A randomised controlled study of the effectiveness of breathing retraining exercises taught by a physiotherapist either by instructional DVD or in face-to-face sessions in the management of asthma in adults

Mike Thomas,[1]* Anne Bruton,[2] Paul Little,[1] Stephen Holgate,[1] Amanda Lee,[3] Lucy Yardley,[4] Steve George,[1] James Raftery,[1] Jennifer Versnel,[5] David Price,[3] Ian Pavord,[6] Ratko Djukanovic,[1] Michael Moore,[1] Sarah Kirby,[4] Guiqing Yao,[1] Shihua Zhu,[1] Emily Arden-Close,[7] Manimekalai Thiruvothiyur,[3] Frances Webley,[8] Mark Stafford-Watson,[9] Elizabeth Dixon[8] and Lynda Taylor[8]

[1]Faculty of Medicine, University of Southampton, Southampton, UK
[2]Faculty of Health Sciences, University of Southampton, Southampton, UK
[3]Institute of Applied Health Sciences, University of Aberdeen, Aberdeen, UK
[4]School of Psychology, University of Southampton, Southampton, UK
[5]Asthma UK, London, UK
[6]Nuffield Department of Medicine, University of Oxford, Oxford, UK
[7]Department of Psychology, Bournemouth University, Bournemouth, UK
[8]Southampton Clinical Trials Unit, University of Southampton, Southampton, UK
[9]Patient and public involvement representative

*Corresponding author D.M.Thomas@soton.ac.uk

Declared competing interests of authors: Mike Thomas is a member of the Health Technology Assessment (HTA) Primary Care, Community and Preventive Interventions (PCCPI) Panel. In the last 3 years he has received speaker's honoraria for speaking at sponsored meetings or satellite symposia at conferences from the following companies, marketing respiratory and allergy products: Aerocrine, GlaxoSmithKline (GSK) and Novartis International AG. He has received honoraria for attending advisory panels with Aerocrine, AstraZeneca, Boehringer Ingelheim, GSK and Novartis. He has received sponsorship to attend international scientific meetings from GSK and AstraZeneca and has received funding for research projects from GSK. He is a member of the British Thoracic Society (BTS)/Scottish Intercollegiate Guidelines Network (SIGN) Asthma Guideline Group and the National Institute for Health and Care Excellence (NICE) Asthma Guideline Group. Paul Little is Editor-in-Chief of the *Programme Grants for Applied Research* journal and is a member of the National Institute for Health Research (NIHR) Journals

