy or its components, for example: melodic intonation therapy (MIT) or modified melodic intonation therapy, group and individual singing programs (eg therapeutic singing), rhythm-based therapy (eg rhythmic speech cueing - RSC), musical speech stimulation (MUSTIM), musical improvisation or vocal intonation therapy. 3) Type of interventions: the study must have any type of comparator group (eg language therapy, waiting list). 4)Variables of interest: improvement of speech, understanding, mood and emotions, social skills and quality of life. There were no restrictions on the type of instrument or questionnaire as long as these variables were measured. 5) Types of studies: Studies were eligible if they were randomized clinical trials (RCTs). There was no restriction on basis of language, follow-up time, type of publication (eg editorial, conference summary) or publication time. In addition, this meta-analysis attempts to summarize aggregate data, studies with a single patient in each group were excluded.

**information sources and search strategy**

The search strategy was designed and performed by an experienced librarian (LP). We searched the following databases from inception to February 14, 2019 in any language~~:~~ Ovid MEDLINE Epub Ahead of Print, Ovid Medline In-Process and other appointments not indexed, Ovid MEDLINE, Ovid EMBASE, Ovid PsycINFO, Ovid Cochrane Central Register of controlled trials (CENTRAL), Ovid Cochrane Database of systematic reviews and Scopus. A controlled vocabulary complemented with keywords was used to search Music therapy for PWA. (Supplement 1)

**Study selection process**

The web-based systematic review software DistillerSR (Evidence Partners, Ottawa, Canada) was used to manage the search, upload and review the references systematically (18). Retrieved titles, abstracts and full text articles were screened independently and in duplicate by two reviewers (CK, JY)

We performed a pilot-testing the eligibility criteria on a sample of 30 abstracts (selected by the principal investigator) to ensure that the articles were assessed consistently across reviewers. Subsequently, reviewers assessed the eligibility of all the articles based on the abstracts. References selected by at least one member of the review team and references without abstracts were retrieved in full text and uploaded for full-text evaluation against eligibility criteria.

In a second phase, a pilot-testing the eligibility criteria on a sample of 20 full-text articles was conducted with the same purpose. Immediately after, we started the screening of all references included. Disagreements were discussed and resolved by consensus. However, if there was no consensus, a third or fourth reviewer was consulted (OJP, GM). Cohen's Kappa coefficient for this phase was 0.71.

**Data extraction**

Reviewers independently extracted data on outcomes of interest using a pre-designed data extraction form in Microsoft Excel. Disagreements were resolved by consensus. Data included: (1) inclusion and exclusion criteria for each study (age, sex, type of aphasia, cause of aphasia, native language, history of prior language therapy and comorbidities), (2) characteristics of the intervention (number of compared interventions, type of music therapy, frequency, duration of therapy, language in which the therapy was performed, place and person who administered the therapy), (3) initial characteristics of the population included (age, sex, race, existence of comorbidities, cause of aphasia, time of installation of aphasia, level of education and previous musical experience), (4) scales, exams or questionnaires related to the variables of interest (for example: Boston Diagnosis Aphasia Examination (BDAE)), its total scores, by domain, subdomain and / or question, and finally, (5) Indicators for Risk of bias.

Since only continuous variables were considered, the mean after the intervention were extracted, as well as the mean change (mean after the intervention less mean before the intervention) in each group. If possible, mean differences between both treatments (MD) and standardized mean differences (SMD) calculated by the Cohen (or Cohen's d in English) (19) or Hedges (or Hedges' d in English) method were also extracted (20). For all variables, their standard deviations (SD) or confidence intervals (CI) were extracted. Moreover, if crossover clinical trials were included, it was planned to extract the data obtained before the group crossing and after finishing the first exposure to the intervention.

**Definition and classification of the variables of interest**

All the variables of interest were determined and defined a priori:

• Speech improvement: measures the ability to recover some extent of the oral language expression compared to the basal state of disease.

• Understanding: ability to understand what is heard, spoken or read.

• Mood and emotions: states or attitudes attributable to a given event. They are measured through scales. Eg. The Beck Depression Inventory Depression measures depression symptoms and severity.

• Social skills: aptitudes needed for communication and interaction with others. For example, developing a friendship, visiting relatives or friends, etc.

