Effectiveness of Cognitive Behavioural Therapy for depression in advanced cancer' CanTalk Randomsed Controlled Trial

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Abstract

Background: Depression is one of the most common mental disorders in people with advanced cancer. Although cognitive–behavioural therapy (CBT) has been shown to be effective for depression in people with cancer, it is unclear whether this is the case forpeople with advanced cancer and depression.

Aims: We sought to determine whether CBT is more clinically effective than treatment as usual (TAU) for treating depression in peoplewith advanced cancer (trial registration number ISRCTN07622709).

Method: A multi-centre, parallel-group single-blind randomised controlled trial comparing TAU with CBT (plus TAU). Participants (n = 230) with advanced cancer and depression were randomly allocated to (a) up to 12 sessions of individual CBT or (b) TAU. The primary outcome measure was the Beck Depression Inventory-II (BDI-II). Secondary outcome measures included the Patient Health Questionnaire-9, the Eastern Cooperative Oncology Group Performance Status, and Satisfaction with Care.

Results: Multilevel modelling, including complier-average intention-to treat analysis, found no benefit of CBT. CBT delivery was proficient, but there was no treatment effect (−0.84, 95% CI −2.76 to 1.08) or effects for secondary measures. Exploratory subgroup analysis suggested an effect of CBT on the BDI-II in those widowed, divorced or separated (−7.21, 95% CI −11.15 to −3.28).

Conclusions: UK National Institute for Health and Care Excellence (NICE) guidelines recommend CBT for treating depression. Delivery of CBT through the Improving Access to Psychological Therapies (IAPT) programme has been advocated for long-term conditions such as cancer. Although it is feasible to deliver CBT through IAPT proficiently to people with advanced cancer, this is not clinically effective. CBT for people widowed, divorced or separated needs further exploration. Alternate models of CBT delivery may yield different results.

Declaration of interest: M.S. is a member of the Health Technology Assessment General Board.

INTRODUCTION:

With increasing life expectancy, more people are living with advanced cancer. Clinical depression, is common in people with advanced cancer, with a pooled prevalence of 16.5% [1]. Although many people may have a diagnosis of adjustment disorder as they adapt to life-threatening illness, this is distinct from depression which is associated with a negative impact on quality of life for the individual and their carers, and also untreated depression is a predictor of early death [2]. In the UK, the National Institute for Clinical and Care Excellence (NICE) recommends that people with advanced cancer are routinely screened and treated for depression within the National Health Service (NHS) [3]. However, evidence supporting the clinical and cost effectiveness of psychological therapies, including CBT, is limited. Tricyclic antidepressants are used in cancer, preferentially over SSRIs, and even low doses, may be helpful. However, in the context of advanced cancer, people face particular challenges linked to life-threatening illness; uncertainty about prognosis, symptom burden, and personal, family and practical issues. CBT may be a promising treatment [4], but good evidence is lacking and earlier studies in advanced cancer have largely focussed on psychological interventions in women with metastatic breast cancer [5] in which results on effectiveness have been inconclusive.

In England, since 2008 a stepped-care approach for people with depression and anxiety disorders has been available in some areas through Improving Access to Psychological Therapies (IAPT), delivered through IAPT/wellbeing centres [6], located in the community or in GP practices. At the highest level, level 3, High Intensity Therapists, with at least two years post graduate diploma experience, offer face-to-face, evidence-based therapies for people with complex problems using an adaptation of CBT developed by Beck et al [7].

The CanTalk study was a multicentre Randomised Controlled Trial (RCT) evaluating the clinical effectiveness of IAPT-delivered context-specific CBT compared to treatment as usual for reducing depressive symptoms in people with advanced cancer. We recruited participants from routine clinical settings across England where IAPT services were available. Given the particular challenges faced by our population, we used a manual-based CBT programme that was specific for the context of living with advanced cancer. We devised the study in response to a call from the UK's National

Institute of Health Research, Health Technology Assessment (NIHR HTA) Programme. The research formed part of the National Cancer Research Network (NCRN) clinical trials portfolio, registration number 10255; ISTCRN trial registration number 07622709.

METHODS:

This multi-centre study [NIHR HTA funded project 09/33/02] was undertaken between 5th March 2012 and 30th November 2016 with ethical approval (London –Camberwell St Giles NRES committee, Central London REC3 ref 11/LO/0376). As a detailed trial protocol has already been published [8], a summary of the method is provided here.

Patient involvement

The research project was presented to the North London Service User Research Forum (SURF) during the planning phase, and feedback from this user forum helped in formulating the research. Additionally a cancer services user contributed to the design of the trial, contributed to the preparation of study documents including the clarity of the layout and sensitivity of the wording, and contributed to discussion of ethical considerations. This user also attended steering group meetings throughout the trial and provided input on methods to boost recruitment, contributed to the interpretation of the results, and provided useful feedback on how best to distribute results to participants.

Results of the study were disseminated to participants via letters which were prepared by the trial team and distributed via each participant's clinical team.

