Cognitive behavioural therapy as an adjunct to pharmacotherapy for primary care based patients with treatment resistant depression: results of the CoBalT randomised controlled trial

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Abstract [266 words]

Background: Only one-third of patients with depression respond fully to antidepressant medication but there is little evidence regarding the best 'next step' treatment for those whose symptoms are 'treatment resistant'. The CoBalT trial examined the effectiveness of CBT as an adjunct to usual care (including pharmacotherapy) for primary care patients with treatment resistant depression (TRD) compared with usual care alone.

Methods: This two parallel-group multi-centre randomised controlled trial recruited 469 patients with TRD (on antidepressants for ≥6 weeks, Beck Depression Inventory (BDI) score ≥14 and ICD-10 criteria for depression) from 73 UK general practices. Participants were randomised, using a computer generated code, to one of two groups: usual care (n = 235) or CBT in addition to usual care (n = 234), and were followed up for 12 months. The primary outcome was 'response', defined as ≥50% reduction in depressive symptoms (BDI score) at 6 months compared to baseline. Trial registration was ISRCTN38231611.

Findings: 422 participants (90%) were followed up at 6 months and 396 (84%) at 12 months. 95 participants (46.1%) in the intervention group met criteria for 'response' at 6 months compared with 46 (21.6%) in the usual care group (odds ratio (OR): 3.26 (95%CI: 2.10, 5.06) p<0.001). In repeated measures analyses using data from 6 and 12 months, the OR for 'response' was 2.89 (2.03, 4.10), p<0.001 and for a secondary 'remission' outcome (BDI score <10) was 2.74 (1.82, 4.13), p<0.001.

Interpretation: Amongst patients who have not responded to antidepressants, CBT in addition to pharmacotherapy is effective in reducing depressive symptoms, and these effects, including outcomes reflecting remission, are maintained over 12 months.

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Introduction

Depression is a major public health problem. It is predicted to be the leading cause of disability in high income countries by 2030, with only HIV/AIDS and perinatal conditions ranking higher for low and middle income countries[1]. Antidepressants are often the first-line treatment for depression and prescriptions for such medication have increased dramatically in recent years[2;3]. However, only one-third of patients respond fully to pharmacotherapy and half do not experience at least a 50% reduction in depressive symptoms after 12-14 weeks of medication[4]. Where an adequate dose and duration of treatment has been given, such non-response may be termed 'treatment resistance'. There is no agreed definition of treatment resistance[5] but, given the extent of non-response, it is clear that treatment resistant depression (TRD) has a substantial impact on individuals, health services and society.

There is no standard approach to the management of TRD. 'Next step' options include increasing the dose of pharmacotherapy, switching to a different antidepressant or augmentation with another pharmacological or psychological treatment. However, there is little robust evidence that these approaches improve outcome[6;7].

There is good evidence that cognitive behavioural therapy (CBT), the most widely available structured psychotherapy for depression, is effective for previously untreated episodes of depression. There has been some investigation of CBT and its variants in treating chronic and treatment resistant depression. The STAR*D trial evaluated a number of alternative treatment strategies (including switching to, or augmentation with, CBT[8]) following non-response to medication. However, it did not include a comparison group of patients who continued on their existing medication; hence it is not possible to evaluate the effect of augmenting antidepressant medication with CBT as a 'next step' treatment option from STAR*D. In patients with chronic depression, Keller et al[9] investigated a variant of CBT, cognitive behavioural analysis system of psychotherapy (CBASP) that puts more emphasis on behavioural and interpersonal factors than more traditional CBT. Keller et al[9] found that combined psychotherapy and nefazodone (now withdrawn) was more effective than either component alone. However, a more recent trial of patients with chronic depression that had not responded to antidepressant medication found no difference in response between those who received combined treatment (CBSAP and medication) compared with medication alone[10].

Limited access to psychological treatment in the UK and elsewhere has meant that, in clinical practice, CBT has often been reserved for those who have not responded to antidepressants. No large-scale randomised controlled trials (RCTs)[6;7] have evaluated the effectiveness of CBT following non-response to pharmacotherapy compared with continuing pharmacotherapy as part of usual care for patients with TRD..We chose to investigate CBT rather than CBASP as there is evidence that CBT may reduce rates of relapse[11], including amongst those with residual depressive symptoms[12]. Furthermore , some models of more persistent depression put emphasis on the cognitive rather than behavioural aspects of treatment[13].

The aim of the CoBalT trial was to examine the effectiveness of CBT as an adjunct to usual care including pharmacotherapy for primary care patients with treatment resistant depression compared with usual care alone. The economic evaluation will be reported separately.

Methods

Study design

CoBalT was a multi-centre pragmatic RCT with two parallel groups[14]. Ethical approval was given by the West Midlands Research Ethics Committee (NRES/07/H1208/60) and research governance approval was obtained from the local Primary Care Trusts/Health Boards.

Setting and Participants

Participants were recruited from 73 general practices in urban and rural settings in three UK centres: Bristol, Exeter and Glasgow. Most participants were identified through a search of practice computerised medical records, although general practitioners (GPs) were able to refer patients directly to the research team. The first record search took place in November 2008 and the last patient was randomised in October 2010.