• Quality of life: perception of the patient's general well-being, including health status, independence and interpersonal relationships. This is measured through different scales. Eg Stroke and Aphasia Quality of Life Scale (SAQOL)

Due to the fact that there are different ways to measure these variables, we established a priori a method to prioritize an instrument (its domain, subdomain or question) for each one. In case of speech improvement, priority was given to the instrument, domain, subdomain or question that measured the speech capacity closest to reality, id est the ability to initiate and continue a conversation on random topics, since we consider it as the most useful ability in daily live. For example, in one study spontaneous speech was chosen rather than the repeating and imitating speech sounds or naming.

In case of understanding, priority was given to the instruments that measured patient’s ability to express and understand in real life and pragmatic situations (eg ability to understand a conversation or read news). Finally, regarding mood and emotions, they both were considered as a single one. It included depression and emotional stability; if both variables were reported, priority was given to the last one.

Subrogated or indirect variables were also extracted for exploratory purposes. These included:

(1) Speech improvement: repeating (which was also subclassified in: trained/untrained), naming, storytelling and spontaneous speech.

(2) Mood and emotions: symptoms of depression, emotional stability and energy level.

(3) Comprehension: listening and reading comprehension.

**Risk‐of‐bias assessment**

The risk of bias was assessed independently by the reviewers, using the latest Cochrane Collaboration's tool for assessing risk of bias in randomized trials “Risk of Bias 2” (ROB2) updated on March 15, 2019 (21). If possible, published protocols and RCTs records (e.g. ClinicalTrials.gov) were obtained for this evaluation. Furthermore, a pre-designed data extraction form in Microsoft Excel was generated to address the following domains: (1) Bias arising from the randomization process, (2) Bias due to deviations from intended interventions. (3) Bias due to missing outcome data, (4) Bias in measurement of the outcome (5) Bias in selection of the reported result.

The risk of bias for each domain was reported as “low risk of bias”, “some concerns” or “high risk of bias”. Each study was assessed for an overall risk of bias according to the following criteria: studies were assessed as “low risk of bias” if all individual domains were low; studies were reported as “some concerns” if at least one domain was assessed as “some concerns” and the other domains were not high risk of bias; finally, studies were “high risk of bias” if at least one domain was assessed as high. Over and above that, our study assessed the potential impact, reporting, extent, and handling of loss to follow-up, intention to treat approach, early stopping of clinical trials and other sources of bias.

one domain was assessed as unclear and the other

domains were low, and studies were high if at least one

domain was assessed as high

one domain was assessed as unclear and the other

domains were low, and studies were high if at least one

domain was assessed as high

**Statistical analysis and Synthesis of results**

All analyses were done using Stata v15.1 (Stata Corp, College Station, TX, USA). The SMD for each variable of interest was estimated by the mean and standard deviation reported after the treatment period. To calculate the SMD, we preferred the Hedge's g formula, owing to the fact that Cohen's d formula gives a biased estimate of the population effect size, especially for small samples (tending to overestimate the SMD value) (20). Standard error, variance, and confidence intervals were estimated by Hedge's g formula. These formulas are published (23). Effect sizes result were prioritized over the raw data in case they were provided in the paper. If required, SMD and confidence intervals, calculated by Cohen’s d formula, were converted into SMD and confidence intervals calculated by Hedge’s g formula (20) (23). Lastly, all SMDs were synthesized according to the random effect model or DerSimonian-Laird method (24). Subrogated variables followed the same methodology.

If a study compared two or more groups, the comparator group was defined as the most active intervention. By way of illustration, language therapy had a higher priority than observation. Therefore, two types of sensitivity analysis were considered:

1) Multi-arm clinical trials, less active or non-selected groups were included in a sensitivity analysis.

2) SMD and confidence intervals were estimated using the mean change instead of mean after the intervention period, due to the fact that these two types of measurements may generate discrepancies in meta-analysis results. This might have an impact on the conclusions and translation of the evidence into clinical practice (25). On the other hand, changes in means and standard deviations were calculated indirectly without imputations because the proposed methodology required that the correlation coefficients were 0.5 to 1 (26), and in the studies those coefficients were less than 0.5.

An SMD of 0.2, 0.5 and 0.8 were considered as a small, medium and large treatment effect, respectively (27). The inconsistency or heterogeneity in each variable of interest, not likely to occur randomly, was assessed visually through the forest plots and I2. I2 <25% was considered low inconsistency, meanwhile I2> 75% was considered high inconsistency.

