Manualised cognitive–behavioural therapy in treating depression in advanced cancer: the CanTalk RCT

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Scientific summary

The CanTalk RCT

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Scientific summary

Background

The CanTalk trial was a randomised controlled trial (RCT) testing the clinical effectiveness and cost-effectiveness of cognitive–behavioural therapy (CBT) for depression in 'advanced cancer', defined as cancer that is not amenable to cure or cancer in people with metastatic disease for whom standard curative therapies have failed and/or in those with a poor prognosis.

A meta-analysis of depression in advanced cancer suggested the prevalence of clinical depression to be 16.5%. There is a considerable economic cost associated with depression, and individuals with cancer and depression face several negative health outcomes.

An updated Cochrane review has considered which psychosocial therapies are effective in advanced cancer and depression (Akechi T, Okuyama T, Onishi J, Morita T, Furukawa TA. Psychotherapy for depression among incurable cancer patients. *Cochrane Database Syst Rev* 2008;**2**:CD005537). A recent review suggested that CBT appeared to be the most promising. CBT challenges negative ways of thinking and unhelpful ways of behaving by teaching the individual to challenge and modify negative thoughts and unhelpful behaviours to help improve mood.

Currently, the UK agenda for treating depression aims to widen access to psychological treatment delivered in primary care by trained mental health practitioners attached to the Improving Access to Psychological Therapies (IAPT) programme.

As RCTs are the gold standard in research, we chose a parallel RCT design comparing treatment as usual (TAU) with TAU plus the addition of individual manualised CBT for treating depression in advanced cancer.

Stirling Moorey, Kathryn Mannix and Marc Serfaty (co-applicants) developed a treatment manual and a training package for IAPT therapists and supervisors on how to apply their CBT skills to people with advanced cancer.

The revised Consolidated Standards of Reporting Trials guidelines for reporting non-pharmacological trials recommend that a description of different components of the intervention is provided when evaluating non-pharmacological interventions. It is recommended that three measures are recorded to evaluate treatment implementation: (1) delivery, (2) receipt and (3) enactment. We used mixed methods to record all measures except enactment.

Objectives

To conduct a RCT to test the clinical effectiveness and cost-effectiveness of TAU compared with TAU plus individual CBT (delivered through IAPT) for treating depressive symptoms in people with advanced cancer.

Methods

Design

Parallel-group RCT.

Participants

Patients ($n = 230$) with advanced cancer and depression.

Inclusion criteria

- Diagnosis of cancer not amenable to cure.
- A *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition diagnosis of depressive disorder using the Mini-International Neuropsychiatric Interview (MINI).
- Sufficient understanding of English.
- Eligibility for treatment in an IAPT centre.

Exclusion criteria

- Clinician-estimated survival of < 4 months.
- High suicide risk established using the MINI.
- Currently receiving, or having received in the last 2 months, a psychological intervention recommended by the National Institute for Health and Care Excellence (NICE) for treating depression.

Setting

Participants were recruited from oncology centres, general practitioner practices, a local hospice and through self-referral.

Randomisation

Participants were randomised 1 : 1 to TAU or TAU plus CBT using Sealed Envelope™ (Sealed Envelope Ltd, London, UK), a web-based system. Randomisation was conducted using permuted blocks with sizes of four or six, stratified for antidepressant usage (yes/no).

Masking

Researchers and Primary Care Research Network assessors were blinded to group allocation.

Interventions

Treatment as usual

All participants received TAU from clinicians involved in their care.

Cognitive–behavioural therapy (in addition to treatment as usual)

Cognitive–behavioural therapy was delivered by high-level British Association for Behavioural and Cognitive Psychotherapies-accredited IAPT therapists. The intervention comprised up to 12 sessions of individual, manualised CBT delivered either face to face or over the telephone over 3 months. These sessions are outlined below:

- session 1 – assessing and introducing the cognitive–behavioural model
- session 2 – developing an understanding of problems within a cognitive framework
- session 3 – reviewing the formulation, identifying new insights/changes through guided discovery. Identifying helpful versus ‘unhelpful’ thinking
- sessions 4–5 – reformulating success experiences, identifying triggers and developing new coping strategies through guided discovery
- session 6–7 – challenging thoughts and generating alternative ‘helpful’ ways of thinking
- session 8 – problem solving, checking that concepts are understood and realistic concerns addressed along with introducing ‘worry time’
- session 9 – consolidating CBT strategies, prioritising problems and using worry management strategies
- session 10 – reviewing progress

- session 11 – conducting relapse prevention through reviewing difficulties, identifying achievements and promoting personal resilience
- session 12 – future planning by creating relapse prevention checklists and planning for action if distress or unhelpful behaviours/thinking recurs.

Training

Improving Access to Psychological Therapies therapists were given a day's training by the CanTalk team (SM, MS and KM) to help apply existing CBT skills to people with advanced cancer.

