Clinical effectiveness and cost-effectiveness of collaborative care for depression in UK primary care (CADET): a cluster randomised controlled trial

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Scientific summary

CADET: a cluster randomised controlled trial

Scientific summary

Background

Depression results in substantial disability and is recognised as a major health problem; it is currently the second largest cause of global disability. Around 350 million people are impacted by depression across the world and each year up to 5.8% of men and 9.5% of women will suffer from an episode of depression. Depression has a very significant impact on physical health, occupational functioning and the social lives of sufferers. Often anxiety is also present, causing further disability.

A systematic review of 36 organisational intervention studies concluded that simple models such as guidelines and practitioner education were ineffective in improving the management of depression. However, evidence is stronger on the role of organisational interventions in improving the management of a range of chronic conditions. The application of organisational strategies to the management of depression includes 'collaborative care', a complex intervention developed in the USA. Previous reviews of the management of depression have identified collaborative care as the most effective of organisational approaches.

Collaborative care incorporates a multiprofessional approach to patient care; a structured management plan; scheduled patient follow-ups; and enhanced interprofessional communication. In practice, this is achieved by the introduction of a care manager into primary care, responsible for delivering care to depressed patients under supervision from a specialist and for liaising between primary care clinicians and mental health specialists. Systematic reviews demonstrate that collaborative care improves depression outcomes, with some studies showing benefit for up to 5 years.

In 2008, at the commencement of the CollAborative DEpression Trial (CADET), collaborative care had generally been developed and tested in the USA within managed health-care settings. The limited non-US data and the relatively small effect size in trials of patients with depression alone led the UK National Institute for Health and Care Excellence (NICE) to issue a research recommendation that 'The efficacy of organisational interventions, such as chronic disease management programmes or other programmes of enhanced care for depression, should be tested in large-scale multicentre trials in the NHS'. This provided us with the rationale to undertake a fully powered UK evaluation of collaborative care. Prior to this trial in a Phase II test, we found preliminary evidence that collaborative care adapted to the UK was acceptable to patients and clinicians and may be effective outside the USA, but that a cluster randomised controlled trial was required to guard against potential contamination between trial arms.

Objectives

- To determine the clinical effectiveness and cost-effectiveness of collaborative care compared with usual care in the management of patients with moderate to severe depression.
- To investigate the potential moderators of differential participant response, the possible mechanisms of symptom change and the process of implementation of collaborative care.

Design

This study was a cluster randomised controlled trial.

Setting

This study took place in 51 UK primary care practices in three UK primary care districts.

Participants

A total of 581 adults aged ≥ 18 years who met *International Classification of Diseases*, Tenth Edition (ICD-10) criteria for a depressive episode on the revised Clinical Interview Schedule were included in the trial. We excluded acutely suicidal patients and those with psychosis or type I or type II bipolar disorder, patients whose low mood was associated with bereavement or whose primary presenting problem was alcohol or drug abuse and those receiving psychological treatment for their depression from specialist mental health services. We identified potentially eligible participants by searching general practice computerised case records for patients with depression.

Randomisation

We randomly allocated primary care practices to either collaborative care or treatment as usual as they were recruited into the trial, minimised within sites by Index of Multiple Deprivation (IMD) rank, number of general practitioners (GPs) and practice size.

Allocation concealment

The allocation sequence was concealed from researchers who recruited practices and was administered centrally by the trial statistician using Minim (www.sghms.ac.uk/depts/phs/guide/randser.htm). The Peninsula Clinical Trials Unit (PenCTU) remotely managed participant identification and the trial databases.

Blinding

Research workers blind to practice allocation assessed participants for eligibility and collected outcome measures using participant self-report questionnaires to minimise the effect of potential unblinding. Because of the nature of the intervention, it was not possible to blind participants, care managers or GPs to allocations.

Interventions

Collaborative care
Developed in our previous studies, collaborative care was delivered by a team of care managers, supervised by mental health specialists. Supervision of care managers for their trial work was provided by psychiatrists and psychological therapists from the trial team. During sessions, care managers:

- assessed participants' views of depression and their attitudes to and concordance with psychosocial and pharmacological treatments
- negotiated shared treatment decisions with participants
- assisted participants to manage antidepressant medication if prescribed
- delivered a brief low-intensity psychosocial intervention in the form of behavioural activation
- provided participants with relapse prevention advice.

Usual care

Participants received care from their GP according to usual clinical practice, which for these participants included treatment with antidepressants and referral for other treatments. We recorded every aspect of usual care but did not specify a treatment programme, in line with the pragmatic nature of this trial.