Eligible patients were those aged 18 to 75 years who had adhered[15;16] to an adequate dose (based on the British National Formulary (www.bnf.org.uk/bnf) and advice from psychopharmacology experts (Web Appendix 1)) of antidepressant medication for at least 6 weeks and had a Beck Depression Inventory (BDI)[17] score of 14 or more. They also met ICD-10 criteria for a depressive episode assessed using the revised Clinical Interview Schedule (CIS-R)[18;19]. GPs were asked to exclude

patients who: (i) had bipolar disorder, psychosis or major alcohol/substance abuse problems; (ii) were unable to complete the questionnaires; and (iii) were pregnant. Individuals who were currently receiving CBT or other psychotherapy (including counselling) or secondary care for their depression, or who received CBT in the past three years, or who were taking part in another intervention study were also excluded.

Recruitment

A three-stage recruitment process was used[14]. The record search identified patients who had received repeated prescriptions for antidepressants. Those who agreed to be contacted by the research team were mailed a short questionnaire that included questions about their depression and adherence to antidepressants. Those who met the definition of TRD (BDI score ≥14 and adhered to antidepressants at an adequate dose for at least 6 weeks) were contacted by telephone by a researcher to ascertain their eligibility with respect to current/past psychological treatment and current secondary care for depression. Potentially eligible patients were invited to attend a face-to-face appointment with a researcher to discuss participating in the trial and confirm their eligibility (BDI score ≥14, continuing to take antidepressants at an adequate dose and fulfilling ICD-10 criteria for depression). Ineligible patients (and those who declined participation) were referred back to their GP.

Randomisation, concealment of allocation and blinding

After the collection of baseline data and obtaining written informed consent for trial participation, eligible patients were randomised to one of two groups: (1) usual care or (2) CBT in addition to usual care. Allocation was stratified by centre and minimised (with a probability weighting of 0.8[20]) on: (i) baseline BDI score (14-19; 20-28; ≥29); (ii) whether the general practice had a counsellor (yes/no); (iii) prior treatment with antidepressants (yes/no); and (iv) duration of their current episode of depression (<1 year; 1-2 years; ≥2 years).

Participants were taking antidepressants at the time of randomisation and were expected to continue with these as part of their usual care from their GP. Treatment allocation was concealed from the researcher through the use of an automated telephone randomisation service that was administered remotely and used a computer-generated code. Given the nature of the intervention it was not possible to blind participants, GPs, CBT therapists or researchers to the treatment allocation.

Intervention and comparator (usual care) groups

Usual care

There were no restrictions on the treatment options for patients randomised to be managed as usual by their GP. Participants could be referred for counselling, CBT or to secondary care, if it was clinically appropriate.

Intervention

Participants received 12 sessions of individual CBT (each lasting 50-60 minutes), with (up to) a further six sessions if judged to be clinically appropriate by the therapist (maximum of 18 sessions)) in addition to usual care from their GP. Therapy took place in the patient's GP surgery or at nearby National Health Service (NHS)/University premises. Therapists used the seminal CBT for depression treatment manuals[21;22] and, where appropriate, elaborations designed to address treatment resistance[13]. Therapists received at least 1 day of training specific to the trial from an experienced CBT therapist (AG) and weekly supervision from experienced CBT supervisors at each centre (GL, WK & CK). Therapists were flexible in responding to problems raised by the patient (e.g. by targeting symptoms of anxiety using appropriate cognitive behavioural models, if these were considered important). Emphasis was also given to formulating the psychopathology in terms of conditional beliefs.

The intervention was delivered by 11 part-time therapists in the three sites who were representative of those working within NHS psychological services[14]. Ten out of the 11 therapists were female, their mean age was 39.2 years (SD 8.1) and they had practised as a therapist for a mean of 9.7 years (range: newly qualified to 30 years).

With patient consent, therapy sessions were audio-recorded. Fidelity of the intervention to the CBT model was evaluated[14] for a random sample of recordings by three independent raters from the Oxford Cognitive Therapy Centre using the Cognitive Therapy Rating scale (CTS-R), a valid and reliable CBT rating scale[23].

Follow-up

Participants were followed up 3, 6, 9 and 12 months after randomisation[14]. Wherever possible, to maximise retention, researchers met with the participant face-to-face at 6 months and 12 months. Follow-ups at 3 and 9 months were conducted by telephone. Follow-up data were collected between March 2009 and October 2011.

Outcome measures

The primary outcome was the BDI score at 6 months, specifically a binary variable representing response, defined as a reduction in depressive symptoms of at least 50% compared to baseline.

Secondary outcomes included the BDI score as a continuous variable, remission of symptoms (BDI score of less than 10), and quality of life (SF-12)[24] at 6 and 12 months[14]. Other secondary outcomes at 6 and 12 months were panic[25], and measures of depression (PHQ-9[26]), and anxiety (GAD-7[27]) used in psychological services[28]. Data on use of, and adherence to, antidepressant medication were also collected.

Sample size

The original sample size calculation (using nQuery 5.0) indicated that 472 participants would provide 90% power to detect a difference of 16 percentage points in 'response' between the two groups based on a 2-sided 5% significance level and 15% loss to follow-up at 6 months. This corresponds to an odds ratio of 2, considered clinically important and smaller than that derived from a systematic review of CBT[29]. However, a slightly lower recruitment rate in one centre and difficulty matching recruitment rates to therapist capacity in two centres resulted in a revised sample size target of 432, which had 90% power to detect a 17 percentage point difference (30% versus 47%) in the binary 'response' outcome and 87% power to detect the original difference[14].