Location of therapy

Therapy was offered at the local IAPT centre or by telephone CBT for those who had seen the therapist at least three times.

Assessment of delivery of cognitive–behavioural therapy

Delivery of CBT was assessed using the Cognitive Therapy Scale – Revised (CTS-R) and through qualitative interviews.

Qualitative methods

Three embedded qualitative studies were included:

1. clinicians' experiences of referring into the CanTalk trial
2. therapists' experiences of delivering CBT
3. patients' experiences of CBT.

Primary outcome

- Beck Depression Inventory, version 2 (BDI-II): a 21-item self-report measure with a maximum score of 63 points.

Secondary outcomes

- Patient Health Questionnaire-9 (PHQ-9): a nine-item measure validated as a measure of depression in primary care.
- EuroQol-5 Dimensions (EQ-5D): a generic utility measure of quality of life.
- Satisfaction with care: a five-item scale.
- Eastern Cooperative Oncology Group Performance Status (ECOG-PS): a measure of physical functioning.
- Client Service Receipt Inventory (CSRI): a short, modified CSRI that collects data on service use.

Timing of measures

The BDI-II, PHQ-9, EQ-5D, ECOG-PS and CSRI were collected at baseline, 12 and 24 weeks. The BDI-II was also collected at 6 and 18 weeks.

Sample size

Our primary outcome was an overall effect of treatment over the 24 weeks. The power was to enable a detection of a difference in BDI-II of 6 points [standard deviation (SD) 12 points] between the TAU and CBT groups measured at 12 weeks, assuming a treatment effect of 3 points after 6 weeks and a sustained 6-point difference after 18 and 24 weeks. We assumed a 70% follow-up at 6 weeks, decreasing to 65% at 12 weeks and 60% at 24 weeks.

The correlation between BDI-II values from sessions 1 week apart is reported as 0.93. We estimated the correlation between measures taken 6 weeks apart to be $0.935 = 0.65$.

Sample size calculations estimated that, at 90% power and 5% significance, 109 participants were required per trial arm. This was inflated by a factor of 1.10 to allow for therapist clustering, giving 120 participants per trial arm.

Analysis

Clinical outcomes

The primary analysis was a comparison on an intention-to-treat basis between the CBT and control arms for the BDI-II score measured at 6, 12, 18 and 24 weeks using multilevel modelling, allowing for repeated measurements with equal weighting for each time point, adjusting for therapist clustering. The model comprised three levels: (1) repeated measures, (2) individuals and (3) therapists. Baseline BDI-II score and antidepressant use were included as fixed effects. The model was fitted using a linear mixed-effects model assuming a Gaussian error distribution.

Supportive analysis included the primary analysis, which was repeated (1) using clustering by IAPT service, (2) ignoring clustering, (3) including additional covariates and (4) with separate analyses carried out for each follow-up point. Exploratory and subgroup analysis included the primary analysis in addition to (1) a treatment by time interaction, (2) a treatment by marital status interaction and (3) a treatment by education status interaction. We also conducted a contamination-adjusted intention-to-treat (CAITT) analysis using the 18- and/or 24-week total BDI-II score.

For the secondary outcomes of PHQ-9 and satisfaction with care, we used a similar approach to the primary analysis.

Cost-effectiveness

Quality-adjusted life-years (QALYs) were calculated from EQ-5D scores at baseline, 12 and 24 weeks' follow-up. Service use costs were calculated from resource data to calculate the total cost of resources used by each study participant.

Costs were compared for the groups using a bootstrap regression model to account for non-normality in the distribution of cost data. A cost–utility analysis was undertaken using QALYs calculated from the EQ-5D measure. Cost-effectiveness was assessed by estimating an incremental cost-effectiveness ratio (ICER) to show the extra cost incurred by CBT to generate one extra QALY. To deal with uncertainty around the ICER, a cost-effectiveness plane (CEP) and cost-effectiveness acceptability curves (CEACs) were created.

Qualitative data

Semistructured interviews were conducted and transcribed. Data were analysed using thematic content analysis.

Results

Recruitment and follow-up

We screened 2224 patients with advanced cancer. Of those, 819 did not meet the inclusion criteria, 1021 declined to participate, 144 were excluded for reasons not recorded and 240 participants were referred for baseline. Of the 240 patients referred for baseline, 230 consented to participate and were randomised.

Participants were predominantly female (66%) and of white ethnicity (73%) with a mean age of 59.5 years. Two-thirds of patients had tumours in one of the five main groups: (1) breast, (2) colorectal, (3) lung, (4) prostate and (5) haematological. A total of 60% of participants had a previous history of depression.

Over the follow-up period, 37 participants in the CBT group and 25 participants in the TAU group died or withdrew from the study. The number of participants with at least one follow-up point was 93 in the CBT group and 92 in the TAU group.