Eligibility and Screening

People who had a diagnosis of cancer not amenable to curative treatment, as assessed by their clinician, were screened for depression using the PHQ-2, the first two questions of the PHQ-9 [9]. Participants were recruited from general practices, a local hospice, and oncology departments in London, the Midlands, South, West, North West, and North East of England; if positive, a score of 3 or more on the PHQ-2, they were assessed for the following entry criteria: a confirmed diagnosis of advanced

cancer; a DSM-IV diagnosis of major depressive disorder using the Mini International Neuropsychiatric Interview (MINI) [10]; sufficient understanding of English; and eligible for treatment in an IAPT centre. People were excluded if they had a clinician-estimated survival of less than 4 months as they would be too ill or not able to complete therapy; were high suicide risk; were receiving or had received, in the last 2 months, a psychological intervention for depression recommended by NICE; or had suspected alcohol dependence on the Alcohol Use Disorders Identification Test (AUDIT; [11]). We avoided recruiting in areas where the local palliative care service included routine access to CBT.

Randomisation:

Participants were randomised to treatment as usual (TAU) or CBT (plus TAU), by PRIMENT, a UKCRC registered clinical trials unit, using a web based system developed by Sealed Envelope, an independent data provider. Randomisation was conducted using permuted blocks with block sizes of 4 or 6, stratified for antidepressant prescription (yes or no).

The Intervention:

1. **Treatment as usual (TAU)**

TAU included assessment by GPs, clinical nurse specialists, oncologists and palliative care clinicians. Referral for external psychological support or psychotropic medication was discouraged but not excluded for ethical reasons.

2. **Cognitive Behaviour Therapy (in addition to TAU)**

High intensity therapists were trained for one day to adapt their existing skills and use context-specific CBT treatment according to the CanTalk study intervention manual. They provided up to 12 sessions of individual CBT delivered, usually weekly and within three months, either face-to-face or by telephone.

Context-specific CBT Treatment Manual

Therapists used a treatment manual, informed from previous work [12] and developed by Moorey, Mannix, and Serfaty. This guide enabled therapists to apply and adapt their existing skills to be context-specific for people with advanced cancer and provided a step-by-step approach, used flexibly. Sessions consisted broadly of the following: *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 vs '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, promoting personal resilience. *Session 12:* Future planning by creating relapse prevention checklists, and planning for action if distress or unhelpful behaviours/thinking recurs. Details of the intervention are described in Serfaty et al [8]. Where possible, sessions were digitally-recorded and the therapist was asked to complete a modified therapy components checklist (TCC; see Serfaty et al [8]) detailing what elements of the intervention they believed they had delivered. Both the CanTalk manual and TCC are available from the lead author.

Study Measures:

Potential participants were screened by UCL researchers, Cancer Research and GP practice nurses. They were followed up by UCL researchers and/or Cancer Research Nurses allocated to the project.

(i) Screening measures

Before study entry, initial screening:

PHQ – 2: The PHQ-2 consists of the first two questions of the Patient Health Questionnaire (PHQ-9; [9]), a valid screening measure of depression that has been used in cancer services.

After assessment for eligibility, second screening measure:

The **Mini-International Neuropsychiatric Interview *(*M.I.N.I.*)*** is a short structured diagnostic interview, which takes 15 minutes to complete and has been widely used in cancer patients.

Those satisfying a diagnosis of major depression on the M.I.N.I had the following baseline information collected**:**

(ii) Demographic and related information:

We collected gender, date of birth, marital status, ethnicity, employment status, highest level of education, previous history of depression and cancer diagnosis. We noted other treatments and prescribed medication, dose and frequency.

(iii) Outcome measures

(a) Primary outcome- collected at baseline, 6, 12, 18 and 24 weeks

Beck Depression Inventory-II (BDI-II; [13]).

The BDI-II is a 21 item self-report measure with a maximum score of 63 suggesting severe depressive symptoms and has been used in trials of psychotherapy for people with advanced cancer [14]. This updated version has similar psychometric properties to the BDI, one of the most widely used self-report instruments for depressive symptoms.

(b) Secondary outcomes - collected at baseline, 12 and 24 weeks

Patient Health Questionnaire (PHQ9; [9])

The PHQ9 screens for depression. It is used in primary care settings including IAPT services. It has been validated [15], and can be administered over the telephone.

EuroQol (EQ5D; [16])

The EQ5D is a generic utility measure of quality of life. It consists of 5-domains and a visual analogue scale. It is intended for use in cost-effectiveness analyses.

Satisfaction with care

As there was no standardised measure of satisfaction with cancer services, we used the visual analogue scales for satisfaction, developed by King et al, [17]. Scales assessed overall care, continuity of care, supportive care, information needs, and quality of communication (scored 0 to 10 towards higher satisfaction). The five scales were summed to a total score of 50.

Eastern Cooperative Oncology Group-Performance Status (ECOG-PS; [18])
The ECOG-PS is an observer-rated scale assessing physical functioning. There are five levels: 0, asymptomatic, normal activity; 1, symptomatic, but fully ambulatory; 2, symptomatic and in bed less than 50% of time; 3, symptomatic and in bed more than 50% of time; 4, 100% restricted to bed; 5, dead.

(iv) Measures of potential bias:

Expectations of therapy and treatment preference were collected at baseline. Antidepressant use and other psychological therapies were collected at baseline, 12 and 24 weeks. Measures of blindness were collected at 12 and 24 weeks. Attrition was measured at 6, 12, 18 and 24 weeks.

Antidepressant use: We collected information about prescribed antidepressants, dose and any changes, as this may influence outcome of depression [19]. Amitriptyline is commonly prescribed at low doses for neuropathic pain in advanced cancer. Mean equivalent doses of fluoxetine were calculated using data from a meta-analysis by Hayasaka et al. [20].