Library Board. Lucy Yardley Is a member of the *Public Health Research* journal Research Funding Board and a member of the HTA Efficient Study Designs Board and reports grants from the NIHR during the conduct of the study. James Raftery is a member of the NIHR Journals Library Editorial Group and the HTA and EME Editorial Board and was previously Director of the Wessex Institute and head of the NIHR Evaluation, Trials and Studies Coordinating Centre (NETSCC). He is also a former member of the NIHR HSDR Research Led Board. Ian Pavord has received speaker's honoraria for speaking at sponsored meetings in the last 5 years from AstraZeneca, Boehringer Ingelheim, Aerocrine, Almirall Ltd, Novartis and GSK. He has received honoraria for attending advisory panels with Almirall, AstraZeneca, Boehringer Ingelheim, GSK, MSD, Schering-Plough, Novartis, Dey Pharma, Napp Pharmaceuticals and RespiVert Ltd. He has received sponsorship to attend international scientific meetings from Boehringer Ingelheim, GSK, AstraZeneca and Napp. He is Chief Medical Advisor to Asthma UK, a member of the UK Department of Health Asthma Strategy Group, a member of the BTS/SIGN Asthma Guideline Group and joint Editor-in-Chief of *Thorax*. Neither Ian Pavord nor any member of his family has any shares in pharmaceutical companies. David Price reports other Board Membership (fees paid to Research in Real Life Ltd) from Aerocrine, Almirall, Amgen Inc., AstraZeneca, Boehringer Ingelheim, Chiesi Ltd, Meda, Mundipharma, Napp, Novartis and Teva Pharmaceutical Industries Ltd; consultancy (fees paid to Research in Real Life Ltd) from Almirall, Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, Meda, Mundipharma, Napp, Novartis, Pfizer Inc. and Teva; grants from the UK NHS, British Lung Foundation, Aerocrine, AKL Ltd, Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, Eli Lilly and Co., GSK, Meda, Merck & Co., Inc., Mundipharma, Napp, Novartis, Orion, Pfizer, Respiratory Effectiveness Group, Takeda, Teva and Zentiva; lectures/speaking engagement fees (paid to Research in Real Life Ltd) from Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla Ltd, GSK, Kyorin Pharmaceutical Co., Inc., Meda, Merck, Mundipharma, Novartis, Pfizer, Skyepharma, Takeda and Teva; manuscript preparation fees (paid to Research in Real Life Ltd) from Mundipharma and Teva; payment for travel/accommodation/meeting expenses (paid to Research in Real Life Ltd) from Aerocrine, Boehringer Ingelheim, Mundipharma, Napp, Novartis and Teva; funding for patient enrolment or completion of research (paid to Research in Real Life Ltd) from Almirall, Chiesi, Teva and Zentiva; and payment for the development of educational materials (paid to Research in Real Life Ltd) from GSK and Novartis, outside the submitted work. In addition, David Price has an AKL Ltd patent pending and owns shares in AKL Ltd, which produces phytopharmaceuticals. He owns 80% of Research in Real Life Ltd (which is subcontracted by Observational and Pragmatic Research Institute Pte Ltd), 75% of the social enterprise Optimum Patient Care Ltd and 75% of the Observational and Pragmatic Research Institute Pte Ltd. Ratko Djukanovic has received fees for lectures at symposia organised by Novartis and Teva and for consultation for these two companies as a member of advisory boards. He is a co-founder and current consultant, and has shares in, Synairgen, a University of Southampton spin-out company.

Published September 2017
DOI: 10.3310/hta21530

Scientific summary

Breathing retraining exercises in the management of asthma in adults

Health Technology Assessment 2017; Vol. 21: No. 53
DOI: 10.3310/hta21530

NIHR Journals Library www.journalslibrary.nihr.ac.uk

Scientific summary

Background

Asthma affects > 5 million people in the UK, with costs in excess of £1B annually. Although pharmacotherapy is effective and can provide full control for some, surveys repeatedly show that outcomes remain suboptimal, with persisting symptoms and quality of life (QoL) impairment for the majority. Symptoms attributed to dysfunctional breathing overlap with those of asthma and have been reported to be more frequent in people with asthma, providing a rationale for using breathing retraining to improve asthma control. Randomised controlled trials (RCTs) have reported beneficial outcomes from breathing retraining in asthma, particularly from physiotherapist-administered breathing exercises, which are now advocated in guidelines as adjuvant treatment for those who remain uncontrolled on pharmacological treatment. Previous research from members of this study group provided evidence supporting this recommendation, with two positive RCTs supporting physiotherapist-delivered breathing retraining. However, the cost-effectiveness of this intervention was not addressed and resource constraints mean that the majority of people with asthma who could benefit are not able to access a suitably trained respiratory physiotherapist. Two preliminary studies have investigated the use of breathing retraining delivered by videotape or digital versatile disc (DVD), with some evidence of effectiveness. Such self-guided programmes have the potential to be accessed easily, conveniently and inexpensively by large numbers of people. No studies have compared the clinical effectiveness and cost-effectiveness of a self-guided programme with those of face-to-face breathing retraining interventions.

We hypothesised that breathing retraining exercises taught as a self-guided programme would improve asthma-related QoL above 'usual care' and would be equivalent to 'face-to-face' physiotherapist instruction.

Objectives

- To use an iterative patient-focused approach to transfer the contents of a three-session physiotherapist-delivered breathing retraining programme, previously shown to improve asthma control, to a self-guided format that is acceptable to patients.
- To perform a RCT in adults with impaired asthma control, comparing the effectiveness of breathing retraining delivered by the self-guided programme with the effectiveness of a face-to-face breathing retraining programme delivered by a respiratory physiotherapist and with usual care, for asthma-related QoL and other asthma control measures.
- To perform quantitative and qualitative process evaluations.
- To perform a health economic assessment using data collected from the trial and from general practice clinical records.

