Aerobic and strength training exercise programme for cognitive impairment in people with mild to moderate dementia: the DAPA RCT

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Disclaimer: This report contains transcripts of interviews conducted in the course of the research and contains language that may offend some readers.

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Scientific summary

The DAPA RCT

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Scientific summary

Background

Dementia prevalence in the UK is estimated to be around 670,000 people. Previous literature suggests that physical exercise could slow or prevent dementia symptom progression.

Objectives

To undertake a definitive randomised controlled trial (RCT) to estimate the effects of an exercise or physical activity intervention that is feasible for delivery within the current constraints of NHS delivery, compared with usual NHS care in community-dwelling adults with mild to moderate dementia (MMD).

The specific objectives of the Dementia and Physical Activity (DAPA) trial were to:

1. refine an exercise intervention for delivery to community-dwelling populations of people with dementia, including a systematic review to inform intervention development
2. pilot critical procedures in the intervention and trial
3. complete a definitive, individual RCT to estimate the effectiveness of exercise, in addition to usual care, on cognitive impairment (primary outcome), function and quality of life in people with mild or moderate dementia, and on carer burden for carers
4. complete a parallel cost study and conduct an economic evaluation from a NHS and Personal Social Services perspective
5. investigate intervention effects in predefined subgroups of gender and dementia severity
6. undertake a qualitative study into the experiences of participants and carers taking part in the intervention.

Methods

Trial design

A multicentred RCT was undertaken with an embedded systematic review, qualitative study and economic evaluation. The trial compared treatment as usual with treatment as usual plus a 4-month group exercise intervention and ongoing support to encourage increased physical activity. We randomised individuals using a stratified unbalanced randomisation (2 : 1 in favour of the intervention arm).

Setting

The trial took place in 15 regions across England, including NHS primary, secondary and community care services. The intervention was delivered predominantly in community gym facilities.

Control intervention

Routinely delivered usual care was consistent with the recommendations of the National Institute for Health and Care Excellence clinical guidance (CG42). We stratified the randomisation by regions (with regions representing large NHS trusts and/or Clinical Commissioning Groups) to account for regional differences in standard care. All participants were provided with information sheets detailing the recommended physical activity levels for their age category.

Intervention (groups exercise) arm

We developed a prespecified and manualised intervention. Physiotherapists and exercise assistants received training to deliver the trial intervention and underwent a minimum of two quality assurance checks. The intervention comprised a 4-month individually tailored intervention that was delivered to groups of, on average, 6–8 participants. Exercise included moderate- to high-intensity aerobic (fixed cycles) and resistance (weighted jackets and dumb-bells) training. Exercise sessions lasted for 1 hour and took place twice per week, in addition to 50 minutes of recommended home exercises at moderate intensity. After 4 months, participants were encouraged to continue exercising in the community, with motivational support telephone calls and face-to-face review sessions. Behavioural strategies were used throughout to enhance adherence levels.

Recruitment

Interested people were first contacted to ascertain eligibility, the criteria for which comprised a diagnosis of dementia according to the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, as well as the participant having dementia severity lying between mild and moderate, being community-dwelling, being able to stand from a chair independently, being able to walk 10 feet without human assistance and not having any acute, unstable or terminal illness that may have precluded their participation in the exercise.

Follow-up

We collected outcome data from participants and carers in their own homes at baseline and follow-up data at 6 and 12 months after randomisation.

Randomisation and masking (blinding)

The random allocation sequence was generated by an independent statistician, using a computerised random number generator, and implemented by a central telephone registration and randomisation service at the Warwick Clinical Trials Unit. The unit of randomisation was the individual participant. Randomisation was stratified by region and dementia severity (moderate or mild). Participants were randomised to:

1. usual care
2. usual care plus exercise intervention.

Randomisation was 2 : 1 in favour of the exercise intervention group, to allow exercise groups to be assembled in a shorter period of time and to reduce the chance of participants withdrawing between randomisation and the exercise classes commencing. In addition, the baseline measures were taken close to the exercise classes commencing.

Neither intervention providers nor participants could be masked to treatment allocation. If a research clinician became unmasked, then follow-up assessments were conducted by different research workers. All study personnel involved with data entry, follow-up assessments and management were masked until the final analysis was complete.