Measures

Baseline information

We collected demographic data at baseline through a purposely designed form. We recorded data on sex, age, ethnic origin, education level, employment, marital status, presence or absence of antidepressant treatment, previous history of depression, severity of depression, any secondary diagnosis of an anxiety disorder, any long-standing physical illness, health and social care resource use by participants over the previous 6 months and informal care from friends/relatives, and patient costs over the previous 6 months.

Primary clinical outcome

Our primary clinical outcome was individual participant depression severity measured by the [Patient Health Questionnaire-9 (PHQ-9)] at 4 months.

Secondary clinical outcomes

Our secondary outcomes were the PHQ-9 at 12 months, quality of life [Short Form questionnaire-36 items (SF-36)], worry and anxiety [General Anxiety Disorder-7 (GAD-7)] at 4 and 12 months, health state values (health-related quality-of-life) [European Quality of Life-5 Dimensions three-level version (EQ-5D-3L)] at 4 and 12 months and participant satisfaction (Client Satisfaction Questionnaire-8) at 4 months. We also collected PHQ-9, GAD-7 and SF-36 data at 36 months.

Economic outcomes

Our primary economic end point was the cost per quality-adjusted life-year (QALY) at 12 months' follow-up. We derived these QALY estimates using EQ-5D-3L trial data from the baseline and 4- and 12-month assessments, applying the area under the curve approach, a recognised approach for assessing repeated measures. We collected resource use associated with delivery of the collaborative care intervention within the trial, consisting of care manager contact time and supervision of care managers by specialists. We collected other health and social care resource use by participants over the 12-month follow-up and data on informal care from friends/relatives and patient costs using self-report, interviewer-administered questionnaires (at 4 and 12 months, covering the previous 4-month and 8-month time periods, respectively).

Process analysis outcomes

At baseline we recorded six possible moderators: measures of patient attitudes towards antidepressant medication, attitudes towards behavioural activation, depression severity (PHQ-9), history of depression (number of previous episodes), physical health (comorbidity) and socioeconomic status using the postcode for participants' residence to obtain an IMD score at the lower super output area level. We measured participants' adherence to antidepressant medication and level of behavioural activation at 4 and 12 months through self-report of medication adherence and the Behavioural Activation for Depression Scale – Short Form. We conducted face-to-face interviews with care managers and supervisors involved in delivering and supervising collaborative care and undertook telephone interviews with a sample of GPs from intervention practices. We used routinely collected data from session audio tapes collected by care managers for supervision to analyse the process of implementation.

Sample size

We powered the trial at 90% (alpha = 0.05) to detect an effect size of 0.4, which we regarded as a clinically meaningful difference between interventions. This figure was within the 95% confidence interval (CI) of the effect predicted from data collected during our pilot work (effect size 0.63, 95% CI 0.18 to 1.07). To detect this difference would have required 132 participants per group in a two-armed participant-randomised trial. For our cluster trial, with 12 participants per primary care cluster and an intracluster correlation (ICC) of 0.06 from our pilot trial, the design effect was 1.65 leading to a sample size of 440. To follow up 440 participants, we aimed to randomise 550 participants (anticipating 20% attrition). Because recruitment would not be uniform between practices, we aimed to recruit 48 practices with up to 14 participants in a practice.

Statistical methods and analyses

Clinical outcomes

We undertook intention-to-treat analyses for all outcomes, reported in accordance with Consolidated Standards of Reporting Trials (CONSORT) guidelines. All analyses were undertaken in Stata 10.1 (StataCorp LP, College Station, TX, USA), following a predefined analysis plan agreed with the Trial Steering Committee. We analysed outcome data at 4, 12 and 36 months by ordinary least squares or logistic regression, allowing for clustering by use of robust standard errors, adjusting at the cluster level for minimisation variables and site and at the individual level for age and, when appropriate, the baseline measurement of the variable. We analysed the effect of missing data as a sensitivity analysis, estimated by chained regression equations multiple imputation using all available scale clinical scores, age, sex, practice variables, site and treatment group.

Economic outcomes

We adopted the perspective of the UK NHS and Personal Social Services (third-party payer perspective), with a broader participant and carer perspective considered in sensitivity analyses. We estimated the costs associated with health and social care service use and the additional cost for delivery of the collaborative care intervention and estimated QALYs. The primary economic analyses estimated mean cost and mean QALYs by treatment allocation and used prespecified covariates for age (at the individual level) and deprivation (IMD), site and practice size (at the cluster level). We used a multilevel regression model for the primary analyses, to consider the hierarchical (clustered) nature of the data, presenting the ICC for the main analyses.

Process data

To explore the role of moderators, we analysed the direct effects of our six baseline covariates on depression severity (PHQ-9) at 4 and 12 months using multilevel multiple linear regression. Potential mediating effects of collaborative care were investigated using structural equation modelling in Stata. We used an iterative approach using constant comparison techniques to analyse interview transcripts. Following the thematic analysis we conducted a further theory-driven analysis of the data guided by the four main constructs of normalisation process theory. We analysed the implementation of the intervention by transcription and analysis of audio files using a thematic analysis similar to that for the interview data.

