Clinical effectiveness and cost-effectiveness of cognitive behavioural therapy as an adjunct to pharmacotherapy for treatment-resistant depression in primary care: the CoBalT randomised controlled trial

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Scientific summary

The CoBalT randomised controlled trial

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Scientific summary

Background

Depression is ranked among the top five contributors to the global burden of disease, and by 2030 is predicted to be the leading cause of disability in high-income countries. Antidepressants are often the first-line treatment for depression and the number of prescriptions for antidepressants has risen dramatically in recent years in the UK and elsewhere. Over 46 million prescriptions were issued in England in 2011, at a cost of more than £27M. However, the recent STAR*D study (Sequenced Treatment Alternatives to Relieve Depression) found that only one-third of patients responded fully to pharmacotherapy and that half did not experience at least a 50% reduction in depressive symptoms following 12–14 weeks of antidepressant medication. The reasons for this non-response are complex but include treatment resistance (when an adequate dose and duration of treatment has been given).

Many definitions of treatment resistance have been proposed. These cover a broad spectrum, ranging from failure to respond to at least 4 weeks of antidepressant medication given at an adequate dose to classification systems based on non-response to multiple courses of treatment. Irrespective of the definition used, it is clear that treatment-resistant depression (TRD) has a considerable 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.

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. However, 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. CBT has been shown to reduce rates of relapse, including among those with residual depressive symptoms, and combined pharmacological and psychological treatment has been found to be more effective than either component alone for patients with chronic depression, who are likely to include non-responders to medication. However, to date, no large-scale randomised controlled trials (RCTs) have evaluated the effectiveness of augmenting antidepressant medication with CBT following non-response to pharmacotherapy compared with continuing pharmacotherapy as part of usual care as a 'next-step' option for patients with TRD. Similarly, robust evidence regarding cost-effectiveness is lacking.

Objectives

Amongst patients with TRD (defined as those who have significant depressive symptoms following at least 6 weeks' treatment with antidepressant medication at an adequate dose) in primary care, to determine (1) the effectiveness of CBT in addition to pharmacotherapy in reducing depressive symptoms and improving quality of life over the following 12 months (compared with usual care that includes pharmacotherapy) and (2) the cost-effectiveness of this intervention.

In addition, this study incorporated a qualitative study to: (1) explore patients' views and experiences of CBT; (2) identify patients' reasons for completing or not completing therapy; and (3) describe 'usual care' for this patient group.

Methods

This was an individually randomised, two-parallel group, pragmatic, multicentre RCT. Patients with TRD were recruited from general practices in Bristol, Exeter and Glasgow, and surrounding areas.

Eligible patients were those who (1) were aged 18–75 years; (2) were currently taking antidepressants and had done so for at least 6 weeks, and who had adhered to their medication; (3) had a Beck Depression Inventory, 2nd version (BDI-II) score of at least 14; and (4) fulfilled *International Classification of Diseases and Related Health Problems*, Tenth Edition (ICD-10) criteria for depression. Excluded were those who had bipolar disorder, psychosis or major alcohol/substance abuse; those who were unable to complete the questionnaires; and women who were pregnant. Also excluded were those who were currently receiving psychotherapy (including CBT and counselling) or secondary care for their depression, and those who had received CBT in the past 3 years.

A three-stage recruitment process was used to identify those who were eligible to participate in the trial. Initially, general practices conducted a search of their computerised records to identify all patients who had received repeated prescriptions for an antidepressant during the previous 4 months and who were currently being prescribed an antidepressant at an adequate dose for depression. General practitioners (GPs) then screened this list of patients and excluded those patients who fulfilled any of the exclusion criteria described above. A letter of invitation and brief information leaflet about the study was sent by the general practice to the potentially eligible participants. This letter sought permission for the research team to contact them and to send a questionnaire asking about their depressive symptoms and adherence to antidepressant medication. Patients replied directly to the study team, indicating whether or not they agreed to be contacted.

