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Cost-utility analysis of transdiagnostic cognitive behavioural therapy for people with persistent physical symptoms in contact with specialist services evaluated in the PRINCE secondary trial

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ABSTRACT

Objective: To compare the cost-utility of transdiagnostic cognitive behavioural therapy (TDT-CBT) plus standardised medical care (SMC) to SMC alone to support people with persistent physical symptoms in contact with specialist services.

Methods: This study compared the cost-utility of TDT-CBT. A two-arm randomised controlled trial was conducted in secondary care settings. Participants received either TDT-CBT + SMC or SMC alone. Measures were taken at baseline and at 9-, 20-, 40-, and 52-week follow-up. Service use was measured, and costs calculated. Costs were combined with quality-adjusted life years (QALYs) based on the EQ-5D-5L using incremental cost-utility ratios with uncertainty addressed using cost-effectiveness planes and acceptability curves.

Results: The costs during the follow-up period were £3473 for TDT-CBT + SMC and £3104 for SMC alone. The incremental cost for TDT-CBT + SMC adjusting for baseline was £482 (95 % CI, −£399 to £1233). QALYs over the follow-up were 0.578 for TDT-CBT + SMC and 0.542 for SMC alone. The incremental QALY was 0.038 (95 % CI, −0.005 to 0.080). The incremental cost per QALY was £12,684 for TDT-CBT + SMC. There was a 68.3 % likelihood that TDT-CBT + SMC was the most cost-effective option at a threshold of £20,000 per QALY.

Conclusion: Adding TDT-CTB to SMC results in slightly increased costs and slightly better outcomes in terms of QALYs. This represents a cost-effective option based on the conventional QALY threshold value.

1. Introduction

It is relatively common for people to present to health services with symptoms for which there is no clear structural biomedical explanation. Such conditions include chronic fatigue syndrome, irritable bowel syndrome, and fibromyalgia. Persistent physical symptoms (PPS), or medically unexplained symptoms, can lead to substantial suffering and impaired quality of life. They may also require extensive medical investigation and support leading to high healthcare costs [1–3]. The impact of these conditions can also be substantial in terms of reduced work opportunities and support needed from family and friends [1,4].

Treatment options are varied. In the absence of clearly identified biomedical explanations which may be addressed through medicinal interventions, support through psychological interventions specifically tailored to reducing the impact and severity of symptoms may be helpful. There have been a number of systematic reviews and meta-analyses that demonstrate the effectiveness of cognitive behavioural therapy (CBT) for PPS [5–8]. Effect sizes vary depending on the outcome in question and the type of therapy being evaluated. To assess whether CBT reduced health care costs a systematic review and meta-analysis

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[1] Mark Ashworth sadly passed away shortly before this paper was accepted. We dedicate the paper to Mark's memory.

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was conducted using data from 18 trials. Small reductions in healthcare contacts and medication use were found for CBT compared with active controls, treatment as usual and waiting list controls. However, there were no reductions in medical investigations or healthcare costs [9].

Given the overlap in some of the cognitive behavioural factors which perpetuate syndromes including irritable bowel syndrome, chronic fatigue syndrome and fibromyalgia we developed a transdiagnostic approach based on a theoretical model that assumes that common processes can be targeted simultaneously across symptom clusters with a view to reducing symptoms and improving quality of life. We called this approach transdiagnostic CBT (TDT-CBT). We evaluated the approach in the context of a randomised controlled trial [10].

Although we didn't see a significant treatment effect on the primary outcome (WSAS) at 52 weeks there was a difference at 20 weeks which corresponded to the end of therapy. However, we demonstrated that TDT-CBT added to standard medical care (TDT-CBT + SMC) led to significant improvements in secondary outcomes, specifically functioning after 20 weeks, physical symptoms and self-rated global clinical change after 52 weeks compared to SMC alone [10]. Any new healthcare intervention uses resources that have an opportunity cost (i.e. they can be used in alternative ways). As such, it is imperative to assess their 'value for money'. The most common way of doing this, and the approach favoured by the National Institute for Health and Care Excellence (NICE) in England and Wales, is to determine the extra healthcare costs incurred to produce one extra quality-adjusted life year (QALY) compared to an alternative approach. A QALY is a measure of the state of health of a person or group in which the benefits, in length of life, are adjusted to reflect the quality of life.