Statistical Analysis

Analysis and reporting of this trial was in accordance with Consolidated Standards of Reporting Trials (CONSORT) guidelines[30]. All analyses were undertaken in Stata 11.2, following a pre-defined analysis plan agreed with the Trial Steering Committee.

Patient characteristics were compared at various stages of study recruitment, including using descriptive statistics to assess the baseline comparability of the randomised groups. The primary comparative analyses between the randomised groups were conducted according to the principle of intention-to-treat (ITT) without imputation of missing data. Logistic regression was used to compare the binary primary outcome at 6 months between the groups as randomised, adjusting for study centre, baseline BDI score and the other three minimisation variables. Secondary analyses used similar regression models with additional adjustment for any variables that demonstrated marked imbalance at baseline and any differences in the actual time to follow-up. The analysis of other

secondary outcomes used linear or logistic regression as appropriate, and adjusted for any baseline imbalances. Repeated measures logistic and linear regression models were used to summarise the effect of the intervention on outcomes over 12 months. Odds ratios (OR) or differences in means, 95% confidence intervals (95%CIs) and p values are reported.

Secondary analyses used generalised latent and linear mixed models to obtain a fully specified heteroscedastic model[31] to examine the influence of clustering by therapist. In addition, sensitivity analyses examined the impact of missing data using the method of multiple imputation by chained equation (*ice* procedure version 1.9.5 dated 15 April 2011; 25 datasets ; 10 switching procedures). The imputation model included the variables in the primary ITT model, together with variables associated with missing BDI data at 6 or 12 months and other measures of depression/anxiety. Instrumental variable regression methods were used to estimate the Complier-Average Causal Effect (CACE)[32] for those who were viewed as 'on track' to receive the full course of therapy at the time of the 6-month follow-up (defined as having received 9 or more sessions of CBT) and the longer-term 12-month outcome (based on having received at least 12 sessions of CBT) for the binary 'response' (probit regression) and continuous (linear regression) BDI outcomes. (The original definition[14] of a 'complier' included those whose therapy goals were achieved but this was made stricter as it included those who had received fewer than 8 sessions.) Finally, two pre-planned subgroup analyses were conducted by including an interaction between treatment allocation and patient expectation of outcome or degree of treatment resistance (based on duration of current symptoms and past treatment with antidepressant medication).

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, interpretation of data, or writing of the paper. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Participant flow and retention

A detailed description of the recruitment process is outlined in Web Appendix 2 and a summary CONSORT diagram is presented in Figure 1. In total, 912 patients were identified as having TRD and invited to attend a baseline appointment, but 163 (18%) declined. There were no age or gender differences between those who declined and agreed to attend such an appointment (data not

shown), although those who agreed were more highly educated (p=0.009). At baseline, men were more likely to be ineligible (p=0.02) but there were no differences in age or educational background between those who were or were not eligible to participate in the trial (data not shown). Of the 749 who attended a baseline appointment, 63% (n=469) were eligible to participate and gave written informed consent.

Of those randomised, 234 were allocated to receive the intervention and 235 to continue with usual care from their GP. Ninety percent of participants were followed up at 6 months and 84% at 12 months (Figure 1). Older individuals, women, those from higher socio-economic backgrounds, with more social support and better physical function were less likely to have missing BDI outcome data (data not shown). There was some evidence that those who were single, those with more severe depression at baseline, and those who scored more highly on measures of panic were more likely to have missing outcome data (data not shown).

Baseline characteristics of participants

The majority of participants were women (n=339, 72%), the mean age was 49.6 years (SD 11.7) and 44% (n=206) were in paid employment (full/part-time). The mean BDI score at baseline was 31.8 (SD 10.7). Twenty-eight percent (n=129) currently fulfilled ICD-10 criteria for a severe depressive episode and the majority (n=415, 88%) had suffered from depression in the past. The duration of the current episode of depression was 2 years or longer for 59% (n=276) of participants and 70% (n=327) had been on their current antidepressant(s) for more than 12 months. Selective Serotonin Reuptake Inhibitors (SSRIs) were the most common antidepressant taken at baseline (n =334) (further details are given in Web Appendix 3).

Most participants (n=347) had a secondary diagnosis of an anxiety disorder according to the CIS-R (generalised anxiety: n=245; panic disorder: n=67; phobias: n=35). Forty-three percent (n=202) of participants reported another longstanding illness or disability (diabetes, asthma, arthritis, heart disease, high blood pressure or lung disease).

Amongst those randomised, the intervention group included more men, more individuals in paid employment and more who reported financial difficulty, fewer individuals with caring responsibilities or longstanding illness/disability and better physical function (SF-12) (Table 1). A smaller proportion of those in the intervention group had taken their current antidepressants for

more than 12 months and they were less likely to have experienced 5 or more prior episodes of depression, although a greater proportion had a family history of depression.

Delivery and receipt of the intervention

Nine of the 11 therapists delivered 97% of the intervention and, for these, the number of patients per therapist ranged from 13 (5.6%) to 41 (17.5%). The mean CTS-R rating (adjusted for caseload) based on a random sample of 54 sessions was 38.8 (95%CI: 36.7, 40.8) which is above the threshold of competence expected in UK CBT training programmes.