Other psychological therapies: We noted any psychological intervention reported by participants or recorded in their case notes at baseline and throughout the trial.

Expectations of therapy: Participants were asked to predict the degree to which they thought their mood would improve or not during the trial period using a 10 point Likert scale ranging from not at all to completely.

Treatment preference: Patients were asked to indicate their group preferences (CBT, TAU, no preference).

Assessment of blindness: We conducted a limited measure of blindness by asking UCL researchers (other research staff could not undertake this task) to guess the patient's trial arm (CBT, TAU, don't know) as this may introduce bias where observer ratings are being collected.

Attrition: We recorded when possible reasons for missing a follow-up assessment (e.g. too ill, died).

(v) Therapy related measures:

Non-attendance for CBT:

We recorded, where known, the reasons for not attending therapy sessions (e.g. did not like therapy, became too unwell or died).

Competence and Adherence with treatment:

Competence

An accredited member of the British Association of Behavioural and Cognitive Psychotherapies independently rated digital-recordings of therapy using the Cognitive Therapy Scale Revised (CTS-R; [21]). We adopted a pragmatic approach and randomly selected at least 1 in 10 therapy sessions, stratified by the phase of therapy (early: session 1-4, mid: session 5-8, or late: sessions 9-12), to obtain a broad evaluation of treatment delivery.

Adherence to treatment manual:

Therapists were asked to record at the end of each session the main components of therapy delivered using a checklist (available from the authors). The independent rater also completed this checklist and the results were compared for congruence.

Statistical considerations:

We agreed an analysis plan prior to unlocking the database for analysis.

Power and sample size:

The study was powered to detect the overall effect of treatment on depression as measured on the BDI-II over the 24-week follow-up period, assuming a difference between the TAU and CBT groups of three points when measured at 6 weeks, rising further to six points after 12 weeks and sustained at that level thereafter (i.e. at 18 and 24 weeks). We assumed a standard deviation of 12 for each individual BDI-II measurement, and a correlation between measurements 6 weeks apart in the same individual of 0.65. These latter figures are based on the reported correlation between BDI-II values from sessions 1 week apart of 0.93 given in the BDI-II manual (Beck and Steer), and the assumption that this correlation decays exponentially with time. We allowed for 30% drop-out at 6 weeks, rising to 35% by 12 weeks and to 40% after 24 weeks. We further allowed for a possible within-therapist correlation coefficient of 0.02 (and assuming an average of six participants per therapist post-intervention) by inflating the sample size by a factor of 1.10 [8].

Based on the above assumptions, the sample size to be recruited to the study so as to detect an overall difference between the two groups at 90% power and 5% significance, was 120 participants per trial arm. (For more information see Serfaty et al. [8]).

Statistical analysis:

The primary analysis tested for an overall treatment effect on the BDI-II over the four follow-up points, using multi-level modelling allowing for repeated measurements with equal weighting for each time point. The model comprised three levels: 1) repeated measures; 2) individuals; and 3) therapists. Baseline BDI-II score and antidepressant prescribing (yes/no) were included as fixed effects. The model was fitted using a linear mixed effects model assuming a Gaussian error distribution. Assumptions of normality were checked. A sensitivity analysis was conducted using a standard multiple imputation model.

In supportive analyses we repeated the primary analysis with the following modifications: 1) using clustering by IAPT service; 2) without clustering; 3) including baseline history of depression, EQ5D, duration of current depression, and length (in

days) from primary diagnosis to baseline as fixed effects; and 4) conducting separate analyses for each follow-up.

The original analysis [8] was modified to include a Complier Average Intention to Treat (AKA Contamination Adjusted Intention to Treat) (CAITT) analysis. This adjusts for compliance and takes into account a possible lack of adherence to CBT. It differs from the better known Compliers Average Causal Effects ('CACE') analysis. In CAITT, a 'per session' effect of treatment is estimated rather than the effect for 'compliers' (which would require a binary definition of 'complier' in terms of number of sessions attended).

To test for bias, we compared baseline scores between the randomised groups on: 1) non-pharmacological treatment for depression; 2) group preference; and 3) expectations of improvement if they were to receive CBT. To compare antidepressant doses in the two groups, these medicines were converted into equivalent doses of fluoxetine.

Included in our analysis plan were exploration of the potential interaction of treatment with 1) time, 2) marital status and 3) education [22]. These were done in each case by adding the relevant interaction term into the primary analysis model. We regarded these analyses as exploratory, so requiring no adjustment to p-values for multiplicity.

Analysis of secondary outcomes:

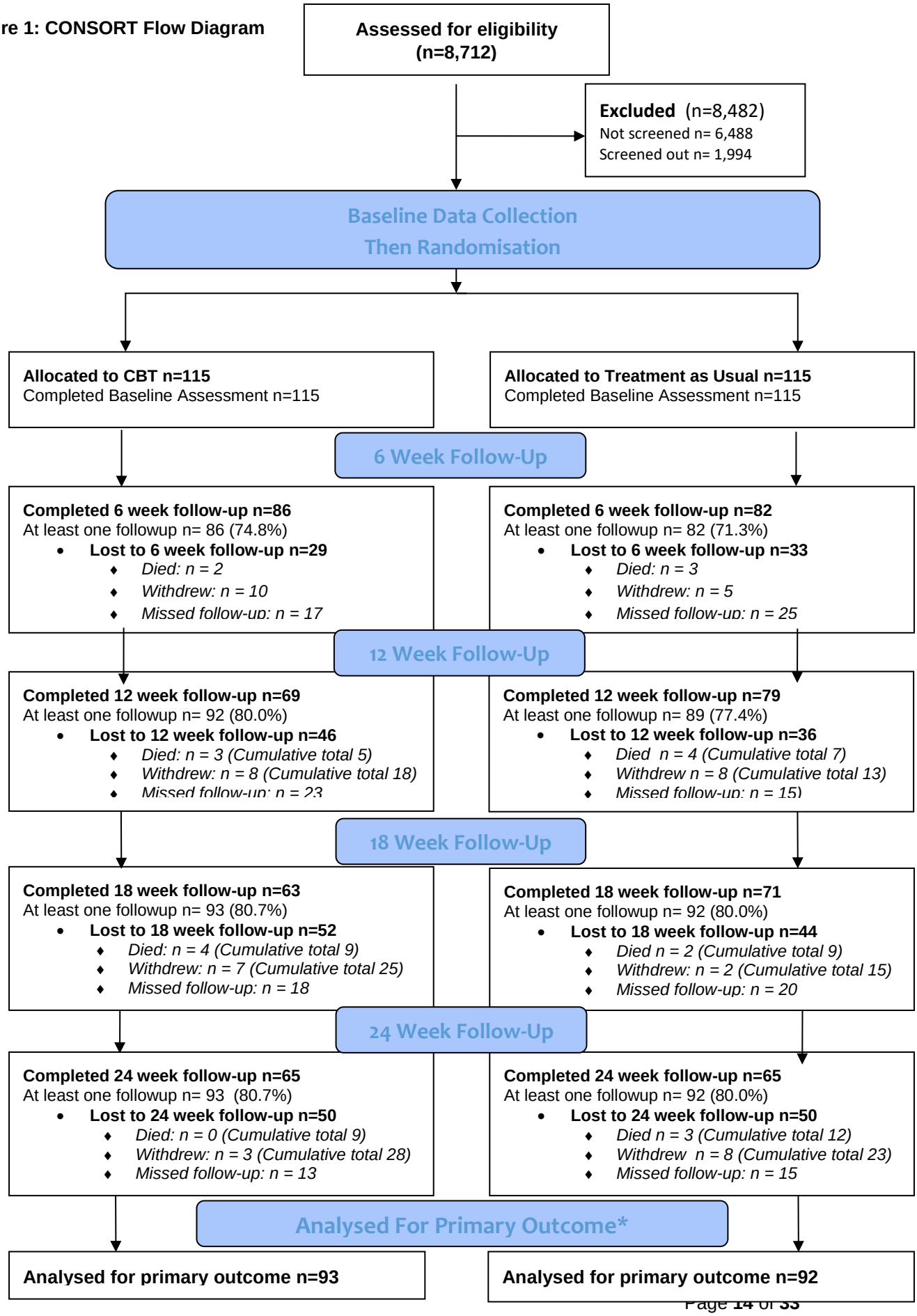
Analysis of PHQ-9 and Satisfaction with Care mirrored the primary analysis. For the ECOG-PS a non-parametric comparison was made between groups of the change from baseline at each time-point.

RESULTS:

Eight thousand seven hundred and twelve patients were considered for the study, of which 6,488 were excluded (figure 1); the main reasons in the pre-screening phase were: IAPT unavailable n=2,614; not a diagnosis of advanced cancer n= 1,668; not screened (other reason) n= 1,250; declined 1,021. The main reasons in the post screening phase were: declined, n= 1,021; PHQ-2 score $\leq$ 3, n=532; other reason, n=221. (Note, multiple reasons could be given for exclusion).

Two hundred and thirty participants were randomised after stratification by antidepressant (Figure 1). With fluctuations in health, participants missed various follow-ups. The number of participants completing the main outcome at various time points is shown, along with the numbers in which at least one follow-up was available; at least one time-point was available for 80% of participants. Also shown are the numbers lost to follow-up and reason with cumulative totals for died or withdrawn in parentheses. Of the 51 reasons for withdrawing from CBT or TAU, 18 (35.3%) were for ill health, and the remainder of reasons was very mixed, although, in accordance with ethics, no reason was given in 11 (21.6%). Of those specifically allocated to the CBT group, of the 71 reasons given for missing follow-up, 21 (29.2%) was due to health problems, 19 (26.4%) that participants could not be contacted at some stage and no reason was given 17 (23.6%) times. (Note that more than one reason could be given for not being followed up).

Figure 1: CONSORT Flow Diagram



Demographic characteristics:

The demographic characteristics of participants were similar in both study arms (table 1). One hundred and ninety six were recruited from oncology services, 28 from a hospice and 6 from GPs and characteristics were similar in each arm by recruitment site. The distribution of tumour sites included was: breast 31.3% (n=72), haematological 18.6% (n=43), colon 12.6% (n=29), lung 11.7 (n=27), prostate 5.2% (n=12), other 20.4% (n=47).