The aim of the analyses in this paper is to assess the cost-effectiveness of TDT-CBT + SMC compared to SMC alone in terms of QALYs over the 12-month follow-up.

2. Methods

This was a two-arm multi-centre randomised controlled trial. The trial registration can be found on ClinicalTrials.gov (Trial Registration Number: NCT02426788). It received ethical approval from the Camberwell St Giles Ethics Committee (REC15/LO/0058).

2.1. Setting and sample

Participants were recruited from specialist secondary care (i.e. hospital) services in London. Specifically, services include those providing rheumatology, cardiology, respiratory, neurology, gastroenterology and urology care. Inclusion criteria were: (i) adults with PPS defined as persistent bodily symptoms without a clear structural biomedical explanation cause, (ii) age 18–65 years, (iii) scoring ten or above on the Work and Social Adjustment Scale (WSAS) [11], (iv) able to write and read in English, and (v) willing to give informed consent and to attend study visits. Exclusion criteria were: (i) psychosis and/or factitious disorder, (ii) headaches as the main/only PPS because of challenges in distinguishing between these and migraine, (iii) non-epileptic seizures as the main/only PPS because of another trial recruiting from this patient group, (iv) drug/alcohol disorder, (v) use of benzodiazepines above an equivalent daily diazepam dose of 10 mg due to potentially attenuating the effect of CBT, (vi) receipt of CBT for PPS in the past year, (vii) high risk of self-harm, and (vii) participated in an associate feasibility study of CBT for PPS in primary care [12].

2.2. Interventions

The intervention group (TDT-CBT + SMC) received up to eight one-hour sessions of CBT over a 22-week period and a self-help manual. CBT was delivered by qualified therapists and covered engagement and rationale giving, exposure techniques to reduce avoidance, dealing with symptom-related cognitions and emotions, and relapse prevention. Full details are provided in our previous papers [10,13]. The comparison group (SMC alone) received the manual after 52 weeks. SMC for both groups consisted of standard care delivered by health services.

2.3. Outcomes and costs

Detailed information on clinical measures used at baseline, and 9-, 20-, 40- and 52-week follow-up are given by Chalder et al. [10] For the cost-utility analysis we combined health and social care costs (including the intervention) with quality-adjusted life years (QALYs). These were derived from the EQ-5D-5L at baseline and each follow-up point. The EQ-5D-5L consist of five domains: mobility, self-care, usual activities, pain and discomfort, and anxiety and depression. Each of these receives an integer score of 1 (no problem) to 5 (extreme problems). These scores were converted to a scale anchored by 1 (full health) and 0 (death) using an algorithm produced by Devlin et al. [14] The scores were then converted to QALYs using area under the curve methods assuming a linear change between time points [15].

Costing was done from a health and social care perspective and figures are presented in 2022/23 UK pounds. Service use was measured with an adapted version of the Client Service Receipt Inventory (CSRI) [16]. We asked participants to report whether, during the six months prior to baseline or since the last time point, they had used specific services including primary care, secondary care from hospitals, and social care. If services were used, then the participant was asked how many times they had used them. For inpatient care, they were asked to report how many days they had spent in hospital.

Costs of the CBT intervention was based on therapy time in minutes received (which was recorded by the trial team) and a nationally applicable cost per CBT session of £99 [17]. Other costs were calculated by combining service use information with appropriate nationally applicable unit costs [17,18]. A list of unit costs is included as an appendix.

