The Impact of Pain on Depression Outcomes of Older Adults in Behavioural Activation: An Exploratory Secondary Data Analysis

STATISTICAL ANALYSIS PLAN

Moderation (effect modification) analysis of CASPER, CASPER+ and SHARD

Version 1.3

Teesside University/ University of York

School of Health & Life Sciences/ Department of Health Sciences

Teesside University/ University of York

Middlesbrough, TS1 3BX / York, YO10 5DD

Version Date: 14/06/2022

Author: Alexandra Carne/ Alan Batterham

Chief Investigator: Alexandra Carne

Statistician: Alan Batterham

Supervisors: Denis Martin/ Dave Ekers

Collaborator: Simon Gilbody

Contents

List of Tables

1. Glossary

BA	Behavioural Activation	
CASPER	Collaborative Care in Screen Positive Elders	
	CASPER Trial	Cohort of participants over 65 years of age *with sub-threshold* depression
	CASPER PLUS (+) Trial	Cohort of participants over 65 years of age *with sub-threshold* depression
CC	Collaborative care	
GP	General Practitioner	
RCT	Randomised Controlled Trial	
SAP	Statistical Analysis Plan	
SHARD	The Self-Help for those at risk of Depression Trial	
NICE	National Institute for Health Care Excellence	

2. Background & Rationale

Previous findings have indicated that pain might be an important barrier in depression treatment both with antidepressant medication (1, 2) and in a US collaborative care model using problem-solving therapy and antidepressant medication (3). It is unknown, however, if pain impacts depression outcomes of older adults in the collaborative care (CC) framework focusing on a brief psychological intervention called behavioural activation (BA). Collectively CASPER, CASPER PLUS (+) and SHARD are three of the largest pragmatic, multicentre randomised controlled trials (RCT) of BA for older adults in UK primary care with low mood and depression. The purpose of this secondary data analysis is, therefore, to explore if pain moderates (modifies) the effect of BA on depression outcomes in older adults, potentially identifying subgroups of older adults who may not respond as well to BA. This statistical analysis plan (SAP) provides the description of the variables to be used and the methods on which the analysis will be based to avoid misleading inferences from exploratory analyses.

3. Research Objectives

1. To what extent does physical health and pain modify the effect of behavioural activation on depression.

4. Trial Design

4.1 Summary

This study is a secondary data analysis of existing data collected from CASPER, CASPER+ and SHARD, which are three of the largest pragmatic, multicentre randomised controlled trials (RCT) of behavioural activation for older adults in UK primary care with low mood and depression. See the below table for a summary of the databases.

Table 1: A summary table of the interventions for CASPER, CASPER + and SHARD

Groups/ Cohort	Interventions
CASPER & CASPER Plus **A multi-centred, pragmatic, two-arm parallel open RCT. Participants with Subthreshold depression (CASPER) and major depression (CASPER+) were individually randomised (1:1) to receive either collaborative care focusing on behavioural activation or usual General Practitioner (GP) care**	**Collaborative care** Participants in the intervention group were allocated to receive a low-intensity programme of behavioural activation specifically designed for adults ≥65 with subthreshold and major depression. An allocated case manager (primary care mental health worker/ Improving Access to Psychological Therapy) delivered collaborative care for an intended 8-10 weeks. This ran alongside GP's usual care. Collaborative care in both CASPER and CASPER+ trials included weekly telephone/ face-to-face support, active surveillance, and symptom monitoring **Usual GP care** Participants allocated to the control group received usual GP care. Participants did not receive any additional care to their usual primary care management for subthreshold (CASPER) or Major (CASPER+) depression in line with National Institute for Health Care Excellence (NICE) guidelines as implemented in their GP and local service provision.
SHARD **A multi-centred, pragmatic, two-arm parallel open RCT. Participants with Subthreshold depression were individually randomised (1:1) to receive the self-help booklet based on the principles of behavioural activation or usual GP care**	**A Behavioural Activation Self-Help guide** Participants in the intervention arm were provided with a self-help booklet based on principles of BA for depression. The purpose of the booklet was to introduce simple behavioural strategies for improving mood. Participants were encouraged to (1) re-establish their daily routine, (2) increase meaningful activities and (3) reduce avoidance behaviours. Participants also received 3 phone calls at weeks 1, 3 and 6 designed to check the booklet had arrived and to encourage the use of the materials. All participants received their usual GP care **Usual GP care** Participants allocated to the control group received usual GP care. Participants did not receive any additional care to their usual primary care management for subthreshold (CASPER) or major (CASPER+) depression in line with NICE guidelines as implemented in their GP and local service provision.

