

Ł Bieleninik, M. Geretsegger, K. Mössler, J. Assmus, G. Thompson, G. Gattino, C. Elefant, T. Gottfried, R. Iglizzi, F. Muratori, F. Suvini, J. Kim, M.J. Crawford, H. Odell-Miller, A. Oldfield, O. Casey, J. Finnemann, J. Carpenter, [AL. Park](#), E. Grozzi, C. Gold, for the TIME-A study team

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Effects of improvisational music therapy versus enhanced standard care on symptom severity among children with autism spectrum disorder: The TIME-A randomized clinical trial

Lucja Bieleninik¹, Monika Geretsegger¹, Karin Mössler¹, Jörg Assmus¹, Grace Thompson², Gustavo Gattino^{3,4}, Cochavit Elefant⁵, Tali Gottfried⁶, Roberta Iglizzi⁷, Filippo Muratori^{7,8}, Ferdinando Suvini⁷, Jinah Kim⁹, Mike J. Crawford¹⁰, Helen Odell-Miller¹¹, Amelia Oldfield¹¹, Órla Casey¹¹, Johanna Finnemann^{11,12}, John Carpentre¹³, A-La Park¹⁴, Enzo Grossi¹⁵, & Christian Gold¹, for the TIME-A study team

¹GAMUT – The Grieg Academy Music Therapy Research Centre, Uni Research Health, Uni Research, Bergen, Norway

²Melbourne Conservatorium of Music, The University of Melbourne, Melbourne, Australia

³Department of Communication and Psychology, Aalborg University, Aalborg, Denmark

⁴Postgraduate Program in Child and Adolescent Health, Faculty of Medicine, Rio Grande do Sul Federal University, Porto Alegre, Brazil

⁵School for Creative Arts Therapies, University of Haifa, Haifa, Israel

⁶M.A.A.T, Music-Therapy Program, David-Yelin College, Jerusalem, Israel

⁷IRCCS Stella Maris Foundation, Pisa, Italy

⁸Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy

⁹Jeonju University, Jeonju, South Korea

¹⁰Centre for Psychiatry, Imperial College London, London, UK

¹¹Anglia Ruskin University, Cambridge, UK

¹²Department of Psychiatry, University of Cambridge, Cambridge, UK

¹³The Rebecca Center for Music Therapy at Molloy College, Rockville Centre, NY, USA

¹⁴PSSRU, LSE Health and Social Care, The London School of Economics and Political Science, London, UK

¹⁵Villa Santa Maria Institute, Tavernerio, Italy

Address correspondence to: Christian Gold, GAMUT – The Grieg Academy Music Therapy Research Centre, Uni Research Health, Uni Research, Postbox 7805, 5020 Bergen, Norway. Email: christian.gold@uni.no. Phone: +47-97501757.

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Authors' contributions: MG and CG conceived the study and developed the study design. LB, MG, and CG drafted the manuscript, while CG led the writing of the report. JA

and CG did the statistical analyses; MJC, JF, ALP, and EG provided additional input on statistical analyses. LB coordinated data collection. MG, KM, GT, GG, CE, TG, FM, FS, JK, MJC, HOM, AO, ÓC, JF, and JC contributed to data collection. All authors contributed to data interpretation and revision of the draft, and all have seen and approved the final version.

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Australia: Anna-Lee Robertson, Jo Rimmer, G.T. (music therapists); Melina Roberts (clinical assessor); G.T. (parent counselor).

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Key points

Question: Does improvisational music therapy improve symptom severity of children with autism spectrum disorder?

Findings: In the TIME-A trial of 364 children in nine countries, mean changes of autism severity were not significantly different in those randomized to improvisational music therapy compared to enhanced standard care, which included parent counseling and other available interventions.

Meaning: In children with autism spectrum disorder, music therapy did not result in marked improvements of mean symptom scores compared to enhanced standard care.

Abstract

Importance: Music therapy may facilitate skills in areas affected by autism spectrum disorder (ASD) such as social interaction and communication.

Objective: To evaluate effects of Improvisational Music Therapy (IMT) on generalized social communication skills of children with autism spectrum disorder (ASD).

Design, setting, and participants: Assessor-blinded, international, multicenter, randomized clinical trial, conducted in nine countries, of children aged 4 to 7 years with ASD. Recruitment November 2011 to November 2015; follow-up January 2012 to November 2016.

Interventions: Enhanced standard care (ESC; usual care plus parent counseling) versus ESC plus IMT (1 or 3 sessions per week), allocated in a 2:1:1 ratio.

Main outcomes and measures: The primary outcome was symptom severity at 5 months, based on the Autism Diagnostic Observation Schedule (ADOS), Social Affect domain (range 0 to 27; higher scores representing greater severity; minimal clinically important difference 1). Prespecified secondary outcomes included parent-rated social responsiveness (Social Responsiveness Scale, SRS) and five SRS subscales. All outcomes were also assessed at 2 and 12 months.