The average duration of the intervention (from randomisation) was 6.3 months (SD 3.0). Twenty participants (8.5%) did not attend any therapy sessions. In total, 74 participants (31.6%) either withdrew from therapy (n=47) or were discharged having repeatedly not attended appointments (n=27). The number withdrawing increased to 70 if those participants who reached an 'agreed end' in less than 12 sessions were included.

By 6 months, those randomised to the intervention had received a median of 11 sessions of CBT [IQR: 5, 13] and 62% (n=144) had received at least 9 sessions. By 12 months, the median was 12 [IQR: 6, 17] and 141 participants had received at least 12 sessions.

Primary outcome – 'response' at 6 months

Those in the intervention group had a three-fold increased odds of 'response' at 6 months compared with those in the usual care group (Table 2). Adjustment for imbalances at baseline had little effect, if anything slightly increasing the estimated effect, and adjustment for the actual time to follow-up did not affect the findings (data not shown). The difference in proportions 'responding' equated to a number needed to treat (NNT) of 4 (95%CI: 3, 6) for each additional 'responding' patient.

Secondary outcomes at 6 months

The beneficial effect of the intervention was confirmed for the secondary outcomes at 6 months (Table 2). Those in the intervention group had a BDI score that was, on average, 5.7 points lower (less depressed) than those in the usual care group, which equated to an effect size of 0.53 using baseline SD for BDI (pooled). Those in the intervention group were also more likely to experience 'remission' (BDI score<10) at 6 months (NNT 8 (95%CI: 5, 20)), to have fewer symptoms of anxiety (GAD-7) and panic at 6 months and had greater improvements in the SF-12 mental health subscale (Table 2). There was weak evidence that those in the intervention group fared worse on the SF-12

physical subscale, but the difference was small and the 95%CI included the null (Table 2). Adjustment for baseline imbalances did not affect any of these findings (data not shown).

Secondary analyses for the primary outcome

There was little evidence of clustering of outcomes by therapist (intracluster correlation coefficient for continuous BDI score, after adjustment for baseline, was 0.0027). In a fully heteroscedastic model that accounted for clustering by therapist, the results obtained for the primary 'response' outcome were identical to those obtained from the primary ITT analysis (data not shown). The results imputing missing data were consistent with the findings of the primary 'complete-case' analysis (Table 3). Regarding *a priori* subgroup analyses, there was no evidence that patient expectation of outcome or degree of treatment resistance had any effect on the difference between intervention and usual care groups (p value for interaction: 0.16 and 0.88 respectively). In a post-hoc sub-group analysis, there was no evidence that study centre had any effect on the difference between the intervention and usual care groups (p value for interaction between treatment allocation and centre: 0.61).

Outcomes over 12 months

In repeated measures analyses using data from 6 and 12 months, those in the intervention group had a three-fold increased odds of response and remission over the 12 months (Table 4). There was little evidence that the effect of the intervention varied over time (p value for interactions >0.10), with the exception of the outcomes on the PHQ-9 and SF-12 physical sub-scale where there was weak evidence for an interaction (p =0.059 and p=0.047 respectively).

Treatment efficacy

Compared with the ITT models in Table 2, the estimates of treatment efficacy obtained from CACE analyses demonstrated that the effect of the intervention was larger amongst those who were 'on track' at 6 months to complete the intervention, and likewise among those who received at least 12 sessions by 12 months. At 6 months the CACE estimate for the continuous BDI outcome was -8.2 (95%CI: -11.4, -5.0), and at 12 months -7.1 (95%CI: -10.4, -3.8) (effect size 0.77 and 0.66 respectively; both p<0.001). Larger effects were also observed for the binary outcomes using probit regression (data not shown).

Of 388 participants with data at 6 and 12 months, 66 participants (17%) had at least one session of 'talking therapy' outwith the trial during the 12 months (usual care: n = 41 (21.0%); intervention: 25

(13.0%)). Only 5 participants (3 usual care; 2 intervention) had received at least 12 sessions of CBT outwith the trial by 12 months. Estimates of treatment efficacy accounting for contamination by the receipt of such CBT were identical (data not shown).

Use of, and adherence to, antidepressants over the study

At 6 months, 93% of both groups were taking antidepressant medication (difference: -0.6% (95%CI: -5.4, 4.2)). At 12 months, 88% of those in the intervention group were taking antidepressants compared with 92% of those randomised to usual care (difference: -4.5% (95%CI: -10.4, 1.3)). Of the 354 participants with self-report data on the type and dose of antidepressant medication taken at 12 months, 154 (43.5%) reported taking a different type or dose of medication from that at baseline (intervention group: n = 76 (44.2%); usual care group: n = 78 (42.9%)).

Of those taking antidepressants at 6 months, 92% of the intervention group and 88% of those in usual care had adhered to their medication over the previous 6 weeks. The comparable figure at 12 months for both groups was 93%.

Discussion

CBT as an adjunct to usual care that included pharmacotherapy was effective in reducing depressive symptoms and improving quality of life in primary care patients with TRD. The beneficial effect of the intervention was also observed for the more stringent criteria of 'remission' and improvements were maintained over 12 months.