General practitioners could also invite patients to take part in the study during a consultation. In such cases, the GP provided the patient with an information leaflet about the study and obtained permission from the patient to pass their contact details to the research team.

All those who agreed to be contacted by the research team (either in response to the postal invitation or to a direct invitation from their GP during the consultation) were sent a postal questionnaire. This included questions about their depressive symptoms (BDI-II) and use of antidepressants.

Those who met the definition of TRD [based on severity of depressive symptoms (BDI-II score of $\geq$14) and adherence to antidepressants at an adequate dose for at least 6 weeks] were contacted by a researcher by telephone to ascertain their eligibility with respect to current/past psychological treatment and current secondary care for depression. Those who were not currently receiving (or scheduled to start) CBT or secondary care for their depression, and who had not received CBT in the past 3 years, were invited to attend a face-to-face appointment with a researcher to discuss participating in the trial and to assess their eligibility.

Baseline assessments to establish eligibility were conducted in the patients' own homes, at their GP surgeries or at nearby NHS/University premises. Only those patients who fulfilled ICD-10 criteria (category F32) for their current depressive episode (assessed using the revised Clinical Interview Schedule), had a BDI-II score of $\geq$14 and who were continuing to take the prescribed antidepressants at an adequate dose were eligible to participate in the trial.

Those who were eligible and gave written informed consent were randomised, using a computer-generated code, to one of two groups: 'usual care' or 'CBT in addition to usual care'. Randomisation was carried out using a remote automated telephone system, and was stratified by centre and minimised on baseline BDI-II score (mild 14–19; moderate 20–28; severe $\geq$29), whether the general practice had a counsellor (yes/no), prior treatment with antidepressants (yes/no) and duration of the

current episode of depression (< 1 year, 1–2 years, ≥ 2 years). At the time of randomisation, all participants were taking antidepressant medication and expected to continue to do so as part of usual care.

Those allocated to the intervention group received a course of individual face-to-face CBT comprising 12 sessions, with (up to) a further six sessions if deemed clinically appropriate by the therapist. There were no restrictions on the treatment options for those randomised to continue with usual care from their GP.

Participants were followed up at 3, 6, 9 and 12 months. To maximise response rates, follow-up assessments at 6 and 12 months were conducted at a face-to-face appointment with a researcher, with the 3- and 9-month follow-up data collected over the telephone.

The primary outcome was 'response', defined as at least a 50% reduction in depressive symptoms (BDI-II score) at 6 months compared with baseline. Secondary outcomes included the BDI-II score as a continuous variable, remission of symptoms (BDI-II score of < 10), quality of life [European Quality of Life-5 Dimensions-3 Levels (EQ-5D-3)], anxiety and antidepressant use at 6 and 12 months. Data on health and social care use, personal expenditure including private treatments and complementary/alternative therapies, and time off work were also collected at 6 and 12 months.

The primary comparative analyses of clinical effectiveness were conducted according to the principle of intention-to-treat without imputation of missing data.

Costs from the three perspectives (health and social care, patients, and lost productivity) were reported using a cost–consequence analysis. A cost–utility analysis compared health and social care costs with quality-adjusted life-years (QALYs). Discounting was not applied.

Patients were contacted about taking part in the qualitative study after they had completed their primary outcome measures for the trial at 6 months post randomisation. A purposeful sampling strategy was used to ensure interviews were held with individuals in both arms of the trial and, within the intervention arm, with patients who had and had not completed therapy.

Interviews were held face to face, audio-taped and fully transcribed. Data were analysed thematically to allow comparisons to be made within and across the interviews, and to highlight patients' views on specific issues, for example, their experiences of CBT. The software package Atlas.ti was used to aid data management. Data collection ended when data saturation had been reached.