Table 1. Baseline demographic characteristics by randomisation group

	TAU		CBT		Total	
	Mean (SD), min, max		*Mean (SD), min, max*		*Mean (SD), min, max*	
Age (years)	59.5 (12.4), 27, 93 (*n* = 115)		59.5(10.3),37,81 (*n* = 115)		59.5(11.4),27,93 (*n* = 230)	
	n	(%)	n	(%)	n	(%)
Gender						
Male	37	32.2%	41	35.7%	78	33.9%
Female	78	67.8%	74	64.3%	152	66.1%
Total	115	100.0%	115	100.0%	230	100.0%
Marital status						
Married	55	48.2%	59	51.3%	114	49.8%
Partner - Living with	9	7.9%	9	7.8%	18	7.9%
Partner - not living with	1	.9%	2	1.7%	3	1.3%
Divorced/separated	18	15.8%	13	11.3%	31	13.5%
Widowed	9	7.9%	10	8.7%	19	8.3%
Single, never married	20	17.5%	22	19.1%	42	18.3%
Other	2	1.8%	0	.0%	2	.9%
Total	114	100.0%	115	100.0%	229	100.0%
Ethnicity						
White	84	73.0%	83	72.2%	167	72.6%
Black – British/African/Caribbean	17	14.8%	14	12.2%	31	13.5.0%
Indian/Pakistani/Bangladeshi	6	5.2%	7	6.1%	13	5.6%
Other	8	7.0%	11	9.6%	19	8.3%
Total	115	100.0%	115	100.0%	230	100.0%
Employment						
Employed	16	14.3%	27	23.7%	43	19.0%
Self employed	5	4.5%	13	11.4%	18	8.0%
Unemployed	12	10.7%	14	12.3%	26	11.5%
Homemaker	2	1.8%	0	.0%	2	.9%
Retired	49	43.8%	38	33.3%	87	38.5%
Unable to work due to health	24	21.4%	20	17.5%	44	19.5%
Other	4	3.6%	2	1.8%	6	2.7%
Total	112	100.0%	114	100.0%	226	100.0%
Education						
Degree/Higher degree	42	36.5%	44	38.3%	86	37.4%
A level/HNC/HNA/NVQ	36	31.3%	36	31.3%	72	31.3.0%
GCSE (or equivalent)	16	13.9%	24	20.9%	40	17.4%
No qualification	8	7.0%	7	6.1%	15	6.5%
Other	13	11.3%	14	12.2%	27	11.7%
Total	115	100.0%	115	100.0%	230	100.0%

Diagnosis of depression, previous psychiatric history and treatment:

All participants satisfied a MINI diagnosis of depressive disorder. Table 2 provides information about previous psychiatric history and treatment for depression. The duration of the current depression was skewed, with a median duration of around 12 weeks, with one person being depressed for 40 years. The proportion of participants taking an antidepressant was similar between groups. UCL researchers guessed the correct group allocation at 12 weeks in 19/26 (73%) and in 15/17 (88%) at 24 weeks.

Table 2. History, sources of bias and treatment of depression

	TAU		CBT		Total	
	Mean (SD), min, max (number).		*Mean (SD), min, max, (number).*		*Mean (SD), min, max, (number).*	
Previous episodes of depression	2.2 (1.9), 1, 10 (*n* = 63)		2.6 (2.4), 1, 12 (*n* = 59)		2.4 (2.1), 1, 12 (*n* = 122)	
Duration of depression (weeks)	74.3 (242.7), 0, 2080 (*n* = 90)		86.6 (266.5), 0, 2080, (*n* = 84)		80.3 (253.8), 0, 2080 (*n* = 174)	
CBT treatment expectation≠	7.0 (1.9), 1, 10 (*n* = 111)		7.2 (1.8), 4, 10 (*n* = 113)		7.1 (1.9), 1, 10 (*n* = 224)	
	n	(%)	n	(%)	n	(%)
Previous depression						
Yes	69	60.0%	68	59.1%	137	59.6%
Total	115	100.0%	115	100.0%	230	100.0%
Previously received CBT						
Yes	12	10.4%	12	10.4%	24	10.4%
Total	115	100.0%	115	100.0%	230	100.0%
Currently being treated for depression†						
Yes	33	29.2%	33	29.2%	66	29.2%
Total	113	100.0%	113	100.0%	226	100.0%
Treatment preference						
The CBT group	92	80.0%	87	75.7%	179	77.8%
The group with no CBT	3	2.6%	2	1.7%	5	2.2%
Do not have a preference	20	17.4%	26	22.6%	46	20.0%
Total	115	100.0%	115	100.0%	230	100.0%
Current antidepressant use						
At baseline	26	22.6%	29	25.2%	55	23.9%
At 12-week follow-up	20	17.4%	22	19.1%	42	18.3%
At 24-week follow-up	16	13.9%	20	17.4%	36	15.7%
Other current psychological therapy (not CBT) At baseline	5	4.3%	3	2.6%	8	3.5%
At 12-week follow-up	6	5.2%	1	0.9%	7	6.1%
At 24-week follow-up	5	4.3%	3	2.6%	8	7.0%

≠ Treatment expectation estimated improvement from not at all= 0 to very much improved =10.
† *includes prescribed medications or over the counter remedies or complementary therapies / self-help books to treat depression*

Delivery and receipt of CBT

The mean time from referral to first IAPT appointment was 29.4 (SD 26.7) days. Of a potential total of 1,380 CBT sessions, 543 (39.3%) were taken up by 74 of the 115 (64%) randomised to CBT. The mean number of CBT sessions received was 4.7 (SD 4.9); 41 people (35.6%) took up no sessions. Thirty-two of the 543 sessions (5.9%) were delivered by telephone. Although only 194 therapy sessions were digitally-recorded, we chose to rate 55 sessions (28% of all sessions recorded), as this represented 1 in 10 of sessions delivered. The mean CTS-R score was 47.6 (SD 13.8), (upper end of the "proficient" range). Cognitive techniques were reported as used in 57% of assessed sessions, behavioural techniques in 37% of sessions and topics specific to cancer discussed in 70%.