Sample size

A sample size of 360 participants provided 80% power to detect a minimum clinical between-group difference of 2.45 [baseline standard deviation (SD) 7.8 based on $n = 66$ participants] on the Alzheimer's Disease Assessment Scale – Cognitive Subscale (ADAS-Cog) at 12 months with a 5% level of significance and 2 : 1 randomisation in favour of the intervention. This equated to a standardised effect size of 0.31. An overall difference of 2–2.5 change points on the ADAS-Cog was considered to be a worthwhile target. To account for therapist effects, the sample size was inflated using a design effect of 1.04 (intracluster correlation = 0.01) assuming that there are five participants per group (and recognising that it may not have been possible to achieve and retain the proposed eight recruits to each group), giving a sample size of 375. The sample size was then further inflated to account for 20% loss to follow-up, of which 10% was predicted to be attributable to death. Thus, a final minimum sample size of 468 participants was required, with 312 participants to be randomly allocated to the intervention arm and 156 participants to the control arm.

Monitoring and ethics

The study benefited from having broad-ranging patient and public involvement at various stages of the project. The National Institute for Health Research (NIHR) involved people with dementia and their representatives in the specifying of the question, including methods, selecting important outcome domains and type of intervention, throughout the commissioning process. The study team involved people with dementia, their representatives and other stakeholders in the intervention and protocol development, including receiving detailed feedback on the intervention, questionnaires, approach and invitation, acceptability of procedures and logistics. Carers of people with dementia were formal members of the study Trial Steering Committee/Data Monitoring Committee. At the end of the study, people with dementia and their carers were invited to a joint feedback day with research and clinical staff, and contributed actively to discussions about the results and interpretation. Trial oversight was undertaken by a Trial Steering Committee and an independent Data Monitoring Committee. Ethics permission was granted for all participating sites.

Clinical outcomes and analysis

The primary outcome was the ADAS-Cog with item-level imputation, which measured global cognitive impairment. The secondary outcomes were the additional subscales of the ADAS-Cog (praxis, memory, attention and language), the Bristol Activities of Daily Living Scale (BADLS), health-related quality of life (HRQoL) [EuroQol-5 Dimensions, three-level version (EQ-5D-3L)], dementia-related quality of life [Quality of Life in Alzheimer's Disease (QoL-AD) scale] and behavioural symptoms [Neuropsychiatric Inventory (NPI)]. Carer-related outcomes were the carer HRQoL (EQ-5D-3L) and carer burden [Zarit Burden Interview (ZBI)], the patient's health- and social-care usage (Client Services Receipt Inventory) and falls and fractures.

For the primary and secondary analyses, multilevel models, adjusted for age, gender, Standardised Mini Mental State Examination and the baseline measure of the outcome, were used with a random effect for region to estimate the treatment effects and 95% confidence intervals (CIs). Sensitivity analyses included (1) excluding participants who were unable to complete all items of the ADAS-Cog, (2) excluding missing ADAS-Cog scores with the worst score assignment and (3) item response theory to assess the effects within specific cognitive domains within the primary outcome of ADAS-Cog. Prespecified subgroup analyses were performed on cognitive impairment severity, type of dementia, physical performance and gender, with formal tests of interaction.

Economic evaluation

In parallel, the costs of the exercise intervention were estimated, including the costs of training the health-care professionals, delivering the group supervision, participant monitoring activities and any follow-up/management. Data were collected on broader health and Personal Social Services and broader societal resource inputs using a modified version of the Client Services Receipt Inventory, which was administered via face-to-face interviews at baseline and at 6 and 12 months post randomisation. Resource inputs were valued using a combination of primary research and data collated from secondary national tariff sets, using standard accounting methods. The economic evaluation took the form of a cost–utility analysis, with quality-adjusted life-year (QALY) profiles for DAPA trial participants based on participant and carer reports of EQ-5D-3L-generated HRQoL outcomes at baseline and at 6 and 12 months post randomisation. We conducted a bivariate regression of costs and QALYs, with multiple imputation of missing data, to estimate the incremental cost per QALY gained associated with the exercise intervention. Several sensitivity analyses were undertaken to assess the impact of uncertainty surrounding aspects of the economic evaluation. Prespecified subgroup analyses were also conducted for the main cost-effectiveness results to explore the effects of heterogeneity in the trial population.