There is no single accepted definition of TRD, hence we used an inclusive and pragmatic definition that would be generalisable to primary care[33]. Participants had not responded to at least 6 weeks treatment with an antidepressant; however, this was a heterogeneous group with many reporting chronic depression often associated with psychological and/or physical co-morbidities. The mean BDI score was 31.8, 29% of participants had severe depression at baseline according to ICD-10 criteria, and most had a past history of depression, with the majority reporting at least five previous episodes. Hence, we think that the results are generalisable to a wide range of patients who have not responded to antidepressants.

Prior to this study, there was no evidence from large-scale RCTs on the effectiveness of CBT as an adjunct to pharmacotherapy as a 'next step' treatment option for primary care patients who had not

responded to antidepressants[6;7]. Recent trials (including our pilot[34]) were small (n<50)[35;36]. In the STAR*D study , only 26% of participants were willing to be randomised to CBT as a second-step option[8] and individuals who could not tolerate citalopram were included, making extrapolation difficult as clinically such individuals would usually be managed by a change of antidepressant. Like CoBalT, many participants in the CBT augmentation group of STAR*D (n = 65) had a history of depression (86%), with an average of seven prior episodes[8]. Thirty-five percent of STAR*D participants whose medication was augmented by CBT fulfilled criteria for response based on self-rated depressive symptoms[8], slightly lower than our findings using the BDI (46.1%), although remission rates were similar. However, STAR*D[8] and other studies[35;36] answered a different question than that posed in CoBalT. They provide evidence on alternative treatment approaches to the management of those who do not respond to antidepressants, rather than examining the effectiveness of augmenting antidepressant medication with CBT as a 'next step' option.

The effects observed are comparable to the findings of an earlier RCT of combined psychological (CBASP) and pharmacological treatment for chronic depression[9]. However, the more recent REVAMP trial of a similar population who had not responded to antidepressant medication found no difference in response after 12 weeks between those who received combined treatment compared with medication alone[10].In the latter, participants attended fewer sessions of CBASP than for the earlier chronic depression trial[9] (mean: 12.5 vs. 16), which may contribute to explaining the differing findings. CBASP and the more 'traditional' CBT delivered in CoBalT differ in terms of emphasis. The Beckian CBT approach adapted by Moore and Garland[13] and used in CoBalT emphasises the cognitive elements of treatment and has also been shown to be effective in those with residual depression[12].

In the REVAMP trial, a treatment algorithm was used and pharmacotherapy changed to the 'next-step' following randomisation[10]. However, the use of a medication algorithm is not a pragmatic approach towards pharmacotherapy. There was a higher remission rate amongst those receiving pharmacotherapy in REVAMP (38.5% at 12 weeks) compared with CoBalT (15.0% for the usual care group at 6 months), but this may relate to differences in the patients recruited. Only 33% of REVAMP participants had previously had an adequate trial of pharmacotherapy, whereas 80% of CoBalT participants had previously been prescribed antidepressants and most (70%) had been on their current medication for more than 12 months.

Strengths and limitations of the study

This was a large study with high follow-up rates at 6 and 12 months. There was no evidence that missing data had biased findings. Though there were some imbalances in baseline characteristics, between the randomised groups, if anything, adjusting for these increased the size of the treatment effect for the primary outcome. Only a minority of participants received CBT outwith the trial so such contamination had little impact on the findings.

We did not compare CBT with an "attention" control as we wanted to ask a pragmatic question about the value of adding CBT to antidepressants in this population. This meant we could not blind patients or researchers to the treatment allocation but we avoided observer bias by using self-report questionnaires to measure outcome. Our primary outcome was depressive symptoms on the BDI. This instrument was also used by the therapists within CBT sessions; hence, for those in the intervention group, the responses on this specific measure may have been influenced by the process of therapy. However, results were consistent for the other mental health outcomes (that were not used in therapy), including for the PHQ-9, which is part of the core outcome dataset within UK psychological services[28].

An independent evaluation confirmed that the therapy was delivered at a 'competent'[23] standard. The therapists were broadly representative of those working in NHS psychological services with a range of experience and backgrounds and thus the results should therefore be generalisable. There was no evidence of any clustering of outcomes by therapist.

We relied on a self-report measure of adherence to medication[15] that had been validated against electronic monitoring bottles[16] in order to define our population with TRD. Whilst some of those recruited may not have adhered to their medication ('false positives'), the vast majority had, at baseline, been on their current antidepressant for more than 12 months, which is likely to minimise the effect of occasional non-adherence.

Implications for practice and directions for future research

A substantial proportion of people do not respond to antidepressants and our results have provided robust evidence that CBT given as an adjunct to usual care that includes antidepressant medication is an effective treatment in reducing depressive symptoms and improving quality of life in this population. The size of the treatment response was substantial and of clinical importance and was maintained at the 12 month follow-up after the CBT treatment had ended. Given the chronic

relapsing nature of depression, it would be important to examine the long-term outcome of this intervention.

Though we did not test different approaches towards the delivery of CBT we think that the complex mental health needs of this population require therapists who are able to tailor the treatment approach to the individual and formulate conditional beliefs that, according to cognitive theory[13;21], underpin the longer term risk of depression. This kind of therapy would be delivered by "high intensity" services in England[28] (http://www.iapt.nhs.uk/) and requires both training and regular supervision.