Clinical outcomes

The primary analysis of the BDI-II score did not find a significant benefit of CBT plus TAU versus TAU alone [treatment effect –0.84, 95% confidence interval (CI) –2.755 to 1.083; $p = 0.39$]. Subsidiary analysis also showed no benefit of CBT over TAU. Out of the exploratory analysis, in our predetermined analysis plan, marital status demonstrated a benefit for CBT plus TAU over TAU alone for participants who were widowed, divorced or separated (treatment effect –7.21, 95% CI –11.15 to –3.28; $p < 0.001$).

For the CAITT analysis, 153 participants were included. The estimated 'per-session' effect on the BDI-II was –0.30 points (95% CI –0.76 to 0.17 points; $p = 0.21$).

Similar to the BDI-II, PHQ-9 scores and satisfaction with care scores showed a lack of significant benefit for CBT plus TAU compared with TAU alone.

Eastern Cooperative Oncology Group Performance Status scores were similar throughout the study, with around one-fifth of participants being fully active and two-fifths being of restricted mobility. Overall satisfaction with care was around 80%.

Cost-effectiveness

At baseline, 12 and 24 weeks, there were no significant differences in service use (excluding CBT) between TAU and TAU plus CBT. The mean service costs for participants (not including the costs of the interventions) were similar across the two groups.

There were no differences in EQ-5D median scores at baseline, nor was there any advantage of CBT over TAU at 12 weeks or 24 weeks. There was no statistically significant improvement in QALYs at 24 weeks.

The CEP indicates a 15.5% chance that CBT is cheaper and produces more QALYs, and a 74% chance that CBT is more expensive and produces more QALYs. The CEAC indicates that, at the NICE threshold, the probability of CBT being effective is 52%.

Intervention

A total of 543 (39.3%) sessions out of a potential total of 1380 were taken up, of which 32 (5.9%) were by telephone. The mean time from being referred to being seen by an IAPT therapist was 29.4 days (SD 26.7 days). For participants randomised to CBT, the mean number of sessions received was 4.7 (SD 4.9) and 41 participants (35.6%) did not take up any sessions.

Of the 543 therapy sessions delivered, 55 tapes (1 in 10) were rated. The mean CTS-R score by phase of therapy was 47.9 points (SD 10.6 points) for 21 early sessions, 48.1 points (SD 18.8 points) for 19 middle sessions and 46.7 points (SD 10.9 points) for 15 late sessions, indicating strong adherence to the therapeutic model in CBT.

Guided discovery, activity scheduling, discussion about specific cancer topics, covering the impact of the physical illness and beliefs and expectations about the illness were most the most common interventions.

Qualitative findings

Health-care workers' views about the CanTalk trial

This substudy asked 14 health-care workers about their views of psychological (non-pharmaceutical) research. Themes included recruitment issues – finding time and money, competing interests, catchment area limits; the role of the clinician – their influence on the team, patient participation and trying to protect

patients; the sensitive nature of the research – clashes with existing services and concerns regarding people not eligible for the trial; and concerns about the trial team mis-selling research to units but wanting the trial team to be involved in recruiting.

Therapists' views of treating patients with advanced cancer

Sixteen therapists were interviewed using semistructured interviews. Themes included knowledge of cancer – would have liked more knowledge, but gained this from talking to the patient; experience of training – would have liked more information about type of cancer; concerns about treating advanced cancer patients – anxiety about treating cancer patients, but surprise at how receptive patients were; supervision – would have liked more specialist support; experience of working with patients – generally easy to co-ordinate meetings and experience more positive than expected; and therapy materials – therapists generally liked the materials, but it was not always easy to adhere to the manual.

Patients' views about cognitive–behavioural therapy

Interviews were conducted with 10 patients who had received CBT. Themes included expectations and knowledge of CBT – some knowledge, but little experience of CBT; structure and delivery of CBT – service location was convenient, but transport could be a barrier; experience of CBT – CBT was helpful, facilitated their ability to talk about cancer and to deal with unhelpful thinking; and other therapeutic options for advanced cancer patients – it was felt that CBT would not be for everyone and that therapy should be tailored to the needs of the patient. Suggested improvements included offering therapy in hospital, a manual/workbook for patients, therapy for carers and reducing the frequency of sessions.

Discussion

In this sufficiently powered trial, CBT delivered through IAPT was not clinically effective or cost-effective for treating depression in those with advanced cancer, despite the quality of therapy delivered being high and the uptake consistent with the number of sessions taken up through IAPT. However, CBT was clinically effective for those widowed, divorced or separated and this is consistent with data on the use of CBT to treat depression in the community.

Conclusions

Cognitive–behavioural therapy delivered through IAPT is not recommended for treating depression in people with advanced cancer, although a subgroup of those who are widowed, divorced or separated may benefit from screening and referral to IAPT for CBT. Alternative research evaluating integrative care models for treating depression in people with a range of cancers is worth testing. It remains to be established whether or not mechanisms of change in our widowed, divorced or separated population was associated with specific or non-specific treatment effect.

Trial registration

The trial is registered as ISRCTN07622709.

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