Methods

Trial design

We carried out a pragmatic, observer-blinded, three-arm, parallel-group RCT comparing a breathing retraining programme delivered in DVD format with a breathing retraining programme delivered face-to-face by a physiotherapist and with a control of usual care for adults with asthma and impaired health status.

Participants

In total, 655 adult patients with diagnosed and currently treated asthma were recruited from 34 primary UK NHS general practices in the Wessex region.

Inclusion criteria

- Full practice registration for 12 months prior to enrolment.
- Age 16–70 years.
- Physician-diagnosed asthma in medical records.
- One or more anti-asthma medication prescriptions in the previous year.
- Impaired asthma-related health status [Asthma Quality of Life Questionnaire (AQLQ) score of < 5.5].
- Able to give informed consent.

Exclusion criteria

- Asthma dangerously unstable and in need of urgent medical review at baseline.
- Concomitant chronic obstructive pulmonary disease if forced expiratory volume in 1 second (FEV_1) is < 60% predicted.

Broad entry criteria were pragmatically used (with the inclusion of smokers and not insisting on physiological demonstration of reversible airflow obstruction) to allow the generalisability of the research findings to mild-to-moderate UK asthma populations treated in primary care NHS practice.

Outcome measures

Primary outcome

The primary outcome was the between-group [intention-to-treat (ITT)] 12-month asthma-specific health status (AQLQ score), adjusted for prespecified covariates.

Secondary outcomes

- Prespecified sensitivity analyses on the main outcome [unadjusted analysis of between-group ITT AQLQ score changes, per-protocol (PP) between-group AQLQ score changes, sensitivity analysis including patients without full AQLQ data].
- Analysis of the between-group ITT and PP changes in:
    - Asthma Control Questionnaire (ACQ) scores
    - lung function [FEV_1, FEV_1-to-forced volume vital capacity (FVC) ratio, peak expiratory flow rate (PEFR)]
    - fraction of exhaled nitric oxide (FeNO)
    - generic health status [EuroQol-5 Dimensions (EQ-5D)]
    - anxiety and depression scores [Hospital Anxiety and Depression Scale (HADS)]
    - hyperventilation (Nijmegen) questionnaire scores
    - asthma exacerbations (oral corticosteroid courses)
    - bronchodilator use
    - asthma-related health resource use
    - cost-effectiveness/utility
    - patient-reported process evaluations (qualitative assessments and questionnaires)
    - patient engagement in breathing retraining programmes.

Study procedures

Development phase

We transferred an existing 'face-to-face' programme of breathing retraining taught by physiotherapists to patients with dysfunctional breathing to a self-guided programme format delivered through a DVD with printed supportive materials, and undertook qualitative piloting of these materials to optimise acceptability and effectiveness. Patient educational materials were developed by a team including physicians, physiotherapists,

health psychologists, communications technology specialists and patient representatives. The DVD and accompanying booklet were created iteratively with extensive patient input. The DVD content included:

- detailed explanations and illustrations of how to carry out the exercises, with footage showing a physiotherapist teaching the exercises to patients
- motivational components explaining the rationale for the exercises and addressing common doubts and concerns.

The materials were piloted with a panel of 29 members of the target population, purposively sampled for diversity in terms of age, sex, education and symptom profile. In audio-recorded face-to-face and telephone interviews we used open-ended questions to explore attitudes to the proposed treatment method in the context of health beliefs and then used 'think-aloud' methods to elicit reactions to the proposed materials, with modification of the scripts based on this feedback. Professional production of the DVD and booklet were undertaken and the materials were reviewed by the panel, who provided final feedback in face-to-face and telephone interviews.