In many countries, access to psychological treatment is limited to those who can afford to pay, or those with health insurance, and amongst the latter, cost-sharing through co-payment is common. Increasing the availability of CBT is more difficult than providing an intervention such as pharmacotherapy. There have been recent initiatives to increase access to psychological therapies in England[28] (IAPT: http://www.iapt.nhs.uk/) and Australia (http://www.health.gov.au/mentalhealth-betteraccess/). The IAPT scheme, for example, has provided training and set minimum standards of competencies and supervision in order to provide a consistent standard of care. Worldwide, such initiatives are rare and more investment is needed. In the United States, less than a quarter of those with depression have seen a psychologist or counsellor in the previous 12 months[37], and half receive less than the recommended number of therapy sessions[38]. Even those who attend therapy often receive an "eclectic mix of psychotherapy techniques"[39] rather than CBT. Only through greater investment in psychological services that deliver evidence-based therapies will it be possible to reduce the significant burden to patients, health care systems and society that is associated with non-response to the most common first-line treatment for depression in primary care.

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Panel: Research in context

Systematic Review

Systematic reviews of psychological interventions for treatment resistant depression have found no large-scale high quality trials of CBT as an adjunct to pharmacotherapy as a 'next step' treatment option compared with continuing pharmacotherapy as part of usual care[6;7]. Using search terms based on these reviews, we identified three trials that have been published subsequently. One of which was our pilot study (n=25) for this RCT[34], the second (n=44) examined augmentation with CBT amongst partial responders to antidepressants[35] and the third study (n=36) of inpatients was published only as a conference abstract[36]. Neither of the latter two studies included a group who remained on antidepressants in order to evaluate the effectiveness of CBT as an adjunct to antidepressant medication (comparators: lithium augmentation[35]; and augmentation with supportive therapy[36]).

Interpretation

The results of this large-scale multi-centre trial are useful in informing the 'next step' treatment for those who do not respond to antidepressant medication. CBT given as an adjunct to usual care that included antidepressant medication was found to be an effective treatment in reducing depressive symptoms and improving quality of life over 12 months compared with usual care alone for primary care patients with treatment resistant depression.

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Contributors: NW, JC, SH, BJ, DK, WK, JM, KT, CW, TP and GL were responsible for the original proposal, securing funding for the trial and drafting the original protocol. NW as chief investigator had overall responsibility for the management of the study and the Bristol site, and as Co-Investigators JC and WK had responsibility for the Exeter site, and JM and CW for the Glasgow site. All authors (with the exception of NT) contributed to refinement of the trial protocol. AG, WK and GL provided training and supervision for the trial therapists. LT, AA and NR were responsible for data collection and revised the draft paper. NW, TP and GL wrote the statistical analysis plan. LT and NT carried out the data cleaning and analyses (under the supervision of NW) and contributed to the interpretation of the data. NW conducted the main analyses with input from GL and TP. NW wrote the initial draft of the manuscript. All authors contributed to, and approved, the final manuscript.

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Conflicts of interest: CW has been a past president of the British Association for Behavioural and Cognitive Psychotherapies (BABCP), a workshop leader and author of texts on depression and self-help resources. WK is Co-Founder of the Mood Disorders Centre, teaches nationally and internationally on CBT and co-authored a cognitive therapy book (Collaborative Case Conceptualization, published by Guilford Press). AG is clinical lead for the Nottingham Specialised Depression Service, Principal Investigator to the CLAHRC-NDL funded Depression Study, a past president of the BABCP, a CBT workshop leader both nationally and internationally and author of texts on depression. The other authors have no conflicts to declare.