Results: Among 364 participants who were randomized (mean age 5.4 years; 83% boys), 314 (86%) and 290 (80%) completed the primary and the last endpoint, respectively. Over 5 months, those assigned to IMT received a median of 19 IMT, 3 parent counseling, and 36 other therapy sessions, compared to 3 parent counseling and 45 other therapy sessions in those assigned to ESC. From baseline to 5 months, mean scores of ADOS Social Affect decreased from 14.08 to 13.23 in the IMT group and from 13.49 to 12.58 in the ESC group (mean difference, IMT vs. ESC: 0.06, 95% CI -0.70 to 0.81; P=0.900), with no significant difference in improvement. Of six prespecified secondary outcomes, four showed no significant difference. IMT was associated with greater improvements than ESC in motivation

at 5 months (mean difference, IMT vs. ESC: -0.99, 95% CI -1.97 to -0.01; P=0.050), mannerisms at 2 months (mean difference, IMT vs. ESC: -1.2, 95% CI -2.39 to -0.02; P=0.048), and mannerisms at 12 months (mean difference, IMT vs. ESC: -1.19, 95% CI -2.37 to -0.01; P=0.049). Low-intensity IMT was associated with greater improvements than ESC in awareness at 2 months (mean difference, IMT vs. ESC: -0.88, 95% CI -1.74 to -0.03; P=0.044). High-intensity IMT was associated with greater improvements than ESC in mannerisms at 5 months (mean difference, IMT vs. ESC: -1.93, 95% CI -3.37 to -0.48; P=0.009).

Conclusions and relevance: Among children with autism spectrum disorder, improvisational music therapy, compared with enhanced standard care, resulted in no significant difference in symptom severity based on the ADOS Social Affect domain at 5 months. These findings do not support the use of IMT for symptom reduction in children with autism spectrum disorder.

Trial registration: ISRCTN registry number: ISRCTN78923965.

1. Background

Autism spectrum disorder (ASD) is characterized by persistent deficits in social communication and interaction and restricted, repetitive behaviors and interests.¹ ASD affects about 1% of the general population and is associated with substantial disability and economic loss across the lifespan.^{2,3} A variety of approaches to improve the core deficits and the lives of people with ASD have been developed, including behavioral, developmental, educational, and medical interventions,^{4,5} but the strength of evidence for most interventions is low and only some of the many suggested approaches hold promise for reducing autism severity.⁴

In the first description of autism, Kanner⁶ noted that many children with autism had a strong preference for music. Music therapy seeks to exploit the potential of music as a medium for social communication,⁷ in analogy to preverbal mother-infant dialogues.^{8,9} In 2017 there were about 7000 music therapists in the United States¹⁰ and 6000 in Europe.¹¹ In improvisational music therapy (IMT), client and therapist spontaneously create music using singing, playing, and movement; music is understood in the widest sense. IMT can be described as a developmental, child-centered approach where a trained music therapist follows the child's focus of attention, behaviors, and interests to facilitate development in the child's social communicative skills and related areas.¹² Randomized trials of limited methodological quality have suggested positive effects of music therapy on social interaction, joint attention, and parent-child relationships.¹³ Evidence on longer-term effects and dose-effect relations is lacking, and evidence that effects observed within therapy sessions generalize to other settings, situations and people needs confirmation.¹³ The objective of this study was to evaluate effects of IMT on generalized social communication skills of children with ASD.

2. Methods

2.1. Trial design

The Trial of Improvisational Music therapy's Effectiveness for children with Autism (TIME-A) was an assessor-blinded, international, multicenter (10 centers), parallel, pragmatic randomized clinical trial that compared IMT added to enhanced standard care (ESC; usual care plus parent counseling) with ESC alone for improving social communicative skills in children with ASD. Ethics approval was obtained by the relevant ethics committees in each of the nine countries worldwide (Australia, Austria, Brazil, Israel, Italy, Korea, Norway, UK, USA). Written informed consent was obtained from parents/guardians. An independent data monitoring committee monitored safety and examined interim efficacy results. Details of trial procedures are published in the study protocol¹⁴ and available in Supplement 1.

2.2. Participants and trial procedures

Trial procedures were piloted to ensure feasibility.¹⁵ Children aged 4 years to 6 years and 11 months meeting criteria for ASD according to ICD-10¹⁶ were enrolled between November 2011 and November 2015 and followed up from January 2012 to November 2016. They were eligible if they were not affected by serious sensory disorders (blindness, deafness) and had not received music therapy in the last 12 months. Clinical diagnosis was confirmed using the ASD cut-off of the Autism Diagnostic Observation Schedule (ADOS)¹⁷ and cut-offs on two of the three main domains of the Autism Diagnostic Interview-Revised (ADI-R).¹⁸ Cognitive ability was assessed using the Kaufman Assessment Battery for Children (K-ABC)¹⁹ or another IQ test, or by clinical judgment when the child was unable to complete a formal test. Participating parents/guardians completed the Social Responsiveness Scale (SRS)²⁰ and two 100mm visual analog scales for quality of life of the participant and the family. Demographic characteristics and information on concomitant treatments were also

collected from parents. Follow-up assessments at 2, 5, and 12 months after randomization included ADOS, SRS, quality of life, and concomitant treatments; at 12 months we also assessed success of blinding and reason for potential drop-out.