2.4. Analysis

The use of services and their costs were compared between the two groups. Total health costs over the follow-up period were compared using a regression model controlling for baseline costs. Similarly, QALYs over the follow-up period were compared controlling for baseline health-related quality of life. In both models, bootstrapped confidence intervals around the coefficient of the group variable were produced. The cost and QALY differences were used to derive an incremental cost-effectiveness ratio (ICER) showing the cost incurred for the intervention to produce one extra QALY. Uncertainty around the results were investigated using cost-effectiveness planes and acceptability curves. The main results were based on a complete case analysis. As a sensitivity analysis we also derived cost and QALY differences and an ICER when multiple imputation was applied. The imputation used chained equations and predictive mean matching based on the five nearest neighbours [19]. Twenty datasets were used in the imputation and missing EQ-5D-5L and non-therapy costs were imputed from other available EQ-5D-5L scores and costs as these were considered to have the greatest predictive power.

3. Results

There were 324 participants randomised, 161 to TDT-CBT + SMC and 163 to SMC alone. The mean age was 43.1 years and 83.0 % were female. White participants accounted for 72.2 % of the sample. Recruitment came from the following clinics: neurology 10.2 %, cardiology 7.1 %, rheumatology 49.1 %, gastroenterology 22.2 %, respiratory 9.3 %, pain 1.9 % and occupational health 0.3 %. Complete data (i.e. service use and EQ-5D-5L scores which allowed costs and QALYs to be estimated for the follow-up period) were available for 105 (65.2 %) of the TDT-CBT + SMC group and 116 (71.2 %) of the SMC alone group.

Further details of the sample are provided by Chalder et al.[10]

Tables 1–3 include information on service use and costs, excluding the therapy received by the TDT-CBT + SMC group. In the 6-month period prior to baseline, the majority of participants received care from general practitioners (GPs) and other doctors (Table 1). The most commonly used other services were practice nurses, pharmacists, physiotherapists, complementary healthcare, and visits to accident and emergency. There were no major differences between the two groups. Service use, particularly from GPs and other doctors, was lower over the follow-up periods and again there were few notable differences between the groups. The average number of service contacts is shown in Table 2. The average number of GP contacts was around five in the period prior to baseline. There were fewer contacts in the follow-up periods, but these were shorter, so this is expected. Again, intensity of service use was similar between groups. Average service costs across the whole sample (i.e. including non-users) were highest for other doctors, GPs and inpatient care (although few used the latter) (Table 3). The cost of the TDT-CBT input was on average £760, ranging from £0 to £1204.

At baseline the average cost over six months for the TDT-SMC + CBT group was £1487 and for SMC alone it was £1726. TDT-CBT + SMC resulted in average total health costs over the follow-up of £3473 with the cost for SMC alone being £3104. After controlling for baseline, the TDT-CBT + SMC group had costs that were £482 higher (bootstrapped 95 % CI, −£399 to £1233). However, TDT-CBT + SMC resulted in 0.576 QALYs over the follow-up compared to 0.533 for SMC. The difference after controlling for baseline health-related quality of life was 0.038 in favour of CBT + SMC (bootstrapped 95 % CI, −0.005 to 0.080). The ICER was £12,684 per QALY.

Uncertainty around the cost-effectiveness result is indicated in the cost-effectiveness plane shown in Fig. 1, where individual dots represent incremental cost and QALY combinations generated from 1000 bootstrapped resamples. It can be seen that the most likely occurrence is that TDT-CBT + SMC results in higher costs and more QALYs (82.3 % of bootstrapped incremental cost-QALY combinations). This is followed by TDT-CBT + SMC being cost saving and producing more QALYs (13.6 %), having higher costs and fewer QALYs (4.0 %), and having lower costs and fewer QALYs (0.1 %). The cost-effectiveness acceptability curve (Fig. 2) shows that at a threshold of £20,000 per QALY there is a 68.3 % likelihood that TDT-CBT + SMC is the most cost-effective option.

After imputation for missing costs and health-related quality of life, the cost difference was £435 and the QALY difference was 0.053. This resulted in an ICER of £8208 per QALY.