We assessed whether treatment effect vary across subgroups based on: 1) Patients; onset time in aphasia (subacute <6 months and chronic> 6 months) and musical experience, and 2) interventions; rhythm and music-based therapy program and Melodic Intonation Therapy

**Assessing the Quality of Evidence**

Quality of the evidence for each variable was evaluated with the Grading of Recommendations Assessment, Development and Evaluation system (GRADE) (28). Randomized clinical trials were classified as high level of evidence prior evaluation. However, many factors may decrease the quality level of evidence of a reference: bias in study design or execution, publication bias, inconsistency of the results, inaccuracy and indirect evidence of reporting biases.

Size effect was evaluated for each domain. Each cause was classified as unlikely (not worrying), likely (worrying), or very likely (very worrying) in terms of its impact on the quality of the results. In addition, inaccuracy was defined as those studies with 95% confidence interval which did not exclude a significant benefit or harm, and those estimates whose general population was smaller than the sample needed to conduct a RCT that compared music-based therapy with another intervention (29).

Results

Study characteristics

We included seven Randomized Clinical Trials (RCT) with a total of 190 adults with aphasia (Fig. 1) (30-36). Forty one percent were women, with ages ranging between 28 and 89 years. Most of the population presented aphasia as a complication of stroke (n=189) (30-35), only one patient presented aphasia because of cerebra tumor (35). Among studies, four included only non-fluent aphasia (n=154) (30,31,33,34). In addition, all of them included only left hemisphere lesion patients (n=109) (30-36). Regarding the location, 30 patients presented Broca’s aphasia (34) and 54 patients had their basal ganglia affected (36). In terms of the period of time elapsed after the stroke, two studies were included with subacute aphasia (3 months or less) (33,34) and three studies with chronic aphasia (6 months or more) (30,31,33), with a period of time post stroke ranging between 6 hours to 14,9 years.

Of all the interventions made, four studies performed only melodic intonation therapy (n=64) (30,31,33) (one of them was adapted to Spanish) (30), another study used the modified melodic intonation therapy (n=30) (34). Moreover, other types of music-based interventions were included (n=96) (Table 1).

The global risk of bias of all the studies was high in four of them and had “some concerns” in the other three (Figure 2). It is worth noting that in the item “Risk of bias due to deviations from the intended interventions”, as neither the participants nor the trial personnel could be blinded, for being an auditory stimulus, the risk of bias increased in every study.

All the tools used to measure all the different variables are presented in Supplementary Table 2.

*“Speech improvement”*

In the seven articles included for this outcome, with 177 participants, the results found that when comparing any type of music-based therapy with different kinds of control groups, the first one moderately improves the speech in people with aphasia of any type (SMD: 0.48 95%CI: 0.18, 0.77) (Figures 3 and 6).

*Sensitivity analysis and subgroups*

Two sensitivity analysis were made for this outcome. In first place, a third group was used (waiting list) from the RCT performed by *Zumbansen et al.* (35) (SMD: 0.62, 95%CI 0.24, 1.01) (Supplementary figure 2) and in the second case, all the mean changes were analyzed for each group instead of using the mean after the treatment (SMD: 0.68, 95%CI 0.20, 1.17) (Figure 5). The direction and size effect remained the same for this outcome. On the other side, in the subgroup analysis, there was a difference between the subacute and chronic groups, while the subacute patients did showed an effect after the intervention (SMD: 0.6, 95%CI: 0.16, 1.04), the chronic group did not (SMD: 0.4, 95%CI: -0.29, 1.09)find any modifications in the effect of the therapy (Table 2, Figure 3).

Surrogate outcomes

An exploratory analysis was made, in which the music-based therapy has a positive effect on the spontaneous speech (SMD: 0.52, 95%CI: 0.21, 0.82). In addition, it seems to also improve their naming (SMD: 0.46, 95%CI: 0.12, 0.8) and repeat capacities (SMD: 0.5, 95%CI: 0.19, 0.81); nonetheless, it was very close to the lower limit or to not presenting any improvement. The same therapy seems to have no effect on motor skills of speech (SMD: 0.62, 95%CI: -0.36, 1.60) and in storytelling (SMD: 0.16, 95%CI: -0.31, 0.63) (Figure 4).

*Comprehension*

When analyzing the five studies included, with 126 people with aphasia, there was no evidence of an important effect in the improvement of comprehension in the participants who undertook a music-based therapy (SMD: 0.23, 95%CI: -0.29, 0.75) (Figure 3).