After consent and baseline assessments, participants were randomly assigned to one of three conditions: low-intensity IMT (once per week) plus ESC, high-intensity IMT (three times per week) plus ESC, or ESC alone over a period of five months. Participants were free to attend any type of treatment or therapeutic interventions, but were asked not to attend music therapy outside the study context.

Individuals were randomly assigned according to a computer generated randomization list with a ratio 1:1:2 (low-intensity IMT : high-intensity IMT : ESC), stratified by site and with randomly varying block sizes of 4 and 8, which was prepared by an investigator with no clinical involvement. When site investigators had enrolled a new participants, a coordinator (LB) with no clinical involvement checked eligibility and baseline data before handing out the randomization via an online system.

All data were stored on an electronic database management system on a secure server with password-controlled access (OpenClinica, version 3.3) and double-entered independently. Changes to the protocol compared to its published version are shown in Table S1.

2.3. Interventions

Improvisational Music Therapy (IMT)

IMT was offered in outpatient settings (clinics, kindergartens, family homes) in 30-minute one-to-one sessions (possibly joined by family members). Depending on the randomization to high- or low-intensity IMT, either one or three weekly sessions were offered for a period of five months. IMT was conducted by 30 qualified music therapists (21 female;

mean age 34.7 years, range 23 to 55 years; mean experience as music therapists 7.3 years, range 0 to 30 years) with clinical experience of working with children with ASD. IMT was conducted in accordance with eight consensus principles described in detail separately¹² and summarized in Table S4. Therapists developed joint musical activities (singing or instrumental play) individually with each child, based on the child's focus of attention, using improvisation techniques such as synchronizing, mirroring, or grounding. These activities aimed to develop and enhance affect sharing and joint attention, which are associated with development of social competencies in ASD.¹⁴ Sessions were videotaped or audiotaped for independent fidelity assessment.^{12,14}

Enhanced Standard Care (ESC)

ESC consisted of the routine care available at the site plus three 60-minute sessions of parent counseling (at intake and after 2 and 5 months), based on general principles described in the protocol.¹⁴ Parent counseling was conducted by 24 parent counselors experienced with ASD (20 female; clinical psychologists, social workers, or music therapists) in accordance with the study protocol.¹⁴ Sessions were videotaped when possible.

2.4. Outcomes

The primary outcome was the Social Affect (SA) score of the ADOS,¹⁷ a measure of autism symptom severity, at 5 months. The ADOS is a semi-structured, standardized observation instrument designed to assess autism symptoms. It is regarded as the gold standard of ASD diagnosis²¹ and has also been used in intervention trials.²²⁻²⁷ In the population relevant for this trial, one of three modules and one of five scoring algorithms is chosen, depending on language abilities and age. Of a total of 28 to 31 ADOS items, 10 are used to calculate the ADOS SA score. Items can range from 0 to 2 or 3; in line with an earlier trial,²⁷ the full range of item scores from 0-3 was retained to improve sensitivity to change.

We applied the same module across time points for each child to ensure consistency.¹⁴ The ADOS SA score, constructed as the sum of the relevant items for the Social Affect domain, can range from 0 to 27 (module 3; 0 to 24 in modules 1 and 2), with higher scores indicating greater severity. We assumed a minimal clinically important difference (MCID) of 1 point, corresponding to a small effect size (Cohen's $d=0.2$, assuming $SD=5$).¹⁴ We used the most current version available in all countries/languages.¹⁷ A later revised version, the ADOS-2, was not used because it had not been translated into all relevant languages. Similarly, formal training in ADOS assessments was available in some but not all countries. All assessors in Australia, Korea, and the UK had completed research level qualification (the highest level); those in Israel, Italy, Norway, and the USA had at least clinical level qualification (the basic level). In Austria and Brazil, no certification was available, but we used experienced ADOS raters. Of the 23 assessors, 10 had research training and 10 had clinical training. We used assessors from different location who were not normally involved with the child to ensure blinding. Success of blinding was verified by asking assessors if and how they had discovered the child's allocation.

Prespecified secondary outcomes

Secondary outcomes were the Social Responsiveness Scale (SRS) total scale and its five subscales. The SRS is a parent-rated measure and was therefore not blinded. A total of 65 items (each ranging from 0 "not true" to 3 "almost always true") assess the severity of ASD symptoms occurring in natural social settings, as observed by parents, for a total score of 0 to 195. A score of 85 or above provides strong evidence of the presence of an ASD and is recommended for clinical settings, whereas lower cutoffs are recommended for screening.²⁰ The subscales social awareness, social cognition, social communication, social motivation, and autistic mannerisms include 8 to 22 items each.²⁰ Secondary time points were two and

twelve months after randomization. An additional outcome, cost-effectiveness, will be reported separately.

Additional exploratory outcomes

Not mentioned in the original protocol, we also analyzed as additional exploratory outcomes: the ADOS total score and subscales; two 100mm visual analogue scales for quality of life of the child and of the family as a whole (0 = worst to 100 = best possible quality of life); and adverse events.