Results

We recruited in 15 different regions in England, using a mixture of NIHR-funded research networks, dementia research networks, primary care and other third-sector organisations. The intervention was delivered in 27 different venues. Between February 2013 and June 2015, 494 participants were randomised: 165 to receive treatment as usual and 329 to receive treatment as usual plus the DAPA exercise intervention. The mean age of participants was 77 years, 39% (193/494) were female and the mean baseline ADAS-Cog score was 21.5. Participants in the intervention arm achieved good compliance rates, with 65% attending > 75% of the scheduled group supervision sessions. Outcome data were obtained for 85% of participants at 12 months. At 12 months, there was evidence of a small, statistically significant negative treatment effect in the primary outcome, ADAS-Cog, with a mean difference of –1.4 (95% CI –2.62 to –0.17). There was no evidence of treatment effects for any of the other patient-related secondary outcomes: for the BADLS there was a mean difference of –0.6 (95% CI –2.05 to 0.78), for the EQ-5D-3L a mean difference of –0.002 (95% CI –0.04 to 0.04), for the QoL-AD scale a mean difference of 0.7 (95% CI –0.21 to 1.65) and for the NPI a mean difference of–2.1 (95% CI –4.83 to 0.65). Neither was there evidence of treatment effects for the carer-related secondary outcomes: for the EQ-5D-3L there was a mean difference of –0.002 (95% CI –0.04 to 0.04), for the ZBI a mean difference of –0.5 (95% CI –2.78 to 1.72) and for falls an incident rate ratio of 1 : 1 (95% CI 0.84 to 1.33). Within-group analyses show that participants from the intervention arm became fitter over a 6-week period, as measured by the 6-minute walk test ($n = 231$) with a mean of 343.7 m walked (SD 112.9 m) pre intervention and a mean of 361.8 m walked (SD 115.3 m) post intervention, with an estimate of the difference between the two of –18.1 (95% CI –24.6 to –11.6; $p < 0.001$). Muscle strength and amount of weight lifted increased.

Qualitative study

We conducted a qualitative study in parallel, the aim of which was to provide insight into participants' and carers' experiences of taking part in the experimental intervention, and physiotherapists' experiences of delivering it. The qualitative study explored patient, carer and therapist attitudes towards the intervention while they were participating in it.

Sampling of participants and their carers was consecutive and participants were drawn from five intervention delivery sites. Sites were selected to reflect a range of settings, and reflexive observations were carried out at each site. Once observations of the sites were completed, we invited participants and carers to take part in an interview. Participants had already consented to be approached to take part in the qualitative study as part of the consent process for the RCT.

Our data comprised:

- notes taken during observations of exercise classes
- interviews with trial participants
- interviews with carers of trial participants
- interviews with physiotherapists delivering the classes.

The data were analysed as a single data set. Identifying information was anonymised to ensure that interviewees' confidentiality was maintained.

We observed five sites four times for approximately 1.5 hours each between November 2013 and March 2015. Settings for the delivery of the intervention included pleasant leisure centres with cafes and soft seating for carers to use, large warehouse-style gyms situated on industrial estates with very loud heating systems and rather run-down local authority amenities with no facilities for carers to use. These were located in a range of urban, suburban and rural settings.

Eight participants and seven carers agreed to take part in an interview. Six participants chose to be interviewed on their own and two chose to have their carer or friend present. Six carers chose to be interviewed on their own and one to be interviewed with the participant. All five physiotherapists delivering the intervention at the included sites agreed to be interviewed (one via a telephone interview).

The qualitative data reflects the quantitative findings, in that participants and carers did not feel that the intervention had changed their cognitive functioning but they did feel fitter and stronger and enjoyed attending the classes.

Economic evaluation results

The mean cost of the exercise programme in participants with complete resource-use data over the entire follow-up period was £1269 [standard error (SE) £30]. Over the entire follow-up period, and for participants with complete data, the mean total NHS and Personal Social Service costs, inclusive of the cost of the intervention, were £5945 (SE £492) in the intervention arm compared with £4597 (SE £444) in the control arm, generating a mean cost difference of £1347 (bootstrap 95% CI £8 to £2136; $p = 0.0426$). There were no (statistically significant) differences in the overall EQ-5D-3L utility scores or EQ-5D-3L visual analogue scale scores between the exercise intervention and usual-care groups at each of the follow-up time points. The mean incremental cost-effectiveness of the exercise intervention was estimated at –£74,227 per QALY gained (north-west quadrant of cost-effectiveness plane), that is, on average, the intervention was associated with a higher net cost and a lower net effect and was dominated in health economic terms. The associated mean incremental net monetary benefits at cost-effectiveness thresholds of £15,000, £20,000 and £30,000 per QALY were –£2158, –£2306 and –£2601, respectively. The probability that the exercise intervention is cost-effective was < 1% in the baseline analysis, a result that remained robust to sensitivity and subgroup analyses.

Conclusions

This was a well-conducted, large, pragmatic trial with good intervention compliance and follow-up rates. The exercise intervention was well tolerated and enjoyed by participants and carers, but did not produce any clinical impact on function and HRQoL in people with dementia or upon their carer's burden, or evidence that it is cost-effective. There was slight worsening of cognitive impairment. The qualitative study suggests that, although the intervention cannot produce long-term improvements to cognitive impairment, function and HRQoL, it did provide respite, social interaction and enjoyment for participants and carers alike during the phase of group supervision of exercise.

Future research

We recommend that future research concentrates on alternative treatments to alter the progress of dementia.

Trial registration

This trial is registered as ISRCTN32612072.

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