4. Discussion

This evaluation of transdiagnostic cognitive behavioural therapy in addition to standardised medical care for patients with persistent physical symptoms referred from secondary care clinics found that at a threshold of £20,000 per QALY there is a 68.3 % likelihood that the intervention is the most cost-effective option. The incremental cost per QALY was £12,684 for the intervention. It is a value judgement as to whether it represents value for money. Transdiagnostic cognitive behavioural therapy resulted in slightly higher health-related quality of life compared to usual care and a corresponding higher number of QALYs. The incremental cost per extra QALY was below the threshold of £20,000 often used to endorse health technologies in England and Wales, which provides evidence for its cost effectiveness according to the NICE threshold. The sensitivity analysis strengthened these findings.

We did not in this paper formally combine the costs with the primary outcome of the trial and instead focussed on QALYs. The primary outcome, Work and Social Adjustment Scale, at 52 weeks was 1.48 points better for the intervention group [10]. Dividing the cost difference of £482 by 1.48 gives a cost per unit improvement on the outcome of £326. A clinically significant difference is assumed to be 3.6 points and so a cost of £1172 would be incurred to achieve this. With QALYs we often have accepted thresholds to use. However, there is no recognised threshold for a change on the Work and Social Adjustment Scale and so it is unclear whether £1172 represents value for money.

In 2012, Konnopka et al. published a systematic review of economic evaluations in this area and found some evidence that interventions reduced costs [1]. More recently, Wortman et al. found that of 32 studies identified, 22 were cost-utility analyses (i.e. using QALYs) and of these 13 showed interventions to be either dominant (cost saving and outcome improving) or to result in cost-effectiveness ratios below an accepted threshold [20]. There were six studies which used CBT and of these five suggested it was cost-effective. This study adds to the evidence base as it reinforces these conclusions and also, unlike many studies in these reviews, it covers unexplained symptoms generally rather than focussing on particular conditions.

There were limitations with the study. First, it relied on self-report of

Table 1
Percentage of participants using specific services derived from the Client Service Receipt Inventory.

	Baseline		9 weeks follow-up		20-weeks follow-up		40-weeks follow-up		52-weeks follow-up	
Service	TDT-CBT +SMC (n = 161)	SMC (n = 163)	TDT-CBT +SMC (n = 125)	SMC (n = 132)	TDT-CBT +SMC (n = 127)	SMC (n = 129)	TDT-CBT +SMC (n = 114)	SMC (n = 120)	TDT-CBT +SMC (n = 111)	SMC (n = 120)
GP	95	94	67	66	69	71	80	72	74	69
Psychiatrist	4	8	2	7	3	5	2	5	4	5
Other doctor	93	91	52	43	37	43	49	48	50	46
Practice nurse	33	32	20	20	23	21	25	25	26	26
Pharmacist	25	33	22	27	20	20	24	26	25	25
Psychologist	8	10	9	10	6	9	11	13	12	12
Physiotherapist	29	30	26	20	17	24	16	21	20	17
Social worker	4	2	3	2	2	2	2	2	2	2
CMHW	1	1	0	2	2	1	3	3	2	2
Comp healthcare	23	20	13	14	10	15	9	13	11	15
OT	11	9	10	6	6	7	8	4	5	6
Inpatient care	12	9	3	5	5	2	9	6	6	8
A&E	27	26	12	14	14	7	18	15	10	11
MRI	25	31	10	12	4	11	14	13	14	11
CT	19	15	5	5	5	5	9	9	10	9
Ultrasound	29	28	18	17	12	13	23	21	19	14
X-ray	35	35	15	15	21	15	21	20	21	20
EEG	9	12	7	4	6	4	5	8	4	9
Blood test	82	80	44	46	43	50	58	53	48	49

GP = general practitioner, CMHW = community mental health worker, OT = occupational therapist, A&E = accident and emergency, MRI = magnetic resonance imaging, CT = computed tomography, EEG = electroencephalogram.

Table 2
Mean number of contacts with services (only including those with at least one contact) derived from the Client Service Receipt Inventory.