Randomised controlled trial

Potentially eligible patients were identified by computer searches of general practice clinical and prescribing records. These patients were mailed the study information and an invitation letter, and were asked to complete the AQLQ and return it by post. Those with an AQLQ score of < 5.5 were recruited. Patients were seen at their general practice by a research nurse for a baseline assessment, consenting and randomisation. The baseline assessment consisted of assessment of clinical data (smoking status, asthma history, comorbidities, medication use), questionnaire data [disease-specific health status (AQLQ), Nijmegen hyperventilation questionnaire, ACQ, generic health status (EQ-5D), anxiety and depression (HADS)] and physiological data [spirometry (FEV_1, FEV_1-to-FVC ratio, PEFR), measured with a standardised calibrated portable spirometer; FeNO, measured with a NIOX MINO® portable monitor (Circassia Ltd, Oxford, UK)]. Randomisation was achieved by the study nurse telephoning the Southampton Clinical Trials Unit (SCTU) telephone randomisation service. Follow-up appointments were also arranged.

All consenting participants received postal questionnaires at 3 and 6 months and a final assessment visit at 12 months post randomisation. Those randomised to usual care received no other additional attention. Those randomised to the DVD were also provided with the booklet. Those randomised to face-to-face physiotherapy received three sessions (30–40 minutes each) with a respiratory physiotherapist at their general practice, at 2-weekly intervals following randomisation, and also received the instructional booklet. The final 12-month assessment was performed by a different study nurse blinded to randomisation group. The assessment consisted of the same clinical, questionnaire and physiological measurements performed at baseline, plus a short questionnaire exploring participants' perceptions and experiences of being in the trial and adherence and collection of routine clinical data.

A group of participants in the active arms selected by purposive sampling underwent qualitative interviews to assess their experiences of the interventions, until data saturation was achieved.

Statistical methods

The primary statistical analysis consisted of a repeated-measures mixed model using the 12-month AQLQ score across the three arms with adjustments for prespecified covariates [baseline AQLQ score, general practice, age, sex, smoking status, British Thoracic Society (BTS) treatment step, baseline HADS score and baseline Nijmegen questionnaire score], with pairwise comparisons between the DVD group and the control group, the physiotherapy group and the control group (superiority study) and the DVD group and the physiotherapy group (equivalence study, equivalence margin 0.3).

Results

Recruitment, retention and missing data

The recruitment target of 585 was increased to 655 by the Data Monitoring and Ethics Committee as an early unblinded analysis suggested a slightly higher dropout rate in the DVD arm. We successfully randomised 655 patients from 34 primary care sites. A total of 15,203 invitation letters were mailed, with 1481 responses received (response rate 9.7%). In total, 680 (45.9%) respondents were ineligible and 655 (81.8% of eligible respondents) were randomised, 261 (39.8%) to the DVD group, 262 (40.0%) to the control (usual care) group and 132 (20.2%) to the physiotherapy group. All 655 randomised participants were included in the ITT population. The PP population included 556 participants (DVD, $n = 215$; physiotherapy, $n = 110$; control, $n = 231$; 84.9% of the randomised population). A very low proportion of data were missing for all other questionnaires (< 2%). Spirometry data (FEV_1, FEV_1-to-FVC ratio) were missing for 4% of participants and FeNO values were missing for 7.5% of participants; missing data values were similar between treatment arms. Only 21 patients withdrew (3.2%), with similar rates of withdrawal between arms. The AQLQ was returned at 12 months by 556 participants and at one or more follow-up points by all 655 participants.