*Sensitivity analysis and subgroups*

The same as with speech improvement outcome, two sensitivity analysis were made. In the first one, a third group was used (waiting list) (35) (SMD: 0.10, 95%CI: -0.53, 0.73) (Supplementary figure 2) and the second analysis took into consideration the mean differences (SMD: 0-27, 95%CI: -0.69, 1.23) (Supplementary figure 3). Both results did not change the direction neither the size effect. Regarding the subgroup analysis for this outcome, only one characteristic seems to change the direction of the treatment effect. Music-based therapy seems to be effective in people with subacute aphasia (SMD: 0.95, 95%CI: 0.39, 1.51) and not effective in chronic aphasia patients (SMD: -0.08, 95%CI: -0.60, 0.45); the difference of SMD of both groups and their respective confidence interval is 1.03 (95%CI: 0.26, 1.80) (Table 2 and figure 3).

Surrogate outcomes

Music-based therapy may not have an effect on auditory comprehension (SMD: -0,12, 95%CI: -0.74, 0.51) nor reading comprehension (SMD: -0.17, 95%CI: -1.13, 0.79) respectively (Figure 4).

*Mood and emotions*

Only two studies with 35 people with aphasia assessed mood and emotions after the intervention. The general estimate found that this therapy has no effect on the outcomes (SMD: -0.33, 95%CI: -1.33, 0.68) (Figure 3).

*Sensitivity analysis and subgroups*

Like the other outcomes previously described, the first sensitivity analysis was made replacing one of the study groups (SMD: -0.69, 95%CI: -2.41, 1.03). While this analysis modified the size effect, it had no effect on the direction. On the other side, there was not enough information for a mean difference analysis. The subgroup analysis made was according to previous music experience and rhythm-based intervention. The results remained the same and the characteristics did not seem to alter the treatment effect (Table 2 and figure 3).

Surrogate outcomes

Music-based therapy may not have an effect on depressive symptoms (SMD: 0.15, 95%CI: -0.69, 0.99) nor emotional stability (SMD: -0.38, 95%CI: -1.23, 0.47) in people with aphasia. However, this intervention might have a negative effect on this people’s energy (SMD: -1.02, 95%CI: -1.91, -0.12) (Figure 4).

Social skills and quality of life

Social skills may not be affected after music-based intervention of people with aphasia (SMD: 0.15, 95%CI: -0.69, 0.99). Moreover, it was found that people who receive this intervention reported to have a worse quality of life than people in the comparator group (SDM: -1.76, 95%CI: -2.91, -0.62). This result is not consistent when analyzing physical health domains (SMD: -0.15, 95%CI: -0.99, 0.69) and mental health (SMD: -0.66, 95%CI: -1.53, 0.20) (Figure 5).

*Sensitivity analysis and subgroups*

Both sensitivity analysis could only be made on the outcome total quality of life. Results seem to remain equal when using the waiting list as the comparator group in Zumbansen et al. (35) (SMD: -1.04, 95%CI: -1.72, -0.36) (Supplementary figure 15). In the second sensitivity analysis, when using the mean differences, the negative effect of music-based therapy remains the same; nonetheless, part of the confidence interval moves to the effectiveness side (SMD: -0.85, 95%CI: -1.85, 0.15) (Supplementary figure 16).

Figures 2 and 3 are the summary of supplementary figures 1-16.

Discussion

A low quality of evidence (Table 3) shows a moderate effect on speech improvement when performing any music-based therapy to people with aphasia when comparing it to any other type of intervention. In addition, a very low quality of evidence finds that quality of life may be lower in patients that undergo music-based therapy than the ones who not. On the other side, there was no evidence of a clear improvement in comprehension, mood and emotions, social skills and quality of life related to mental and physical health. The exploratory analysis showed that music-based therapy might have a positive and negative effect about the spontaneous speech and energy.

There is another systematic review published on 2019 by Yang et al. ([https://sci-hub.tw/https://doi.org/10.1089/acm.2018.0479](https://sci-hub.tw/https:/doi.org/10.1089/acm.2018.0479)), which analyze the efficacy of five element music in language recovery in a population similar to ours. This study would have complemented greatly our analysis; nevertheless, none of their studies were included in our systematic review because they were all published in Chinese journals, that are not found in any of the databases we used in our search strategy.