Results

Collaborative care participants had a mean depression score that was 1.33 PHQ-9 points lower (95% CI 0.35 to 2.31; $p = 0.009$) than that of participants in usual care at 4 months and 1.36 PHQ-9 points lower (95% CI 0.07 to 2.64; $p = 0.04$) at 12 months after adjustment for baseline depression. Quality of mental health but not physical health was significantly better for collaborative care at 4 months but not 12 months and there was no difference for anxiety. Participants receiving collaborative care were significantly more satisfied with treatment. There were no differences between groups at 36 months' follow-up.

Collaborative care had a mean cost of £272.50 per participant with similar health and social care service use between collaborative care and usual care. Collaborative care offered a mean incremental gain of 0.02 (95% CI –0.02 to 0.06) QALYs over 12 months, at a mean incremental cost of £270.72 (95% CI –£202.98 to £886.04) and resulted in an estimated mean cost per QALY of £14,248. When costs associated with informal care were considered in sensitivity analyses collaborative care is expected to be less costly and more effective (–£1114, 95% CI –£3366 to £1117).

There was little evidence of overall moderation of depression severity at 4 months ($\chi^2 = 10.01$; $p = 0.35$) or 12 months ($\chi^2 = 5.63$; $p = 0.78$). The effect of collaborative care at 4 and 12 months was mediated fully by behavioural activation at 4 months (coefficients: 4.00, 95% CI 1.46 to 6.55 and 3.86, 95% CI 1.30 to 6.42, respectively) with no mediation by medication adherence (coefficients: –0.03, 95% CI –0.14 to 0.08 and –0.01, 95% CI –0.12 to 0.17, respectively). We found a similar but weaker pattern of mediation by 12-month variables on outcomes at 12 months.

Supervisors and care managers demonstrated coherence in their understanding of collaborative care and consequently reported good levels of cognitive participation and collective action regarding delivering and supervising the intervention. GPs showed limited understanding of the collaborative care framework and reported limited collaboration with care managers. All participants identified the potential or experienced benefits of a collaborative approach to depression management and were able to discuss ways in which collaboration can be facilitated.

We derived three themes on the process of treatment delivery: (1) engaging the patient, with care managers making efforts to develop a therapeutic relationship with participants, (2) adopting a counselling model, with care managers moving beyond simply being empathic to engage the participant and towards something more recognisable as counselling and (3) variations in the delivery of behavioural activation describing variations in the adherence of the care managers to the behavioural activation protocol.

Conclusions

Collaborative care improves depression up to 12 months after initiation of the intervention, is preferred by patients over usual care, offers health gains at a relatively low cost, is cost-effective compared with usual care and is mediated by patient activation. Future work should test enhanced intervention content not collaborative care per se.

We found that collaborative care improved depression at our primary end point of 4 months compared with usual care, an effect that persisted up to 12 months. Collaborative care is cost-effective when service commissioners are willing to pay up to £20,000 per QALY gained and was preferred by patients over usual care. The differences in clinical outcomes between participants treated by collaborative care and participants treated by usual care were no longer apparent at 36 months' follow-up. In our process analyses we have demonstrated that only one variable, the amount of behavioural activation undertaken by participants, predicted better outcomes, despite the fact that there was considerable variation in how behavioural activation was both explained and operationalised by care managers in sessions. We also found that care managers and supervisors regarded collaborative care as coherent but that the collective action required to implement elements of collaborative care was made difficult by GPs' lack of engagement with the collaborative care framework.

There is now evidence to answer NICE's uncertainty in that collaborative care is a clinically effective and cost-effective system leading to better short- and medium-term (but not long-term) effects compared with usual care that could be applied to the UK NHS. Future trials should test enhancements of the basic collaborative care model by developing, examining and delivering better treatments *within* the effective collaborative care organisational framework, or improve the delivery of existing treatments, rather than test collaborative care per se, given that the effects of collaborative care are now firmly established.

Trial registration

This trial is registered as ISRCTN32829227.

Funding

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This report
This issue of Health Technology Assessment contains a project originally commissioned by the MRC but managed by the Efficacy and Mechanism Evaluation Programme. The EME programme was created as part of the National Institute for Health Research (NIHR) and the Medical Research Council (MRC) coordinated strategy for clinical trials. The EME programme is funded by the MRC and NIHR, with contributions from the CSO in Scotland and NISCHR in Wales and the HSC R&D, Public Health Agency in Northern Ireland. It is managed by the NIHR Evaluation, Trials and Studies Coordinating Centre (NETSCC) based at the University of Southampton.