2.5. Sample size and power

The study was originally conceived as a group sequential design with four interim analyses to detect an MCID of 1 point on ADOS SA,¹⁴ but was stopped after the first prespecified analysis (see Results). As conducted, it had 42% power to detect a difference of 1 point, or 80% power for a difference of 1.6 points.

2.6. Statistical analyses

The main statistical analysis¹⁴ followed the intention-to-treat (ITT) principle as closely as possible by including all participants who had data of at least one follow-up time point in the group to which they had originally been randomized. Analyses compared mean change on the primary outcome in longitudinal models, following confirmation of normality. We calculated linear mixed effects models (LMEs) with maximum likelihood estimation, both unadjusted and adjusted for site as a random effect, for the main two-arm comparison and the three-arm comparison including intensity of IMT, with treatment effects represented as interaction effects (time x group). Sensitivity analyses for the primary outcome and comparison tested the influence of missing data (linear models on 50 data sets multiply imputed using diagnosis, age, and site) and therapist effects (LME with music therapist as a random effect nested within site). Prespecified subgroup analyses were conducted for sex and ASD subtype using linear models with interaction tests.

Secondary outcomes were analyzed using LMEs. Because no adjustments for multiple testing were made, all secondary outcomes (both prespecified and other) were regarded as exploratory. No statistical analysis was conducted for exploratory adverse events.

In a post hoc “responder analysis”²⁸ we compared the proportion of participants who improved by at least the MCID on the primary outcome. In this binary ITT analysis, we included all participants randomized, assuming no improvements for missing data. We calculated risk ratios with two-sided 95% confidence intervals using Wald unconditional maximum likelihood estimation for the ITT sample, the per-protocol sample, and exploratory subgroups (sex, age, ASD subtype, verbal ability, symptom severity, cognitive ability, country, time of enrolment). All tests were two-sided with a significance level of 5%. All statistical analyses were conducted using R version 3.3.1 (www.r-project.org). Individual patient data are available with this article (supplemental material).

3. Results

3.1. Recruitment and study population

Of 702 children who were assessed for eligibility, 315 (109 ineligible; 206 declined) were excluded prior to baseline assessments and another 23 were found ineligible at baseline, before randomization. A total of 364 participants were randomized to IMT or ESC (182 participants each; Figure 1). Of the 182 children enrolled to IMT, 90 were randomized to high-intensity IMT and 92 to low-intensity IMT. The data monitoring committee monitored safety regularly and examined the first interim efficacy analysis in September 2015. Although the formal criterion for early stopping was not met, the study team decided to stop recruitment, in a decision that included considerations of limited funding and therefore limited likelihood of successful and timely additional recruitment. Baseline characteristics were well balanced between conditions (Table 1; Table S2). Of the 364 participants, 302 were

male; 301 were diagnosed with childhood autism; 165 had low cognitive levels (IQ < 70). Twelve participants (3%) had prior experience of music therapy. Fifty participants (14%) were lost to the five-month follow-up (Figure 1). Baseline characteristics of those who dropped out at 5 months were similar to those who were followed up (Table S3).

Blinding of assessors was broken unintentionally in 20 participants (15 in IMT and 5 in ESC), usually due to a parent or other person inadvertently mentioning the intervention. There was no evidence of broken or subverted allocation concealment (Figure S1).

3.2. Interventions: Uptake and fidelity

Concomitant interventions, provided as part of ESC, included speech and language therapy or communication training (58%), sensory-motor therapy (incl. occupational and physiotherapy; 41%), and a number of other therapies (Table S2). These therapies often continued over the course of the trial (Table S2) The median number of sessions of all concomitant interventions (not including parent counseling or IMT) over the 5-month intervention period was 45 in those allocated to ESC, compared to 36 in those allocated to IMT (high-intensity IMT: 31; low-intensity IMT: 40). The parents of 317 (87%) of all participants participated in counseling; the median number of sessions was 3 in all groups (Figure 1).

Of those allocated to IMT, 171 (94%) received IMT, with a median of 19 sessions over the 5-month period (high-intensity IMT: 34; low-intensity IMT: 15; Figure 1). Missed sessions were typically due to holidays or illness (patterns of sessions per week, see Figure S2). However, depending on the setting and circumstances, some parents had difficulties with bringing their child to therapy three times a week. Treatment fidelity according to the IMT manual ¹² was adequate in the great majority of sessions: Two independent raters agreed that 93% (565 of 606 randomly selected 3-minute segments from 63 participants) were conducted

adequately (rater 1: 604/606, 100%; rater 2: 566/606, 94%; results of each principle, see Table S4). Of those allocated to ESC, none received IMT during the 5-month intervention period. However, 1% in each group received music therapy outside the study before the 12-month follow-up (Figure 1).

3.3. Effects of IMT versus ESC on Social Affect at 5 months:

Prespecified analyses of the primary outcome

From baseline to 5 months, mean scores of ADOS Social Affect decreased from 14.08 to 13.23 in the IMT group and from 13.49 to 12.58 in the ESC group (mean difference, IMT vs. ESC: 0.06, 95% CI -0.70 to 0.81; $P=0.900$; Table 2, upper left part), with no significant difference in improvement. Differences in the models adjusted for site were also showed non-significant (Table S5). In the three-arm comparison, no significant differences were found between high- or low-intensity IMT and ESC (Table 2 lower left part; adjusted model see Table S6). Changes over time are shown in Figure 2. Prespecified subgroup analyses did not suggest different effects of IMT versus ESC due to sex ($P=0.4372$) or ASD subtype ($P=0.871$).