If we observe the results of MBT on speech improvement, only two studies had a positive effect (Haro and Qiu) against the other 5, which did not have a significant effect to consider. There are also other studies with a different methodological approach, that report a significant improvement in different language skills, such as spontaneous speech (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4585219/>) in a non-controlled trial of a Melodic Rhythmic Therapy intervention in French. There is also a non-controlled trial done by Akanuma et al., in which half of the population exhibited improvements in speech after singing and naming training [https://sci-hub.tw/https://doi.org/10.3109/00207454.2014.992068](https://sci-hub.tw/https:/doi.org/10.3109/00207454.2014.992068). However, we must take into account that both of these studies did not have a control group and their population was really small.

Regarding to the effect observed in speech improvement, this is consistent with the systematic review written by *Magee et al.* in 2017 (38). However, unlike this study, which found that music-based interventions had a beneficial effect in repetition and naming; our study showed that spontaneous speech has a significant progress in this population. This ability seems to be valuable for daily life; nonetheless, has a very low quality of evidence (Supplementary table 1). On the other hand, Pierce et al. concluded that singing specific phrases improves patients’ ability to produce these better modulated phrases (14). Our study found that naming and repetition had a positive effect after a music-based intervention. Nevertheless, the lower limits of the confidence intervals are very close to interpret as no effect or harmful.

While comparing MIT with other music-based therapies, the first one does not seem to have a significant effect in speech improvement unlike the other therapies. The pathophysiology behind MIT is still unclear, nonetheless there are several theories that hypothesize the principal mechanism. It is suspected that singing and speaking are processed in both hemispheres (10) (39). Schlaug proposes four theories about MIT effectiveness: (1) reduction of speed in articulated words, (2) syllable lengthening, (3) syllable “chunking” and (4) left-hand tapping (40).

On the other side, there was not a significant effect regarding mood and emotions perceived by the patients themselves. We would fall into a wrong statement if we say MBT does not generate any emotional reaction in aphasia patients, because of the low population, we could be underestimating the effect. There is evidence that proof anxiety levels and depression are lowered by music in different clinical setting (41-43). There is an systematic review that reported a significant effect of medium-term (6-12 weeks) music based therapy intervention in reducing depression in people with dementia ([https://sci-hub.tw/https://doi.org/10.1016/j.gerinurse.2019.03.017](https://sci-hub.tw/https:/doi.org/10.1016/j.gerinurse.2019.03.017)).

We could also find a study in which patients with aphasia suggest a possible reduction in adverse mood symptoms after a choral intervention. However, there was also a reduction in the “happy” item of the Visual Analogue Mood Scale (<https://sci-hub.tw/10.3233/NRE-130916>), so further research should be made to clarify this unknown.

A negative effect was found about quality of life aphasia patients, who received MBT, perception. This has caught our attention, as there is multiple evidence that shows how music improves quality of life of different populations (44-47). However, this result could be altered by different reasons. In first place, one of the studies analyzed used a group intervention (35), in which the interpersonal relationship between the individuals may have influenced the patients’ perception of their own quality of life (48). Another factor could be the patients’ little interest on this type of therapy because it may not be gratifying for them, or their perception of not having independency during the whole therapy experience, from being taken to the place where the therapy takes place to the MBT itself (49). In addition, it is important to bear in mind the low population analyzed, as only two studies evaluated this outcome, with a total of 35 patients, for which more studies should be made.

One of our limitations was the total population size, which is really small. This might occur because most of the RCT about this topic have a low population size. That is why we strongly recommend to keep studying MBT’s effect in patients with aphasia. Nevertheless, we know, in clinical practice, it is very difficult to find homogenous populations of aphasia patients with similar specific lesions that approve to participate in these studies. Another limitation was the fact of not including 11 articles in the systematic review, due to not having the full texts, in spite of an exhaustive search and contacting the authors with no response.

On the other hand, one of our strengths would be the sensitivity analysis, which was made in one case for a third intervention arm, and the other, when mean change was used. Furthermore, ROB2 was used, that allows perform the evaluation of risk of bias easier and in a more precise way. In addition, when using Hedges, bias was reduced for having a low population.

Finally, because uncertainty is still taking over this research field, we strongly recommend to perform more studies that evaluate the different effects that MBT has on aphasia patients.

Conclusion

In summary, after having performed a systematic review of randomized clinical trials in speech improvement in aphasia patients who received MBT, we could recommend music-based therapy as a rehabilitation therapy in aphasia patients. However, it would be very important to deepen studies in this area, because of the low evidence quality. Moreover, due to our low population size, we believe further studies are needed to confirm the effect found in our study. With that said, we strongly encourage to keep studying different types of music-based therapy, because at the moment, none of them has proven to be superior to the rest of them, especially in this population.