	Baseline		9-weeks follow-up		20-weeks follow-up		40-weeks follow-up		52-weeks follow-up	
Service	TDT-CBT +SMC (n = 161)	SMC (n = 163)	TDT-CBT +SMC (n = 125)	SMC (n = 132)	TDT-CBT +SMC (n = 127)	SMC (n = 129)	TDT-CBT +SMC (n = 114)	SMC (n = 120)	TDT-CBT +SMC (n = 111)	SMC (n = 120)
GP	5.2	5.2	2.5	2.8	2.3	2.6	3.0	2.8	2.6	2.7
Psychiatrist	2.5	2.9	5.0	2.1	1.5	3.2	2.0	1.5	1.3	1.2
Other doctor	3.2	2.8	1.7	2.0	2.0	1.9	2.1	2.7	1.8	2.1
Practice nurse	2.4	2.7	1.7	1.5	1.2	1.2	1.9	1.8	2.4	1.3
Pharmacist	3.1	3.9	1.8	2.1	2.0	2.0	2.1	1.6	2.4	2.0
Psychologist	4.9	5.8	3.8	3.2	3.3	5.6	4.8	6.1	2.5	5.6
Physiotherapist	3.7	5.5	2.5	2.9	2.3	2.7	3.6	3.8	2.9	4.2
Social worker	3.8	2.8	1.3	1.0	1.5	1.5	1.0	1.5	1.5	2.5
CMHW	4.0	4.0	–	2.5	1.5	8.0	1.0	1.0	1.5	1.0
Comp healthcare	4.0	4.3	3.2	3.3	3.4	2.7	5.1	2.4	4.4	3.2
OT	1.9	3.9	1.7	1.4	1.1	1.8	1.7	1.4	1.3	1.3
Inpatient care	4.0	9.6	3.0	2.6	6.0	10.0	3.4	3.7	2.1	3.1
A&E	1.8	1.4	1.3	1.2	1.2	1.1	1.2	1.2	1.3	1.4
MRI	1.6	1.5	1.1	1.3	1.0	1.0	1.2	1.2	1.1	1.2
CT	1.6	1.6	1.0	1.0	1.3	1.0	1.1	1.3	1.0	1.2
Ultrasound	1.3	1.5	1.2	2.5	1.3	2.2	1.4	1.4	1.2	1.2
X-ray	1.7	1.4	1.4	1.3	1.1	1.2	1.3	1.5	1.3	1.5
EEG	1.5	1.6	1.0	1.4	1.4	1.6	1.5	1.4	1.5	1.0
Blood test	3.3	3.5	1.6	2.3	2.0	1.9	2.3	2.5	2.0	1.9

GP = general practitioner, CMHW = community mental health worker, OT = occupational therapist, A&E = accident and emergency, MRI = magnetic resonance imaging, CT = computed tomography, EEG = electroencephalogram.

Table 3
Mean cost of services (£s).

	Baseline		9-weeks follow-up		20-weeks follow-up		40-weeks follow-up		52-weeks follow-up	
Service	TDT-CBT +SMC (n = 161)	SMC (n = 163)	TDT-CBT +SMC (n = 125)	SMC (n = 132)	TDT-CBT +SMC (n = 127)	SMC (n = 129)	TDT-CBT +SMC (n = 114)	SMC (n = 120)	TDT-CBT +SMC (n = 111)	SMC (n = 120)
GP	222	221	75	84	70	84	106	91	85	85
Psychiatrist	20	51	26	31	10	31	7	16	10	12
Other doctor	640	544	193	183	159	181	221	272	198	213
Practice nurse	14	15	6	5	5	5	9	8	11	6
Pharmacist	19	32	10	14	10	10	13	10	15	13
Psychologist	81	133	80	70	45	114	116	175	68	151
Physiotherapist	85	128	51	44	30	50	44	59	45	56
Social worker	10	5	3	1	2	2	1	2	2	3
CMHW	4	2	0	3	2	5	2	3	2	1
Comp healthcare	46	42	21	23	17	20	24	15	25	24
OT	23	35	16	9	7	13	13	6	7	8
Inpatient care	224	337	52	85	173	154	207	142	83	154
A&E	123	98	40	43	43	20	58	46	32	38
MRI	68	78	19	26	7	20	28	26	27	21
CT	34	28	5	6	7	5	11	13	11	12
Ultrasound	24	27	13	28	10	19	21	19	15	11
X-ray	17	14	6	5	6	5	7	8	7	8
EEG	44	64	23	18	26	20	26	38	18	30
Blood test	13	14	4	5	4	5	7	6	5	5