Primary outcome

In the primary efficacy analysis, the between-group comparison of 12-month AQLQ scores in the ITT population adjusted for prespecified covariates, we observed a statistically significant improvement in mean AQLQ score in the DVD arm compared with the control arm [adjusted mean difference 0.28, 95% confidence interval (CI) 0.11 to 0.44] and in the physiotherapy arm compared with the control arm (adjusted mean difference 0.24, 95% CI 0.04 to 0.44), confirming the superiority of both active arms over usual care. The adjusted mean difference between the DVD arm and the physiotherapy arm was 0.04 (95% CI –0.16 to 0.24), confirming equivalence of the active arms. In subdomain analysis, the largest improvements in the active arms compared with usual care were in the emotions domain (DVD vs. control: adjusted mean difference 0.38, 95% CI 0.16 to 0.60; physiotherapy vs. control: adjusted mean difference 0.43, 95% CI 0.16 to 0.71); significant improvements were also seen for symptoms, activities and environment in the DVD arm compared with usual care and for symptoms for the physiotherapy arm compared with usual care, with no significant differences between the active arms. The statistically significant differences were largely unchanged in the sensitivity analyses, with minor changes in magnitude. Analysis of the 3-month and 6-month AQLQ changes showed improvements in both active arms compared with the control arm by the first assessment, which were maintained or increased over 12 months. In the DVD arm, the improvements in mean total AQLQ score from baseline in the ITT population were 0.9 at 3 months, 1.0 at 6 months and 1.1 at 12 months; in the physiotherapy arm the equivalent figures were 1.0, 1.1 and 1.1 respectively. In the control arm, improvements in mean total AQLQ score from baseline were 0.6, 0.6 and 0.8 respectively.

An analysis in the ITT population of individual patient data using a cut-off point of 0.5 to define a clinically important change showed that 62% of participants in the DVD group improved over 12 months, compared with 64% in the physiotherapy group and 56% in the control group. The figures for deterioration were 5%, 4% and 8% respectively. The proportions improving in the PP population were slightly higher. A number needed to treat (NNT) analysis showed a NNT of eight for the DVD group compared with usual care, seven for the physiotherapy arm compared with usual care and 41 for the physiotherapy arm compared with the DVD arm.

Secondary outcomes

Physiology

There were no significant changes in lung function within or between treatment arms. Median (interquartile range) FeNO changes between baseline and 12 months were minor [DVD: from 21 parts per billion (p.p.b.) (14–35 p.p.b.) to 20 p.p.b. (13–33 p.p.b.); physiotherapy: from 23 p.p.b. (15–33 p.p.b.) to 21 p.p.b. (13–32 p.p.b.); control: from 23 p.p.b. (14–34 p.p.b.) to 20 p.p.b. (13–34 p.p.b.)], with no statistically

significant between-group differences when adjusted for covariates. These data indicate that breathing retraining by either modality did not significantly affect airway physiology or inflammation and so did not affect the pathophysiology of asthma.

Questionnaires

We found no significant between-group changes in asthma symptom control (ACQ), anxiety scores or hyperventilation symptom scores in either the ITT population or the PP population, although there were modest within-group changes from baseline in all within-group analyses and consistent trends favouring the intervention groups above the control group. There was a small but statistically significant improvement in depression scores in the DVD group compared with the control group.

Asthma attacks

Only 12% of the ITT population had one or more asthma attack over the 12-month period. The proportion of patients in the three randomisation groups (DVD, physiotherapy, control) having one or more asthma attack was 9%, 11% and 15% respectively. There was no statistically significant difference in exacerbation rate between the DVD group and the physiotherapy group ($p = 0.6$) or between the physiotherapy group and the control group ($p = 0.4$). The DVD group showed a marginal statistically significant reduction in exacerbations compared with the control group ($p = 0.06$). In a negative binomial regression model, the adjusted risk ratio for DVD compared with the control was 0.68 (95% CI 0.39 to 1.20) and for physiotherapy compared with the control was 0.85 (95% CI 0.43 to 1.67).

Short-acting bronchodilator use

A between-group analysis of rescue medication use in the 12 months post randomisation showed trends for lower bronchodilator use in the DVD group compared with the control group [incidence rate ratio (IRR) 0.83, 95% CI 0.68 to 1.03] and in the physiotherapy group compared with the control group (IRR 0.81, 95% CI 0.63 to 1.04).

Patient engagement and experience

In total, 95% of participants attended at least one of the three face-to-face physiotherapy sessions and 93% attended all three. Patient experience of the different intervention components was favourable, with most devoting time to practising techniques, the main hindrance being finding time to practise. Engagement was also good in the DVD group, although with lower engagement scores and practice times than in the physiotherapy group. Qualitative analysis revealed that both interventions were valued, although some in the DVD arm would have liked to be able to receive instruction from a practitioner.