**Annex**

Figure 1. Study Flowchart

Elegible abstracts

(n=1625)

Exclusion criteria:

Wrong study design: 10

Wrong population: 66

Wrong intervention: 30

Wrong objective: 6

Excluded

(n= 1458)

Non-available full text (n= 48)

Authors did not respond:

(n= 11)

Excluded by title screening (n=37):

Wrong study design: 4

Wrong population: 3

Wrong intervention: 1

Wrong objective: 29

Elegible full text (n = 167)

Excluded full text

(n= 112)

Papers included in cuantitative analysis (n= 7)

Table 1.Baseline Characteristics

n: total population, SD: standard deviation, NM: not mentioned, SLT: speech language therapist, MIT: Melodic Intonation Therapy, MT: music therapist.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Author’s last name, year of publication** | **Intervention** | | | | | | | | **Control** | | | | | | |
| **Name** | **Delivered by** | **Type of intervention** | **Language** | **Duration (time of duration per se)** | **n** | **Mean Age (±SD)** | **Women(%)** | **Name** | **Delivered by** | **Language** | **Duration (time of duration per se)** | **n** | **Mean Age (±SD)** | **Women (%)** |
| Haro-Martinez, 2018 | Melodic Intonation | SLT trained to deliver MIT | One to one | Spanish | 6 weeks  (6 hours) | 10 | 66 (±15) | 40 | Waiting list | One to one | NM | NM | 10 | 61 (±14) | 40 |
| Van Der Meulen, 2016 | Melodic Intonation \* | Experienced SLT TL trained to deliver MIT | One to one | Dutch | 6 weeks  (30 hours) | 10 | 58 (±15) | 30 | Waiting list | One to one | NM | NM | 7 | 64 (±13) | 43 |
| Van Der Meulen, 2014 | Melodic Intonation \* | Experienced SLT TL trained to deliver MIT | One to one | Dutch | 6 weeks  (30 hours) | 16 | 53 (±12) | 75 | Other linguistic modalities (writing, language comprehension, nonverbal communication strategies | One to one | Dutch | 6 weeks (30 hours) | 11 | 52 (±7) | 36 |
| Conklyn, 2012 | Modified Melodic Intonation \*\* | MT | One to one | English | 3 sessions (NM) | 16 | 57 (±17) | 57 | Discussion with the music therapist | One to one | English | 3 sessions (NM) | 14 | 67 (±12) | 36 |
| Raglio, 2015 | Active Music Therapy\*\*\* and Speech Language Therapy | MT | One to one | Italian | 15 weeks (22.5 hours) | 10 | 49 (±14) | 70 | SLT\*\*\* (non-verbal communication) | One to one | Italian | 15 weeks (15 hours) | 10 | 62 (±11) | 30 |
| Zumbansen, 2016 | Choral singing | Experienced choir leader | Group | FFrench | 6 months  (48 hours) | 7 | 63 (±8) | 71 | Drama Group | Group | French | 6 months  (48 hours) | 8 | 54 (±20) | 38 |
| Waiting list patients did not receive any treatment. They were not restricted to attend to other activities that were offered because of ethical reasons. | | | | 7 | 53 (±12) | 71 |
| Qiu, 2003 | Acupuncture and programmed  musical electro-acupuncture | NM | One to one | Chinese | 4 weeks (NM) | 29 | NM | NM | Occidental Medicine (intravenous medications) | One to one | Chinese | 4 weeks | 25 | NM | NM |

\*This therapy includes intoned phrases, that progress to spoken phrases; they are repeated associated to left-hand tapping.

\*\* This therapy uses complete phrases from the beginning of the intervention, such as new melodic phrases similar to the prosody of speech.

\*\*\* This therapy includes the active-intersubjective approach, based in musical improvisation (non-verbal musical aspects).

Figure 2. Risk of bias of RCT

Figure 3. Effects of MBT on speech improvement, comprehension and mood and emotions in the population and per subgroups