3.4. Effects of IMT versus ESC on Social Affect at 2 and 12 months

No significant differences between IMT and ESC, or between high- or low-intensity IMT and ESC, were observed (Table 2, Figure 3).

3.5. Effects of IMT versus ESC: Prespecified secondary outcomes

Of six prespecified exploratory secondary outcomes, four showed no significant difference (Tables S5, S6). SRS total scores are shown in Table 2 and Figure 2. Of the SRS subscales, IMT was associated with greater improvements than ESC in motivation at 5

months (mean difference, IMT vs. ESC: -0.99, 95% CI -1.97 to -0.01; P=0.050), mannerisms at 2 months (mean difference, IMT vs. ESC: -1.2, 95% CI -2.39 to -0.02; P=0.048), and mannerisms at 12 months (mean difference, IMT vs. ESC: -1.19, 95% CI -2.37 to -0.01; P=0.049). Low-intensity IMT was associated with greater improvements than ESC in awareness at 2 months (mean difference, IMT vs. ESC: -0.88, 95% CI -1.74 to -0.03; P=0.044). High-intensity IMT was associated with greater improvements than ESC in mannerisms at 5 months (mean difference, IMT vs. ESC: -1.93, 95% CI -3.37 to -0.48; P=0.009).

3.6. Effects of IMT versus ESC on Social Affect at 5 months: Exploratory analyses

No significant difference between IMT and ESC was seen in the sensitivity analysis using multiple imputation (mean difference, IMT vs. ESC: 0.06, 95% CI -0.61 to 0.72; P=0.871) or including the music therapist as a random effect (mean difference, IMT vs. ESC: 0.05, 95% CI -0.71 to 0.80; P=0.904).

Exploratory responder analyses indicated a 25% higher proportion of improved cases on ADOS Social Affect at 5 months in IMT (95/182, 52%) than in ESC (76/182, 42%; risk ratio 1.25, 95% CI 1.00 to 1.56, P=0.047; Figure 3). Those who received at least 15 IMT sessions had a 39% higher rate of improvement than those in ESC (risk ratio 1.39, 95% CI 1.11 to 1.74, P=0.004; Figure 3). Among relevant clinical subgroups, males, those with childhood autism, and those with low IQ showed statistically significant effects (all P<0.05; risk ratios 1.28 to 1.43; Figure 3).

3.7. Effects of IMT versus ESC: Additional exploratory outcomes

Mean changes in participants' quality of life at 5 months were more positive in high-intensity IMT than in ESC (mean difference 4.40, 95% CI 0.38 to 8.43, P=0.033; Table S6).

No significant differences were seen at other time points, in family quality of life, ADOS total, or any of the other ADOS subscales (Tables S5, S6).

3.8. Adverse events

Hospitalization or other institutional stay was rare at baseline (9 assigned to IMT and 3 assigned to ESC had an institutional stay during the last two months). During participation in the study, these rates remained stable in ESC (3, 3, and 4; at 2, 5, and 12 months, respectively) and decreased in IMT (6, 6, and 4). These institutional stays were typically planned and short-term. No other adverse events or serious adverse events were reported.

4. Discussion

4.1 Interpretation of findings

In this international, multicenter clinical trial of children with autism spectrum disorder, improvisational music therapy added to enhanced standard care, compared with enhanced standard care, resulted in no significant difference in symptom severity based on the ADOS Social Affect domain at 5 months. In addition, the amount of improvement in both groups was small, and less than the minimal clinically important difference, suggesting that use of IMT for children with ASD may not lead to meaningful improvement in symptom severity and may not be warranted for improving autistic symptoms.

Most of the exploratory secondary outcomes were also non-significant. Observed differences in social motivation and autistic mannerisms may be due to chance because no multiplicity adjustments were made and were not blinded. The exploratory finding of a higher proportion of responders in IMT compared to ESC should be interpreted with caution and may be biased by differential attrition. No dose effect was found in the prespecified analyses.

The findings of the present study contrast with those of previous studies. A systematic review of ten clinical trials concluded that music therapy may help children with ASD to improve skills in areas constituting the core of the condition.¹³ It may be that music therapy in this international multicenter trial was not applied as consistently as in earlier local trials. Alternatively, it may be that previous trials were more successful in matching therapy procedures and outcomes. Methodological limitations may also be an explanation.