5. Outcomes

5.1 Outcome Definitions

The primary outcome in the above trials is depression severity and symptomology measured by the Patient Health Questionnaire depression module (PHQ-9) at 4 months post-randomisation. The independent variable is the trial arm (BA vs. usual care). The putative effect modifier (moderator) is physical health at baseline, based on the SF-12 PCS at baseline and the effect modifier (moderator) pain is the EQ-5D at baseline

PHQ-9

The PHQ-9 is a nine-item depression scale. Each item is scored between 0 and 3. The total PHQ-9 scores can, therefore, range from 0 to 27. Higher scores denote greater depression severity.

SF-12

The SF-12 is a generic health status measure and a shorter form of the SF-36 health survey. The measure consists of 12 questions measuring 8 domains including General Health, Vitality, Physical, Role Physical, Role Emotional, Social Functioning, Mental Health and Bodily Pain over the past month Two summary scores are reported from the SF-12, a mental health component score (MSC) and a physical health component score (PCS). The PCS score will be used for the moderator variable of physical health. Scores range from 0 to 100 in each component score with higher scores denoting better physical health.

EQ-5D

The EQ-5D is a standardised measure of current health status developed by the EuroQol Group for economic and clinical appraisal. The EQ-5D consists of 5 questions assessing the various quality of life dimensions including mobility, self-care, usual activities, Pain/Discomfort and Anxiety/Depression. Each dimension is rated on three levels: no problem (score=1) some problems (score=2) and extreme problems (score=3). Question 4 relating to pain/discomfort will be used as an indicator for the pain moderator.

6. Analysis

The first step of the analysis plan will be to reproduce the results of the original statistical analysis for the trial's primary outcome of each of the datasets individually (i.e., CASPER, CASPER + and SHARD), using the statistical methods and results detailed in the published reports. This will be

done to validate the datasets. Then, to examine the research question, a secondary analysis will be conducted to explore the extent to which pain might modify the effect of BA on depression, both in the full dataset and stratified by sex. STRATA will be used to carry out analyses. First, treatment response heterogeneity (difference in response variance between intervention and comparator groups) will be quantified as a standard deviation representing the typical between-patient variability around the mean treatment effect (4,5). The effect modification of physical health on depression will be quantified by including a physical health× treatment arm interaction term in the analysis model. Physical health assessed by the SF-12 PCS will be treated as a continuous variable with the effect of BA on depression derived from scores of 0 to 100. The effect modification of pain on depression will be quantified by including a pain x treatment arm interaction term in the analysis model. Pain assessed by the pain/ discomfort dimension of the EQ5-D 3-level will be treated as a categorical variable (no problems/ some problems/ extreme problems), with the effect of BA on depression derived for 'some problems' versus 'no problems' and 'extreme problems' versus 'no problems. For all models, we shall inspect residuals plots to check that the residuals are well behaved, and the models properly specified. As the trials were not powered to detect sub-group (interaction) effects, all effect modification analyses are exploratory. We will report all effects as point estimates together with their 95% confidence intervals. The confidence intervals describe the range of effect sizes compatible with the data and model.

7. Signatures

Name	***Role***	***Signature***	***Date***
Alexandra Carne	Chief investigator		**16/01/2023**
Alan Batterham	Senior Statistician		

8. References

1. Fishbain DA, Cole B, Lewis JE, Gao J. Does pain interfere with antidepressant depression treatment response and remission in patients with depression and pain? An evidence-based structured review. Pain Medicine. 2014;15(9):1522-39.

2. Bair MJ, Robinson RL, Eckert GJ, Stang PE, Croghan TW, Kroenke K. Impact of pain on depression treatment response in primary care. Psychosomatic medicine. 2004;66(1):17-22.

3. Thielke SM, Fan M-Y, Sullivan M, Unützer J. Pain limits the effectiveness of collaborative care for depression. The American Journal of Geriatric Psychiatry. 2007;15(8):699-707.

4. Atkinson, G., & Batterham, A. M. (2015). True and false interindividual differences in the physiological response to an intervention. Experimental Physiology, 100(6): 577– 588.

5. Atkinson G, Williamson P, Batterham AM. (2019). Issues in the determination of 'responders' and 'non-responders' in physiological research. Experimental Physiology. 104(8):1215-1225.