Results

In total, 73 general practices agreed to take part in the study and 749 baseline assessments were conducted. Four hundred and sixty-nine patients were eligible and gave written informed consent for trial participation, and were randomised, with 234 allocated to receive the intervention and 235 to continue with usual care. Ninety per cent of participants ($n = 422$) were followed up at 6 months and 396 (84%) were followed up at 12 months.

The average duration of the intervention (from randomisation) was 6.3 months (standard deviation 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 ($n = 27$). A further 23 participants reached an 'agreed end' in less than 12 sessions.

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

Ninety-five 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% confidence interval (CI) 2.10 to 5.06], $p < 0.001$}. In repeated measures analyses using data from 6 and 12 months, the OR for 'response' was 2.89 (95% CI 2.03 to 4.10), $p < 0.001$, and for a secondary 'remission' outcome (BDI-II score of < 10) the OR was 2.74 (95% CI 1.82 to 4.13), $p < 0.001$. Those in the intervention group were also more likely to report greater improvements in quality of life over the 12 months [difference in mean Short-Form questionnaire-12 items (SF-12) mental health subscale scores between treatment groups: 4.8 (95% CI 2.7 to 6.9) $p < 0.001$].

The mean cost of CBT per participant was £910. The cost of the intervention was slightly offset by the higher cost (£59) of health and social care in the usual-care group, giving an incremental cost of £850. In line with the clinical outcomes, participants receiving the intervention experienced a better health-related quality of life as measured by QALYs (0.61 vs. 0.55), giving a cost per QALY over the 12 months of £14,911 (incremental cost-effectiveness ratio).

If society is willing to pay £20,000 per QALY, the net monetary benefit (NMB) per patient per year is £289 (95% CI –£603 to £1182) and the probability that the intervention is cost-effective is 0.74. At a threshold of £30,000 per QALY, the NMB increases to £859 (95% CI –£455 to £2179), with a commensurate increase in the probability that the intervention is cost-effective (0.91).

In total, 40 interviews were conducted for the nested qualitative study. Twenty-six of these interviews were with patients in the intervention arm, nine of whom had not completed therapy within the trial. On average, the interviews lasted about an hour. Participants who had been allocated to receive the intervention reported that CBT had given them techniques to help them better manage their symptoms. Patients described components of CBT that they struggled with, or were a barrier to them completing the therapy, but still felt they had benefited from the sessions. Patients' accounts of usual care indicated that this mainly consisted of taking antidepressants.

Conclusions

Implications for health care

- CBT given as an adjunct to usual care (that includes pharmacotherapy) was found to be an effective 'next-step' treatment (when compared with usual care alone) for primary care patients with depression, who had not responded to treatment with pharmacotherapy alone. The intervention was effective in both reducing depressive symptoms and improving quality of life, and these benefits were maintained over 12 months.
- The economic evaluation showed that the intervention was cost-effective over 12 months, based on the threshold of £20,000 per QALY used by the National Institute for Health and Care Excellence.
- The qualitative findings suggested that practitioners referring patients for CBT, for example GPs, should discuss the potential challenges of this therapy with patients to help them make an informed choice about referral for CBT.

Future research implications (in order of priority)

- Further research needs to evaluate effectiveness of this intervention over the long term. CBT has the potential to produce a more sustainable improvement than pharmacotherapy alone. If this intervention was found to be cost-effective over the long term, this would have major implications for recommendations as to how depression should be managed.

- Although nearly half of those in the intervention group met the criteria for response, 54% did not. Therefore, it is a priority that the evidence base for the effectiveness of a range of 'next-step' treatments for those who do not respond to medication alone is expanded. Although many different strategies have been evaluated, to date there is little robust evidence regarding the effectiveness of many of these strategies. Only by obtaining robust evidence on the effectiveness and cost-effectiveness of a range of 'next-step' psychological and pharmacological interventions will it be possible to reduce the considerable burden to patients, the NHS and society, which is associated with non-response to the most common first-line treatment for depression in primary care.

Trial registration

This trial is registered as ISRCTN38231611.

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