None of the previous music therapy trials focused on blinded assessment of core symptoms as measured by the ADOS. Designed as a diagnostic measure, this outcome is hard to change.²⁹ Few studies have rigorously demonstrated effects of psychosocial interventions on generalized behaviors⁴ using blinded assessments based on the ADOS. An intervention focused on parents was found efficacious in a small pilot trial in the UK,²² but in a subsequent multicenter trial, effects were not apparent until five years after randomization.^{25,27} A multicenter trial in the US of another parent-mediated intervention observed categorical effects on autism severity²⁶ but cautioned that such effects did not match clinical experience. Among unblinded studies using ADOS, one found effects of a teacher-directed intervention on autism severity,²⁴ whereas another did not find such effects for a child-focused developmental intervention, even with more than 1000 treatment hours per child.²³

The number of treatment hours continues to be an important topic in autism intervention research. Early claims suggesting benefits with early intensive behavioral intervention have not stood up to rigorous randomized evaluations.^{23,30} The burden associated with attending therapy sessions also needs to be considered. In this study, those assigned to IMT tended to receive fewer other therapies, possibly in response to the additional offer. Furthermore, not all participants were able to attend IMT as frequently as planned. This may raise the question how the mode of delivery can be improved to facilitate attendance.

Although the present trial did not capture the child's experience with IMT, it seemed very well accepted by parents, children and staff. In a qualitative study connected to this trial, parents reported their children's enjoyment and benefit from IMT and experienced their own involvement as positive.³¹ Developing a consensus regarding principles of IMT ensured some consistency across countries, but more work will be needed to improve IMT. Current efforts to improve IMT range from improving therapists' ability to attune optimally to the child³² to including family members more actively.³³

4.2 Strengths and limitations

In comparison to previous smaller studies of music therapy for children with ASD,¹³ the present trial was more generalizable. Inclusion criteria were broad, exclusion criteria minimal; ESC was flexible, including a broad and often intensive mix of interventions; IMT was delivered by a number of therapists across countries in accordance with international consensus guidelines;¹² outcomes were assessed in generalized settings and over a longer time frame. The large sample size and the blinded assessment of core features are further strengths of this study compared to other trials in autism.

The study was planned with a group sequential design with the possibility of increasing the sample to about 1000 to reliably detect a minimal clinically important difference,¹⁴ but was stopped early. However, the narrow confidence interval around the mean difference may ameliorate concerns about insufficient power.

The duration of intervention and follow-up may have been too short. In routine practice, music therapy for children with ASD is often continued for years rather than months. Also other interventions for ASD needed five years to show effects on ASD severity.²⁵ In a qualitative study, families who participated in music therapy reported continued benefit after several years³³. In addition, outcomes concerning wellbeing and adaptive functioning – being able to engage in learning, participate successfully in school through childhood and

adolescence, and being able to work and have meaningful relationships as adults – may matter more to people with ASD than reducing severity.³⁴ Although this study did attempt to involve users to some extent, active involvement in choosing outcomes might improve the relevance of future studies further.

4.3 Conclusions

Among children with autism spectrum disorder, improvisational music therapy, compared with enhanced standard care, resulted in no significant difference in symptom severity based on the ADOS Social Affect domain at 5 months. These findings do not support the use of IMT for symptom reduction in children with autism spectrum disorder.

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Tables

Table 1 . Baseline characteristics of the sample

Characteristics	Randomized to ESC		Randomized to high-intensity IMT		Randomized to low-intensity IMT	
	N	Value	N	Value	N	Value
Age (years) ¹	182	5.4 (0.9)	90	5.4 (0.9)	92	5.5 (0.8)
Sex (m) ²	182	149 (81.9%)	90	78 (86.7%)	92	71 (77.2%)
Native speaker of the country's main language ²	182	152 (83.5%)	90	78 (86.7%)	92	74 (80.4%)
Education mother ²	180		89		89	
<12years		17 (9.4%)		9 (10.1%)		10 (11.2%)
≥12years		64 (35.6%)		37 (41.6%)		31 (34.8%)
University		84 (46.7%)		38 (42.7%)		42 (47.2%)
Unknown		15 (8.3%)		5 (5.6%)		6 (6.7%)
Education father ²	178		87		89	
<12years		27 (15.2%)		11 (12.6%)		12 (13.5%)
≥12years		54 (30.3%)		33 (37.9%)		28 (31.5%)
University		77 (43.3%)		34 (39.1%)		40 (44.9%)
Unknown		20 (11.2%)		9 (10.3%)		9 (10.1%)
Employment mother ²	180		89		89	
Unemployed or social support		29 (16.1%)		10 (11.2%)		9 (10.1%)
Working part-time		41 (22.8%)		29 (32.6%)		22 (24.7%)
Working full time		36 (20%)		13 (14.6%)		18 (20.2%)
Homemaker		61 (33.9%)		30 (33.7%)		32 (36%)
Other		2 (1.1%)		3 (3.4%)		2 (2.2%)
Unknown		11 (6.1%)		4 (4.5%)		6 (6.7%)
Employment father ²	179		88		89	
Unemployed or social support		7 (3.9%)		9 (10.2%)		3 (3.4%)
Working part-time		11 (6.1%)		5 (5.7%)		2 (2.2%)
Working full time		136 (76%)		58 (65.9%)		70 (78.7%)
Homemaker		2 (1.1%)		0 (0%)		3 (3.4%)
Other		5 (2.8%)		4 (4.5%)		2 (2.2%)
Unknown		18 (10.1%)		12 (13.6%)		9 (10.1%)
Adults in the household ²	174		87		84	
1 adult		21 (12.1%)		17 (19.5%)		9 (10.7%)
2 adults		137 (78.7%)		62 (71.3%)		72 (85.7%)
>2 adults		16 (9.2%)		8 (9.2%)		3 (3.6%)
Siblings in the family ²	172		87		83	
No siblings		56 (32.6%)		16 (18.4%)		18 (21.7%)
1 sibling		77 (44.8%)		43 (49.4%)		43 (51.8%)
>1 sibling		39 (22.7%)		28 (32.2%)		22 (26.5%)
Diagnosis ²	182		90		92	
Childhood autism (ICD-10 code F84.0)		151 (83%)		78 (86.7%)		72 (78.3%)
Atypical autism (ICD-10 code F84.1)		3 (1.6%)		0 (0%)		0 (0%)
Asperger's syndrome (ICD-10 code F84.5)		8 (4.4%)		2 (2.2%)		4 (4.3%)
PDD (ICD-10 code F84.9) ³		20 (11%)		10 (11.1%)		16 (17.4%)
Previous MT, (>12 months ago) ²	177	8 (4.5%)	89	7 (7.9%)	90	1 (1.1%)