Main outcome:

The results for the BDI-II at baseline and follow-up timepoints are shown in table 4.

Table 4. BDI-II scores at baseline and follow-up.

Time-point		Q1	Median	Q3	Mean	SD	N
Baseline	TAU	18	24	30	24.5	9.7	115
	CBT	17	24	32	25.2	10.4	115
6 weeks	TAU	15	21	30	23.1	10.8	82
	CBT	16	23	30	23.6	10.8	86
12 weeks	TAU	13	20	29	21.4	11.1	79
	CBT	14	20	26	21.3	11.0	69
18 weeks	TAU	12	20	27	21.2	12.5	71
	CBT	12	17	28	20.6	11.9	63
24 weeks	TAU	13	19	27	20.4	11.4	65
	CBT	11	18	25	19.4	11.4	65

TAU= Treatment As Usual; CBT=Cognitive behaviour Therapy

Q1 = Lower Quartile; Q3 = Upper Quartile; SD = Standard Deviation.

The statistical analysis showed no benefit from CBT with time, adjusted for therapist clustering, antidepressant use or educational level (table 5). The sensitivity analysis using data imputation was consistent with this finding.

In accordance with our plan, we conducted two analyses similar to the primary analysis, but with (a) clustering by therapist replaced by clustering by IAPT service and (b) no clustering included. We found no evidence of any effect of clustering (at either the therapist or IAPT level) on the primary outcome and so the results of these two additional analyses are not given.

Table 5. BDI-II Treatment effect adjusted for potential predictors of outcome.

	Treatment Effect (Intervention – TAU)	**95% Confidence Interval**	**P-value**
Model with baseline BDI-II, baseline antidepressant use, time and group – clustering by therapist*			
Number in model = 185			
Estimates	-0.836	(-2.755,1.083)	0.393
Model with baseline BDI, baseline antidepressant use, time and group – clustering by therapist plus: baseline previous history of depression, baseline EQ5D health score, baseline duration of current depression (weeks). length between primary diagnosis and baseline visit (days)			
Number in model = 122			
Estimates	0.105	(-2.273,2.483)	0.931
Model with baseline BDI-II, baseline antidepressant use and group – clustering by therapist. 6 weeks follow-up only			
Number in model = 168			
Estimates	-0.136	(-2.157,1.884)	0.895
Model with baseline BDI, baseline antidepressant use and group – clustering by therapist. 12 weeks follow-up only			
Number in model = 148			
Estimates	-1.504	(-3.714,0.707)	0.182
Model with baseline BDI, baseline antidepressant use and group – clustering by therapist. 18 weeks follow-up only			
Number in model = 134			
Estimates	-0.964	(-4.133,2.205)	0.551
Model with baseline BDI, baseline antidepressant use and group – clustering by therapist 24 weeks follow-up only			
Number in model = 130			
Estimates	-1.875	(-4.845,1.096)	0.216

* The pre-determined primary analysis for the trial

CAITT analysis

A total of 153 individuals were included in the CAITT model [those with relevant outcome data (for control and intervention) and number of CBT sessions available (for the intervention group)]. The estimated "per-session" effect on the BDI-II was -0.295 95% Confidence Interval: (-0.760, 0.170) p= 0.213. Thus, on average, every session of CBT would be expected to decrease the total BDI-II score by 0.3 points (compared to no sessions). This effect, however, was not significant (p=0.213).

Exploratory analysis

Although we noted an improvement in BDI-II of around 5 points for both groups at 6 months followup, people who were widowed, separated or divorced and who did not receive CBT, continued with depressive symptoms (BDI-II) over time (Treatment effect -7.2; 95%CI = -11.1,-3.3; P<0.001). (Table 6)

Table 6. BDI-II Total scores by time-point, marital status and level of education

	Treatment Effect (CBT – TAU)	95% Confidence Interval	P-value
Model with baseline BDI-II, baseline antidepressant use, time and group – clustering by therapist plus: group by time interaction			
	Number in model = 185		
	p-value for interaction = 0.471		
Estimates 6 weeks	0.127	(-2.202,2.456)	0.915
12 weeks	-0.847	(-3.281,1.586)	0.495
18 weeks	-1.365	(-3.875,1.146)	0.287
24 weeks	-1.728	(-4.262,0.806)	0.181
Model with baseline BDI-II, baseline antidepressant use, time and group – clustering by therapist plus: group by marital status interaction			
	Number in model = 183		
	p-value for interaction = 0.002		
Estimates Married/partner	0.645	(-1.791,3.081)	0.604
Divorced/separated/widowed	-7.211	(-11.147,-3.276)	<0.001
Single never married	0.836	(-3.372,5.044)	0.697
Model with baseline BDI, baseline antidepressant use, time and group – clustering by therapist plus: group by education status interaction			
	Number in model = 170		
	p-value for interaction = 0.710		
Estimates Below A level	-0.463	(-3.558,2.631)	0.769
A level and above	-1.234	(-3.862,1.395)	0.358

Secondary outcomes:

Baseline scores were similar for the two groups for PHQ-9, EQ5D and satisfaction with care (Tabe 7). There was no sigificant between group differences at 12 and 24 weeks. The ECOG-PS suggested that at baseline 19.6% (n=45) were fully active, 42.2% (n=97) had restricted movement, 27.4% (n=63 were ambulatory, 10.9% (n=25) were limited and 0% (n=0) were disabled. Both groups were similar at baseline and 12 and 24 weeks.