Table 2. Differences in effects on speech improvement, comprehension and mood and emotions according to different characteristics

|  |  |  |
| --- | --- | --- |
| **Variable** | **Subgroup** | **SMD (95% CI)** |
| Speech Improvement | Subacute aphasia (<6 months) vs.  Chronic aphasia (>6 months) | 0.69 (-0.44, 1.82) |
| Previous musical Experience vs.  Non-previous musical experience | -0.86 (-1.89, 0.17) |
| Rhythm-based therapy vs.  Non-rhythm-based therapy | 0.35 (-0.60, 1.30) |
| Melodic Intonation Therapy vs.  Non-Melodic Intonation Therapy | -0.44 (-1.20, 0.32) |
| Comprehension | Subacute aphasia (<6 months) vs.  Chronic aphasia (>6 months) | 1.03 (0.26, 1.80) |
| Previous musical Experience vs.  Non-previous musical experience | -0.47 (-1.60, 0.66) |
| Rhythm-based therapy vs.  Non-rhythm-based therapy | -0.45 (-1.65, 0.75) |
| Melodic Intonation Therapy vs.  Non-Melodic Intonation Therapy | -0.81 (-1.77, 0.15) |
| Mood and Emotions | Previous musical Experience vs.  Non-previous musical experience | -1.03 (-2.34, 0.28) |
| Rhythm-based therapy vs.  Non-rhythm-based therapy | 1.03 (-0.28, 2.34) |

Figure 4. Effects of MBT on indirect variables related to speech improvement and comprehension

Figure 5. Effects of MBT on social skills and quality of life

Table 3. Quality of Evidence of speech improvement, comprehension, mood and emotions, social skills and quality of life per group

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Variables** | **Population** | **Size effect (SMD 95%CI)** | **n (#RCT)** | **Quality of Evidence\* (important domains)** |
| Speech improvement | **Total** | 0.61 (0.21, 1.01) | 177 (7) | Low (at risk of bias) |
| Rhythm | 0.72 (0.20, 1.24) | 108 (5) | Very Low (at risk of bias) |
| Non-rhithm | 0.37 (-0.43, 1.16) | 69 (2) | Very Low (at imprecision) |
| MIT | 0.84 (0.23, 1.44) | 88 (4) | Very Low (at risk of bias) |
| Non-MIT | 0.40 (-0.07, 0.86) | 89 (3) | Very Low (at risk of bias) |
| Subacute aphasia | 1.09 (0.18, 1.99) | 81 (2) | Very Low (at imprecision and inconsistency) |
| Chronic aphasia | 0.40 (-0.29, 1-09) | 52 (3) | Very Low (at risk of bias) |
| Musical Exp. | -0.15 (-1.10, 0.81) | 15 (1) | Very Low (at imprecision) |
| Non-musical Exp- | 0.71 (0.32, 1.10) | 162 (6) | Very Low (at risk of bias) |
| Comprehension | **Total** | 0.23 (-0.29, 0.75) | 126 (5) | Very Low (at risk of bias, imprecision and inconsistency) |
| Rhythm | 0.01 (-0.49, 0.51) | 57 (3) | Very Low (at imprecision) |
| Non-rhithm | 0.46 (-0.63, 1.55) | 69 (2) | Very Low (at imprecision and inconsistency) |
| MIT | -0.04 (-0.66, 0.59) | 37 (2) | Very Low (at imprecision) |
| Non-MIT | 0.37 (-0.36, 1.10) | 89 (3) | Very Low (at imprecision and inconsistency) |
| Subacute aphasia | 0.95 (0.39, 1.51) | 54 (1) | Very Low (at imprecision) |
| Chronic aphasia | -0.08 (-0.60, 0.45) | 52 (3) | Very Low (at imprecision) |
| Musical Exp. | -0.17 (-1.13, 0.79) | 15 (1) | Very Low (at imprecision) |
| Non-musical Exp- | 0.30 (-0.29, 0.89) | 111 (4) | Very Low (at risk of bias) |
| Mood and emotions | **Total** | -0.33 (-1.33, 0.68) | 35 (2) | Very Low (at imprecision and inconsistency) |
| Rhythm | 0.15 (-0.69, 0.99) | 20 (1) | Very Low (at imprecision) |
| Non-rhythm | -0.88 (-1.88, 0.13) | 15 (1) | Very Low (at imprecision) |
| Musical Exp. | -0.08 (-1.88, 0.13) | 15 (1) | Very Low (at imprecision) |
| Non-musical Exp. | 0.15 (-0.69, 0.99) | 20 (1) | Very Low (at imprecision) |
| Social skills | **Total** | 0.15 (-0.69, 0.99) | 20 (1) | Very Low (at imprecision)\* |
| Quality of life – Mental Health |  | -0.66 (-1.53, 0.20) | 20 (1) | Very Low (at imprecision)\* |
| Quality of life – Physical Health |  | -0.15 (-0.99, 0.69) | 20 (1) | Very Low (at imprecision)\* |
| Quality of life - overall | **Total** | -1.21 (-2.13, -0.29) | 25 (2) | Very Low (at imprecision and inconsistency) |