Adverse events

The adverse event profile was as expected in the recruited population, with fewer events in the active arms than in the control group. There was no indication of treatment-related adverse effects from either the DVD programme or the physiotherapy programme, with both appearing to be well tolerated.

Economic evaluation

Costs were lower in both active treatment arms than in the control group, with the increased intervention costs offset by reductions in total costs, indicating a dominant health economic strategy favouring the DVD intervention. The quality-adjusted life-year changes were in the same direction as the primary outcome but were smaller. The DVD programme dominated the physiotherapy programme, having equivalent outcomes at a lower cost.

Conclusions

Using a rigorous patient-focused iterative development process, we produced a self-guided version of a face-to-face physiotherapy-based breathing retraining programme to improve QoL in people with asthma and performed a pragmatic RCT in primary care asthma patients to test the clinical effectiveness and

cost-effectiveness and patient acceptability of the programme. We showed that the self-guided intervention is superior to usual care and equivalent to face-to-face physiotherapy in improving asthma-related QoL in this patient group, and constitutes a dominant economic strategy. However, lung function and airway inflammation were not significantly affected, with the intervention helping people to cope better and suffer less despite not modifying the underlying pathophysiology of asthma. The exacerbation risk was one-third lower in the DVD group than in the usual-care group, but the study was underpowered to provide statistical significance for this outcome.

In conclusion, this intervention is potentially of benefit to large numbers of asthma patients and may save the NHS money.

Recommendations for future research

Larger studies to investigate a possible effect of the intervention on exacerbations, implementation studies and extensions to paediatric populations are needed.

Trial registration

This trial is registered as ISRCTN88318003.

Funding

Funding for this study was primarily provided by the Health Technology Assessment programme of the National Institute for Health Research, with additional financial support received from Comprehensive Local Research Networks.

Health Technology Assessment

HTA/HTA TAR

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

Impact factor: 4.236

Health Technology Assessment is indexed in MEDLINE, CINAHL, EMBASE, The Cochrane Library and the Clarivate Analytics Science Citation Index.

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (www.publicationethics.org/).

Editorial contact: journals.library@nihr.ac.uk

The full HTA archive is freely available to view online at www.journalslibrary.nihr.ac.uk/hta. Print-on-demand copies can be purchased from the report pages of the NIHR Journals Library website: www.journalslibrary.nihr.ac.uk

Criteria for inclusion in the *Health Technology Assessment* journal

Reports are published in *Health Technology Assessment* (HTA) if (1) they have resulted from work for the HTA programme, and (2) they are of a sufficiently high scientific quality as assessed by the reviewers and editors.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

HTA programme

The HTA programme, part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the effectiveness, costs and broader impact of health technologies for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined as all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care.

The journal is indexed in NHS Evidence via its abstracts included in MEDLINE and its Technology Assessment Reports inform National Institute for Health and Care Excellence (NICE) guidance. HTA research is also an important source of evidence for National Screening Committee (NSC) policy decisions.

For more information about the HTA programme please visit the website: http://www.nets.nihr.ac.uk/programmes/hta

This report

The research reported in this issue of the journal was funded by the HTA programme as project number 09/104/19. The contractual start date was in November 2011. The draft report began editorial review in October 2016 and was accepted for publication in May 2017. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

This report presents independent research funded by the National Institute for Health Research (NIHR). The views and opinions expressed by authors in this publication are those of the authors and do not necessarily reflect those of the NHS, the NIHR, NETSCC, the HTA programme or the Department of Health. If there are verbatim quotations included in this publication the views and opinions expressed by the interviewees are those of the interviewees and do not necessarily reflect those of the authors, those of the NHS, the NIHR, NETSCC, the HTA programme or the Department of Health.

Published by the NIHR Journals Library (www.journalslibrary.nihr.ac.uk), produced by Prepress Projects Ltd, Perth, Scotland (www.prepress-projects.co.uk).