Figure 1 – Trial CONSORT flowchart

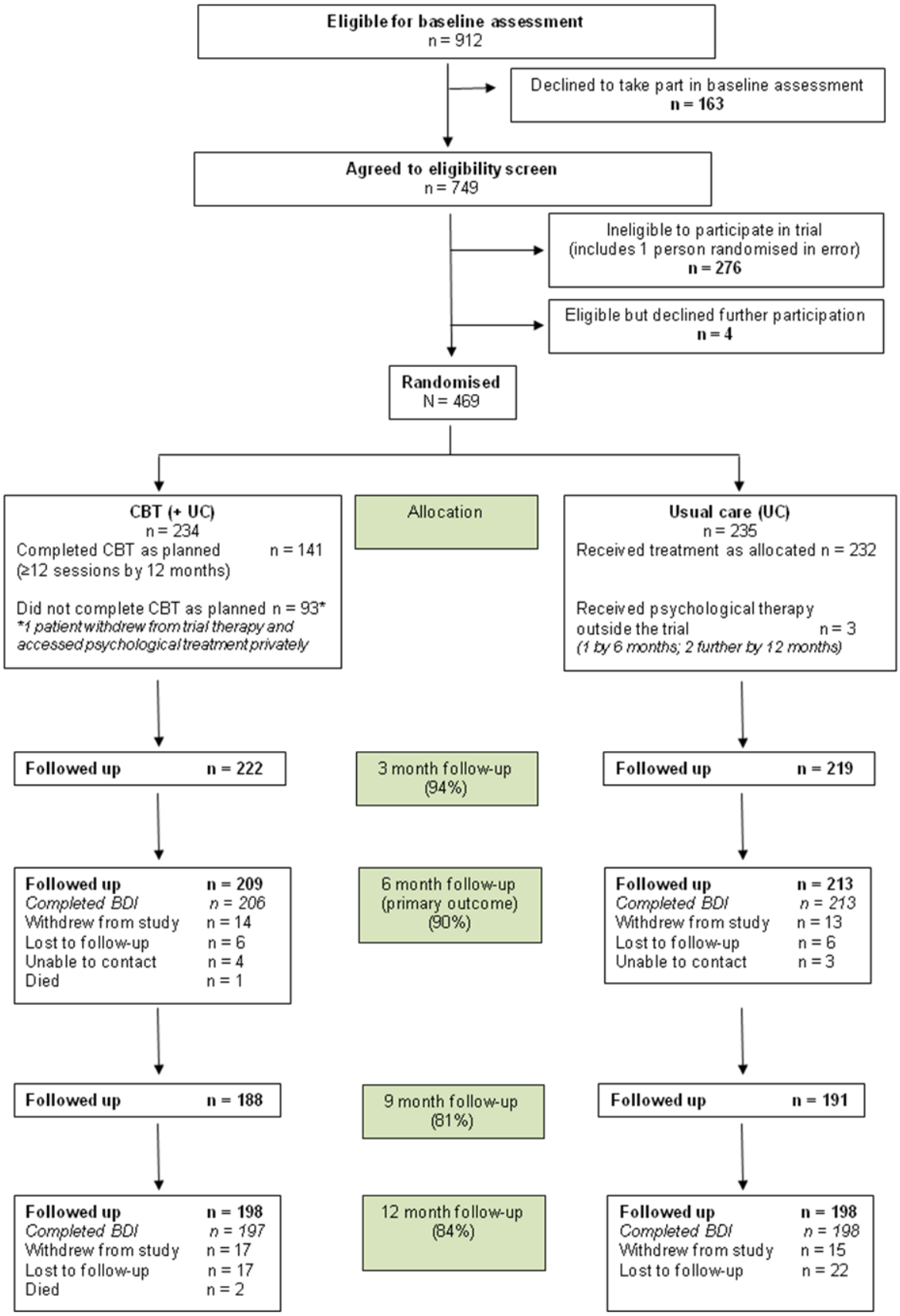

Table 1 – Baseline comparability of randomised groups

	Intervention (n = 234)		Usual care (n = 235)	
Stratification variable: Centre n (%)				
Bristol	95	(40.6%)	95	(40.4%)
Exeter	79	(33.8%)	82	(34.9%)
Glasgow	60	(25.6%)	58	(24.7%)
Minimisation variables: n (%)				
Previously prescribed antidepressants	187	(79.9%)	190	(80.9%)
BDI score				
14-19	24	(10.3%)	28	(11.9%)
20-28	78	(33.3%)	75	(31.9%)
≥29	132	(56.4%)	132	(56.2%)
GP practice has a counsellor	112	(47.9%)	116	(49.4%)
Duration of current episode of depression				
<1 year	58	(24.8%)	52	(22.1%)
1-2 years	40	(17.1%)	43	(18.3%)
> 2 years	136	(58.1%)	140	(59.6%)
Socio-demographic variables				
Age (years): mean (SD)	49.2 yrs	(11.9)	50.0 yrs	(11.5)
Female: n (%)	161	(68.8%)	178	(75.7%)
Ethnic group – White: n (%)	231	(98.7%)	228	(97.0%)
Marital status: n (%)				
Married/living as married	120	(51.3%)	128	(54.5%)
Single	44	(18.8%)	45	(19.2%)
Separated/Divorced/Widowed	70	(29.9%)	62	(26.4%)
Employment status: n (%)				
In paid employment (full/part-time)	109	(46.6%)	97	(41.3%)
Not in employment	58	(24.8%)	75	(31.9%)
Unemployed due to ill health	67	(28.6%)	63	(26.8%)
Highest educational qualification: n (%) *				
A level, Higher grade or above	112	(48.3%)	105	(45.5%)
GCSE, Standard grade or other	63	(27.2%)	67	(29.0%)
No formal qualifications	57	(24.6%)	59	(25.5%)
Financial difficulty: n (%)				
Living comfortably/doing alright	74	(31.6%)	93	(39.6%)
Just about getting by	91	(38.9%)	83	(35.3%)

Finding it difficult/v.difficult to make ends meet	69	(29.5%)	59	(25.1%)
Caring responsibilities	29	(12.4%)	35	(14.9%)
Long-standing illness or disability	170	(72.7%)	181	(77.0%)
Number of life events in past 6 months: mean (SD)	1.3	(1.2)	1.2	(1.1)
Social support score: mean (SD)	11.8	(3.9)	12.2	(3.7)
History of depression				
Suffered from depression in past	206	(88.0%)	209	(88.9%)
Number of prior episodes of depression				
0-1	46	(19.7%)	45	(19.2%)
2-4	72	(30.8%)	61	(26.0%)
≥5	116	(49.6%)	129	(54.9%)
Previous referral to a psychiatrist for depression	95	(40.6%)	93	(39.6%)
Family history of depression	159	(68.0%)	148	(63.0%)
Length of current course of antidepressants				
<6 months	26	(11.1%)	23	(9.8%)
6 – 12 months	51	(21.8%)	42	(17.9%)
>12 months	157	(67.1%)	170	(72.3%)
CIS-R score: mean (SD)	30.1	(9.1)	30.0	(8.8)
ICD-10 primary diagnosis: n (%)				
Mild	35	(15.0%)	31	(13.2%)
Moderate	135	(57.7%)	139	(59.2%)
Severe	64	(27.4%)	65	(27.7%)
BDI score: mean (SD)	31.8	(10.5)	31.8	(10.9)
Suicidal ideation (CIS-R thoughts/plans): n (%)	73	(31.1%)	75	(31.9%)
PHQ-9 score: mean (SD)	16.6	(5.7)	16.6	(5.7)
GAD-7 score: mean (SD)	11.7	(5.0)	11.8	(5.1)
Panic score: median [IQR]†	3	[0, 5]	3	[0, 5]
SF-12 mental subscale: mean (SD)‡	28.5	(9.0)	28.7	(9.3)
SF-12 physical subscale: mean (SD) ‡	45.3	(13.0)	41.6	(13.7)