Figure 6. Effects of MBT on speech improvement, comprehension and mood and emotions in the overall population

Supplement 1. Search Strategy

Ovid

Database(s): APA PsycInfo 1806 to May Week 1 2020, EBM Reviews - Cochrane Central Register of Controlled Trials April 2020, EBM Reviews - Cochrane Database of Systematic Reviews 2005 to May 7, 2020, Embase 1974 to 2020 May 11, Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 1946 to May 11, 2020   
Search Strategy:

|  |  |  |
| --- | --- | --- |
| **#** | **Searches** | **Results** |
| 1 | exp Aphasia/ | 57627 |
| 2 | (Acalculia or agnosia\* or Agrammatism or Agraphia\* or alogia\* or anepia\* or anomia\* or anomy or anosognosia\* or aphasia\* or "dejerine lichtheim phenomenon" or dysphasia\* or "Landau Kleffner" or "lichtheim sign" or "lichtheims sign" or logagnosia\* or logamnesia\* or logasthenia\* or "mesulam syndrome\*" or "mesulams syndrome\*" or prosopagnosia\* or "semantic dementia\*" or "temporal variant frontotemporal dementia\*" or "temporal variant FTD" or "temporal variant of frontotemporal dementia\*" or "temporal variant of FTD" or tvFTD or "Word Deaf\*").ti,ab,hw,kw. | 88391 |
| 3 | 1 or 2 | 94999 |
| 4 | exp Music Therapy/ | 15896 |
| 5 | (((auditory or acoustic) adj5 (stimulat\* or cue\*)) or ((vocal or voice) adj5 intonat\*) or (gait adj5 (puls\* or rhythm\*)) or "acousting stimulation" or chant\* or compose or composing or harmon\* or improvis\* or melodic or melodies or melody or music or musical or rhythmic\* or sing or singer\* or singing or sings or song\*).ti,ab,hw,kw. | 476392 |
| 6 | 4 or 5 | 476392 |
| 7 | 3 and 6 | 2443 |
| 8 | limit 7 to (dissertation abstract or editorial or erratum or note or addresses or autobiography or bibliography or biography or blogs or comment or dictionary or directory or interactive tutorial or interview or lectures or legal cases or legislation or news or newspaper article or overall or patient education handout or periodical index or portraits or published erratum or video-audio media or webcasts) [Limit not valid in APA PsycInfo,CCTR,CDSR,Embase,Ovid MEDLINE(R),Ovid MEDLINE(R) Daily Update,Ovid MEDLINE(R) In-Process,Ovid MEDLINE(R) Publisher; records were retained] | 107 |
| 9 | from 8 keep 58 | 1 |
| 10 | (7 not 8) or 9 | 2337 |
| 11 | remove duplicates from 10 | 1654 |

Scopus

1 TITLE-ABS-KEY(Acalculia or agnosia\* or Agrammatism or Agraphia\* or alogia\* or anepia\* or anomia\* or anomy or anosognosia\* or aphasia\* or "dejerine lichtheim phenomenon" or dysphasia\* or "Landau Kleffner" or "lichtheim sign" or "lichtheims sign" or logagnosia\* or logamnesia\* or logasthenia\* or "mesulam syndrome\*" or "mesulams syndrome\*" or prosopagnosia\* or "semantic dementia\*" or "temporal variant frontotemporal dementia\*" or "temporal variant FTD" or "temporal variant of frontotemporal dementia\*" or "temporal variant of FTD" or tvFTD or "Word Deaf\*")

2 TITLE-ABS-KEY(((auditory or acoustic) W/5 (stimulat\* or cue\*)) or ((vocal or voice) W/5 intonat\*) or (gait W/5 (puls\* or rhythm\*)) or "acousting stimulation" or chant\* or compose or composing or harmon\* or improvis\* or melodic or melodies or melody or music or musical or rhythmic\* or sing or singer\* or singing or sings or song\*)

3 1 and 2

4 DOCTYPE(ed) OR DOCTYPE(bk) OR DOCTYPE(er) OR DOCTYPE(no) OR DOCTYPE(sh)

5 3 and not 4

6 INDEX(embase) OR INDEX(medline) OR PMID(0\* OR 1\* OR 2\* OR 3\* OR 4\* OR 5\* OR 6\* OR 7\* OR 8\* OR 9\*)

7 5 and not 6