Table 7. Secondary outcome mean scores at baseline and follow-up

		PHQ-9			EQ5-D			Satisfaction with care		
Time-point		Mean	SD	N	Mean	SD	N	Mean	SD	N
Baseline	TAU	13.5	4.8	115	0.61	0.23	115	39.7	9.2	114
	CBT	14.0	5.3	115	0.63	0.23	115	39.6	8.3	115
12 weeks	TAU	11.4	5.8	79	0.64	0.24	80	40.8	7.3	79
	CBT	10.3	5.7	68	0.64	0.24	68	39.5	10.1	68
24 weeks	TAU	9.9	6.3	64	0.63	0.27	64	40.8	8.4	64
	CBT	10.0	6.2	64	0.68	0.22	64	39.4	10.1	65

DISCUSSION:

CanTalk is a randomised controlled trial comparing the addition of CBT (plus TAU) delivered by IAPT therapists, for treating depression in people with advanced cancer no longer amenable to cure, compared to TAU alone. No benefit of CBT was found. This finding was supported by CAITT analysis which found non-significant change in BDI-II score with CBT of only 0.3 points per therapy session. An exploratory analysis suggested that CBT for people who were widowed, separated or divorced may be helpful. There were no significant between group differences for secondary outcomes.

Until the CanTalk study, the benefit of CBT for people with advanced cancer was unclear. Previous research was limited by under-powered trials, difficulties in diagnosing and measuring depression in people with advanced cancer, lack of clarity in the intervention model and how it was delivered, and concern about the generalisability of findings. These are addressed below.

Clinical effectiveness and power of the trial

It is possible that we failed to detect a significant difference between CBT and TAU when in fact there was one. However, even if the observed improvement of 2.76 were statistically significant, this would not be a clinically important change.

An updated Cochrane review [5] suggested that psychosocial therapies are effective for advanced cancer, and a recent trial of CBT for depression in 37 people with advanced breast cancer showed positive results [23]. Our trial recruited participants with a wide range of cancers and challenges earlier findings. Our pre-study power analysis required 240 participants at baseline, with variable attrition with time, to detect a 6 point difference in BDI-II. We recruited 230 participants, and as retention was better than anticipated, our achieved power would detect a significant 3-point change on the BDI-II.

Diagnosing and measuring depression in advanced cancer

The MINI has been widely used to diagnose depression in this population. However, it may be difficult, in people with life-limiting physical illnesses, to distinguish depressive disorder from an adjustment disorder with a prolonged depressive reaction (ICD10 F43.21). Indeed, Rayner et al. [24] found palliative care patients diagnosed with Major Depressive Disorder at baseline, 69% (27/39) had remitted four weeks later. As our population had a mean duration of depression for 1.4 years and none had symptoms of less than 4 weeks it is unlikely that our findings could be accounted for by a diagnosis of adjustment disorder.

Measuring depressive symptoms is complicated by the presence of somatic symptoms which frequently occur as part of physical disease in advanced cancer [25]. We chose the BDI-II as it is widely used in trials of psychotherapy for patients with advanced cancer [23]; [26]; [14] and consists of cognitive as well as somato-affective elements.

CBT as an intervention:

It remains unclear whether CBT is beneficial for depression in people with significant physical diseases. Consistent with previous work, CBT was not beneficial for depression in a palliative care population [26]. Our clinical impression was that physically ill people had difficulty in managing the demands of CBT. Although a recent meta-analysis [27] suggested that physical illness does not affect outcomes with psychological treatments, these data were not specific to an advanced cancer population.

CBT is thought to improve mood by changing cognitions and behaviours. Savard et al [23] observed, in advanced cancer, improvement was for somato-affective *rather than* cognitive symptoms, possibly because more behavioural strategies are used in CBT. To our knowledge, we are the only group to have collected therapists' self-report data on intervention delivery, suggesting more cognitive than behavioural techniques were used. Given the findings by Savard et al [23], the use of more behavioural interventions may be worth exploring in this population.

Delivery of CBT The time taken to be seen by an IAPT therapist appeared to favour the CanTalk study which fast tracked participants into therapy; in a typical IAPT service 75% of which are seen within 42 days, but 5% may wait at least 126 days. Nevertheless a small number of participants in the CanTalk study were delayed, not because therapists were not available, but because they were physically unwell and had to attend for additional physical treatment. The CanTalk study aimed to test the effectiveness, rather than the efficacy of CBT. CBT may have been ineffective because participants received insufficient sessions or the quality of therapy was poor. Sixty four percent (74/115) took up at least one session and the mean number of sessions was 4.7. This is similar to up-take of therapy (70%) for general IAPT practice and insufficient therapy sessions does not explain the lack of effectiveness as shown by the CAITT analysis.

Our CTS-R ratings suggest good quality of delivery of CBT. Although there is an assumption that the quality of therapy predicts outcome, this relationship may be weaker than thought [28]. Both therapists and independent raters reported adherence to the model, with a balance of cognitive and behavioural techniques and discussion of cancer related issues. Selection bias, where IAPT centres and therapists participating in research may not be typical of an IAPT service needs to be considered. However, we would expect participating centres to be more experienced in dealing with complex needs and favour the outcome of CBT.