ADOS module ²	182		90		92	
Module1		103 (56.6%)		65 (72.2%)		56 (60.9%)
Module2		73 (40.1%)		25 (27.8%)		31 (33.7%)
Module3		6 (3.3%)		0 (0%)		5 (5.4%)
ADOS Total ¹	181	17.4 (5.2)	90	18.3 (5.1)	92	17.7 (5.7)
ADOS Social Affect ¹	182	13.5 (4.3)	90	14.4 (4.5)	92	13.8 (4.5)
ADOS LC ^{1,4}	182	3.3 (1.4)	90	3.4 (1.5)	92	3.3 (1.6)
ADOS RSI ^{1,5}	182	10.2 (3.5)	90	11 (3.5)	92	10.4 (3.7)
ADOS RRB ^{1,6}	181	3.9 (2)	90	3.9 (2)	92	3.9 (2.2)
Social Responsiveness (SRS) total ¹	179	96.1 (29.5)	89	95.5 (26.1)	91	96.5 (28.5)
SRS awareness ¹	181	12.4 (4.1)	90	12.2 (3.6)	92	12 (4.1)
SRS cognition ¹	182	18.7 (5.9)	90	18 (5.3)	92	18.4 (6.5)
SRS communication ¹	182	32.1 (10.1)	90	31.9 (9.8)	92	32.4 (10.6)
SRS motivation ¹	182	15 (6.2)	90	15 (5)	92	14.6 (5.7)
SRS mannerisms ¹	182	17.6 (7.1)	90	18.1 (7.3)	92	18.7 (6.9)
Quality of life, participant ¹	181	71.1 (18.7)	88	72.3 (18.5)	88	71.9 (18.5)
Quality of life, family ¹	181	68 (19.4)	87	68.7 (21.2)	89	67.8 (19.6)
Parent working reduced hours due to the child's condition (in percent of full-time work) ¹	101	69.1 (31.1)	42	67.9 (29.6)	38	69.5 (30.5)
IQ source ²	182		90		92	
K-ABC		3 (1.6%)		3 (3.3%)		2 (2.2%)
Other standardized test		107 (58.8%)		50 (55.6%)		53 (57.6%)
Clinical judgment		72 (39.6%)		37 (41.1%)		37 (40.2%)
IQ, standardized test ¹	108	76.1 (27.4)	50	73.4 (27.5)	53	75.9 (22.7)
Mental retardation (IQ<70) ²	180	84 (46.7%)	87	44 (50.6%)	89	40 (44.9%)
ADI-R A: Reciprocal social interaction ¹	182	18.2 (5.8)	90	18.8 (5.6)	92	18 (5.9)
ADI-R B: Language/communication ¹	182	13.1 (4.3)	90	13.3 (4.2)	92	12.5 (4)
ADI-R C: Repetitive behaviors/interests ¹	182	5.9 (2.5)	90	5.9 (2.4)	92	5.8 (2.1)
ADI-R D: Early onset ¹	182	3.9 (1.1)	90	4.1 (1)	92	4 (1.1)
Child care ²	182		90		92	
Attends school		112 (61.5%)		56 (62.2%)		61 (66.3%)
Full-time care (≥7h per day)		40 (22%)		19 (21.1%)		21 (22.8%)
Part-time care (<7h per day)		19 (10.4%)		13 (14.4%)		6 (6.5%)
None of the above		11 (6%)		2 (2.2%)		4 (4.3%)

¹Mean (SD). ²N(%). ³Pervasive developmental disorder unspecified. ⁴Language and communication. ⁵Reciprocal social interaction. ⁶Restricted and repetitive behavior.

ADI-R – Autism Diagnostic Interview-Revised (higher scores indicate greater severity); ADOS – Autism Diagnostic Observation Schedule (higher scores indicate greater severity); IQ – intelligence quotient (higher scores indicate greater cognitive ability); K-ABC – Kaufman Assessment Battery for Children; SRS – Social Responsiveness Scale (higher scores indicate greater severity).