Incomplete data on some items, numbers with information available as listed:
*CBT n = 232, UC n = 231; †CBT n = 233, UC n = 235; ‡CBT n = 231, UC n = 233

Table 2 – Intention-to-treat analyses of primary and secondary outcomes at 6 month follow-up

	Intervention			Usual care			Adjusted OR or adjusted difference in means*	95%CI	p value	Effect size for continuous outcomes†
	N	n or Mean	% or SD	N	n or Mean	% or SD				
Primary outcome										
Response	206	95	(46.1)	213	46	(21.6)	3.26	(2.10, 5.06)	<0.001	-
Secondary outcomes										
BDI score	206	18.9	(14.2)	213	24.5	(13.1)	-5.7	(-7.9, -3.4)	<0.001	0.53
Remission (BDI<10)	206	57	(27.7)	213	32	(15.0)	2.30	(1.39, 3.81)	0.001	-
PHQ-9	209	9.5	(6.7)	213	12.5	(6.6)	-3.0	(-4.2, -1.8)	<0.001	0.53
GAD-7	207	7.0	(5.9)	213	9.5	(5.6)	-2.5	(-3.4, -1.5)	<0.001	0.49
Panic	205	1.6	(2.1)	213	2.1	(2.2)	-0.6	(-1.0, -0.3)	0.001	0.26
SF-12 mental subscale	201	39.1	(14.1)	209	33.7	(12.6)	5.8	(3.5, 8.2)	<0.001	0.63
SF-12 physical subscale	201	44.1	(14.2)	209	42.1	(14.0)	-1.6	(-3.3, 0.05)	0.057	0.12

*****_ITT analysis adjusted for baseline measure of the outcome and the stratification (centre) and minimisation variables (BDI score, previously prescribed antidepressants, whether the GP practice has a counsellor and duration of current episode of depression)_

†_Effect size based on pooled SD of baseline measure_

Table 3 – Sensitivity analyses of the primary and secondary BDI outcomes at 6 months including imputed data for those with missing BDI outcome data

	N	Adjusted OR or adjusted difference in means*	95%CI	p value
Response at 6 months	469	3.10	(2.00, 4.80)	<0.001
BDI score at 6 months	469	-5.5	(-7.8, -3.3)	<0.001
Remission at 6 months	469	2.34	(1.43, 3.85)	<0.001

**Adjusted for baseline BDI score and the stratification (centre) and other minimisation variables (previously prescribed antidepressants, whether the GP practice has a counsellor and duration of current episode of depression)*

Table 4 – Intention-to-treat repeated measures analyses of outcomes at 6 and 12 month follow-up

	Intervention			Usual care			Repeated measures analyses			
	N	n or Mean at 12 months	% or SD	N	n or Mean at 12 months	% or SD	N	Adjusted OR or adjusted difference in means*	95%CI	p value
Response	197	109	(55.3)	198	62	(31.3)	814	2.89	(2.03, 4.10)	<0.001
BDI score	197	17.0	(14.0)	198	21.7	(12.9)	814	-5.1	(-7.1, -3.1)	<0.001
Remission (BDI<10)	197	78	(39.6)	198	36	(18.2)	814	2.74	(1.82, 4.13)	<0.001
PHQ-9†	197	9.0	(7.0)	198	10.9	(6.4)	1196	-2.8	(-3.7, -1.8)	<0.001
GAD-7	197	6.7	(6.2)	198	8.5	(5.8)	815	-2.2	(-3.0, -1.3)	<0.001
Panic	195	1.5	(2.1)	198	1.7	(2.2)	811	-0.5	(-0.8, -0.2)	0.001
SF-12 mental subscale	194	39.1	(14.6)	195	35.4	(12.8)	799	4.8	(2.7, 6.9)	<0.001
SF-12 physical subscale	194	44.6	(13.2)	195	41.1	(13.5)	799	-0.7	(-2.1, 0.8)	0.35

*****_ITT analysis adjusted for baseline measure of outcome and the stratification (centre) and minimisation variables (BDI score, previously prescribed antidepressants, whether the GP practice has a counsellor and duration of current episode of depression)_

†Data on PHQ-9 were available at three time points (6, 9 and 12 months): mean (SD) at 9 months: intervention: n=188, 8.8 (6.9); usual care: n=191, 12.0 (6.2)