Impact of bias

Eighty percent of participants had a preference for CBT, although only half were randomised to this. If anything, this bias would be in favour of CBT. Participants cannot be blind to the intervention group. Using a self-report measure such as the BDI-II should minimise impact of researcher bias. Differential attrition may bias outcome and attrition in people with advanced cancer is high [29]. However, retention of participants was similar between the two treatment groups, 92 for TAU and 93 for CBT. We are aware it could be argued that TAU is not strictly TAU as we discouraged the use of CBT as part of usual care, however in reality, participants are rarely referred for CBT nor indeed any other psychological treatment.

Implications of findings

CBT in advanced cancer may be delivered in 3 ways: CBT specialists may be trained to apply their skills to cancer-specific problems; cancer specialists may be trained in CBT skills; specialist CBT therapists may be imbedded within a cancer service. High intensity IAPT therapists were not effective, which raises questions about the policy of recommending the inclusion of *incurable* cancer in the IAPT long term conditions programme. Using IAPT therapists to treat depression in *early* stage cancer, or anxiety disorders may warrant further testing. Training clinical nurse specialists within a cancer service to use CBT techniques has not been shown to be effective for depressive symptoms [26]. However, there may be benefits of specialist CBT therapists embedded within cancer and palliative care teams. A study in advanced lung cancer [30] found that integrated collaborative care, delivered in secondary care, uses a variety of elements, including CBT. Integrative collaborative care was substantially more efficacious than usual care. Unlike our work, previous studies [5] [4] treated specific tumour groups. Applying an integrative approach to a range of tumour groups may worth testing. Although under a quarter of people in the CanTalk study were prescribed an antidepressant, the evidence for their use remains to be evaluated.

The CanTalk study was not powered to examine the observed benefit of CBT for depressive symptoms in people who were widowed, separated or divorced. However, given these demographic variables have been identified as moderators of response to CBT in adults [22] these were examined as part of our predefined analysis plan. People who are more emotionally isolated or have suffered a bereavement or separation, may benefit from non-specific components of CBT, such as having someone warm and friendly to talk to. Although separating the specific or non-specific treatment effects of CBT is complex, this may warrant further research.

CONCLUSIONS:

A meta-analysis [27] suggested that the effectiveness of CBT for depression in general may be overestimated, possibly due to publication bias, small sample size

and a lack of suitable control groups. Whilst IAPT practitioners can be trained to deliver CBT to an advanced cancer population, our results suggest that resources for a relatively costly therapy like IAPT-delivered CBT should not be considered as a first line treatment for depression in advanced cancer. Indeed these findings raise important questions about the need to further evaluate the use of IAPT for people with comorbid severe illness.

WHAT IS ALREADY KNOWN ABOUT THE TOPIC

Depression commonly occurs in people with advanced cancer. NICE recommends psychological support for this group.

Talking therapies (including cognitive Behavioural therapy [CBT]) are increasingly being delivered in the community through the Improving Access to Psychological Therapies (IAPT) service.

CBT is an effective treatment for depression and some benefit has been shown in cancer in its earlier stages and within integrative care to a specific tumour group with a shorter prognosis.

Evaluating use of CBT as a treatment for depression in *a range of advanced* cancers delivered through IAPT in a primary care setting has never been robustly tested.

WHAT THIS STUDY ADDS

The CanTalk study is a national (UK) multi-centred randomised controlled trial of individual CBT, delivered through IAPT, for treating people with a *wide range* of advanced cancers and depression.

Whilst the CBT intervention was of high quality and well received, the results of the trial show that there was no clinical benefit of CBT.

Existing guidance recommending CBT for depression, delivered through IAPT, should not be applied to an *advanced* cancer population.

For those with advanced cancer, CBT delivered through other routes such as hospice-based psychological services requires further investigation.

The CanTalk trial raises questions about whether further evidence is needed to support the use of IAPT to deliver CBT to people with long term conditions.

Data sharing

The studies dataset is available from the corresponding author on request.

Words: 4630

Contribution of Authors:

Marc Serfaty was Chief Investigator of the CanTalk study. He led the grant application for the study and was involved in the analysis and write up.

Michael King was involved in the design, planning, and the management of the study. He provided input into the analysis plan, the interpretation of findings, the design of the treatment manual, and therapist training.

Irwin Nazareth was involved in the design, planning and management of the study. He provided input into the analysis plan and interpretation of findings.

Stirling Moorey was involved in the design, planning and management of the study. He contributed to the design of the treatment manual and was involved in the training of therapists. He was also involved in interpretation of the results and write up.

Trefor Aspden was involved in the management of the study, the interpretation of the results, and the write up.

Kathryn Mannix was involved in the design, planning and management of the study. She contributed to the design of the treatment manual and was involved in training therapists. She was also involved in interpreting results and write up.

Sarah Davis was involved in the design, planning, and management of the study. She was also involved with participant identification, follow up, and write up.

John Wood was involved in the management of the study, the analysis plan, and interpreting the study findings.

Louise Jones was involved in the design, planning, and management of the study. She was involved in the day to day running of the study as well as in the interpretation of the findings and write up.

Declaration of Competing Interests:

Dr Serfaty is a member of HTA General Board, and declares no other conflict of interest. All other authors declare no conflict of interest.

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The lead author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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