Table 2. Linear mixed-effects analyses for main outcomes

Model 1: IMT vs ESC	ADOS Social Affect (primary outcome)			Social Responsiveness (SRS) total		
	Beta coefficient	95%CI	P-value	Beta coefficient	95%CI	P-value
Intercept	13.49	(12.82, 14.16)	<0.001	95.81	(91.58, 100.04)	<0.001
Group (IMT)	0.59	(-0.37, 1.54)	.324	0.05	(-5.94, 6.03)	.899
2 months vs. BL	-0.38	(-0.96, 0.21)	.266	0.47	(-2.67, 3.61)	.613
5 months vs. BL	-0.91	(-1.45, -0.36)	.001	-1.81	(-4.87, 1.26)	.327
12 months vs. BL	-1.63	(-2.20, -1.07)	<0.001	-4.61	(-7.70, -1.52)	.006
Group * (2 months vs. BL)	0.21	(-0.59, 1.01)	.663	-2.37	(-6.70, 1.95)	.230
Group * (5 months vs. BL)	0.06	(-0.70, 0.81)	.900	-3.32	(-7.56, 0.91)	.099
Group * (12 months vs. BL)	0.16	(-0.62, 0.94)	.729	-2.47	(-6.77, 1.84)	.226

Model 2: IMT (3x/week), IMT (1x/week) vs ESC	Beta coefficient	95%CI	P-value	Beta coefficient	95%CI	p-value
Intercept	13.49	(12.82, 14.16)	<0.001	95.81	(91.58, 100.04)	<0.001
IMT-HI (3x/week) vs. ESC	0.91	(-0.26, 2.08)	.130	-0.27	(-7.62, 7.09)	.859
IMT-LO (1x/week) vs. ESC	0.27	(-0.89, 1.43)	.920	0.35	(-6.95, 7.64)	.975
2 months vs. BL	-0.38	(-0.96, 0.21)	.266	0.47	(-2.67, 3.60)	.614
5 months vs. BL	-0.91	(-1.45, -0.36)	.001	-1.81	(-4.86, 1.25)	.328
12 months vs. BL	-1.63	(-2.20, -1.07)	<0.001	-4.61	(-7.69, -1.52)	.006
(IMT-HI (3x/week) vs. SC) * (2 months vs. BL)	0.21	(-0.78, 1.20)	.717	-1.54	(-6.89, 3.81)	.501
(IMT-LO (1x/week) vs. SC) * (2 months vs. BL)	0.22	(-0.73, 1.17)	.699	-3.11	(-8.25, 2.03)	.201
(IMT-HI (3x/week) vs. SC) * (5 months vs. BL)	-0.24	(-1.18, 0.69)	.593	-4.52	(-9.81, 0.76)	.076
(IMT-LO (1x/week) vs. SC) * (5 months vs. BL)	0.34	(-0.57, 1.24)	.475	-2.39	(-7.41, 2.63)	.309
(IMT-HI (3x/week) vs. SC) * (12 months vs. BL)	0.18	(-0.78, 1.14)	.751	-1.52	(-6.87, 3.84)	.524
(IMT-LO (1x/week) vs. SC) * (12 months vs. BL)	0.15	(-0.78, 1.08)	.780	-3.29	(-8.43, 1.85)	.188

Note. BL – baseline; ESC – enhanced standard care; HI – high-intensity; IMT – Improvisational Music Therapy; LO – low-intensity.

Measures: ADOS Social Affect – possible range 0 to 27, higher scores indicate greater severity. SRS total – possible range 0 to 195, higher scores indicate greater severity.

Explanation of the model: Intercept – mean value in ESC at baseline. Group (IMT) – difference from Intercept if in IMT. 2 months vs. BL – difference from baseline in ESC at 2 months; similar for 5 and 12 months. Group * (2 months vs. BL) – interaction effect, representing the difference between IMT and ESC change from baseline at 2 months

(i.e. the treatment effect); similar for 5 and 12 months. The beta coefficients can be added to predict values for each group and time point, e.g. for IMT at 5 months:

$$13.49+0.59+(-0.91)+0.06=13.23.$$

Figure captions

Figure 1. Flow of participants through the study

Note. Numbers assessed are based on valid data for the primary outcome. The intermediate assessment at 2 months was optional at UK sites. ADI-R – Autism Diagnostic Interview-Revised; ADOS – Autism Diagnostic Observation Schedule; ASD – autism spectrum disorder; ESC – enhanced standard care; IMT – improvisational music therapy; K-ABC – Kaufman Assessment Battery for Children; MT – music therapy; PC – parent counseling; SRS – Social Responsiveness Scale.

Figure 2. Effects of interventions over time: Predicted mean values from linear mixed-effects models

Figure 3. Effects of IMT vs. ESC on the primary outcome by clinical subgroup: Responders versus non-responders

Note. A responder was defined as being improved by at least the minimally clinically important difference; see Methods.

Abbreviations: ADOS – Autism Diagnostic Observation Schedule; ASD – autism spectrum disorder; ESC – enhanced standard care; IMT – improvisational music therapy.