GP = general practitioner, CMHW = community mental health worker, OT = occupational therapist, A&E = accident and emergency, MRI = magnetic resonance imaging, CT = computerised tomography, EEG = electroencephalogram.

service use which is a limitation if recall was inaccurate. The CSRI was though administered four times during the follow-up period and so no retrospective period for recall was particularly long. However, some CSRI data were missing at one time point but were collected at a later point. Ideally the latter should have covered the missing period, but it is unclear if this would always have happened. There is no reason though to assume that any bias would have occurred in these cases. Second, the outcome used in these economic analyses was the QALY derived from the EQ-5D-5L and the cost perspective was that of the healthcare system. While this approach is used widely and is recommended by NICE, it may not be capturing all relevant effects. Third, as planned we used the value set that applies specifically to the EQ-5D-5L, but recognise that 'cross walking' to the original three-level version of the questionnaire is frequently done instead.

In conclusion, this study has shown that TDT-CBT + SMC may be a cost-effective option for supporting people with persistent physical symptoms in secondary care. Further work should follow participants over a longer time period, make comparisons with other treatment options, and explore ways of delivering therapy to this group at a lower cost. Although speculative, combinations of face to face and digital interventions may be promising in terms of cutting costs. Given our study found that catastrophizing and symptom focusing mediated change in outcomes it is possible that additional emotional regulation strategies targeting these processes could improve outcomes including cost-effectiveness [21].

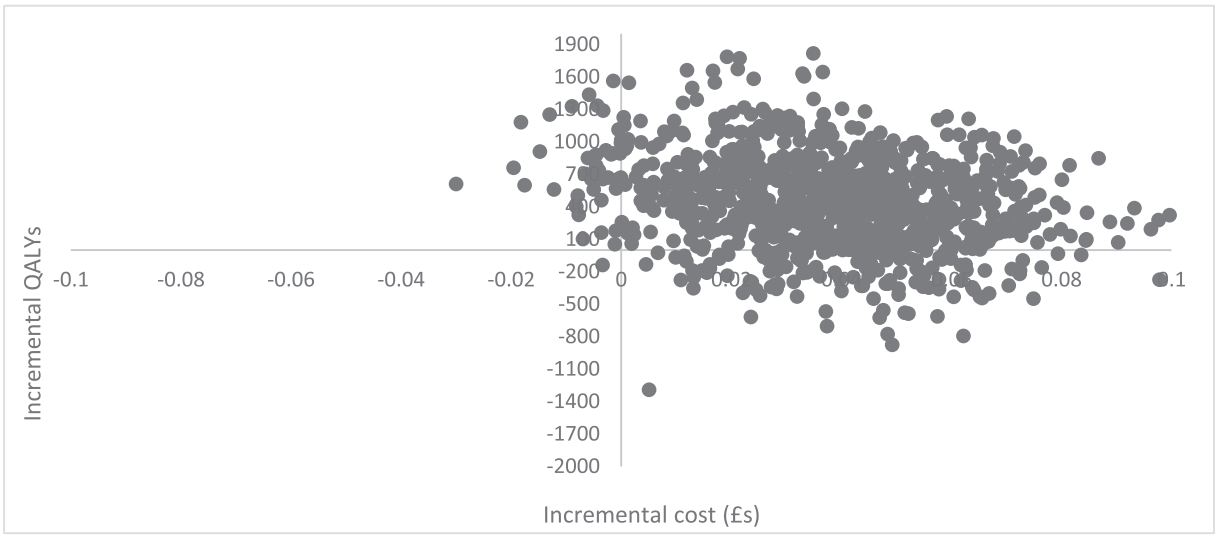

Fig. 1. Cost-effectiveness plane.
Note: Each dot represents an incremental cost-QALY combination obtained from 1000 bootstrapped resamples.

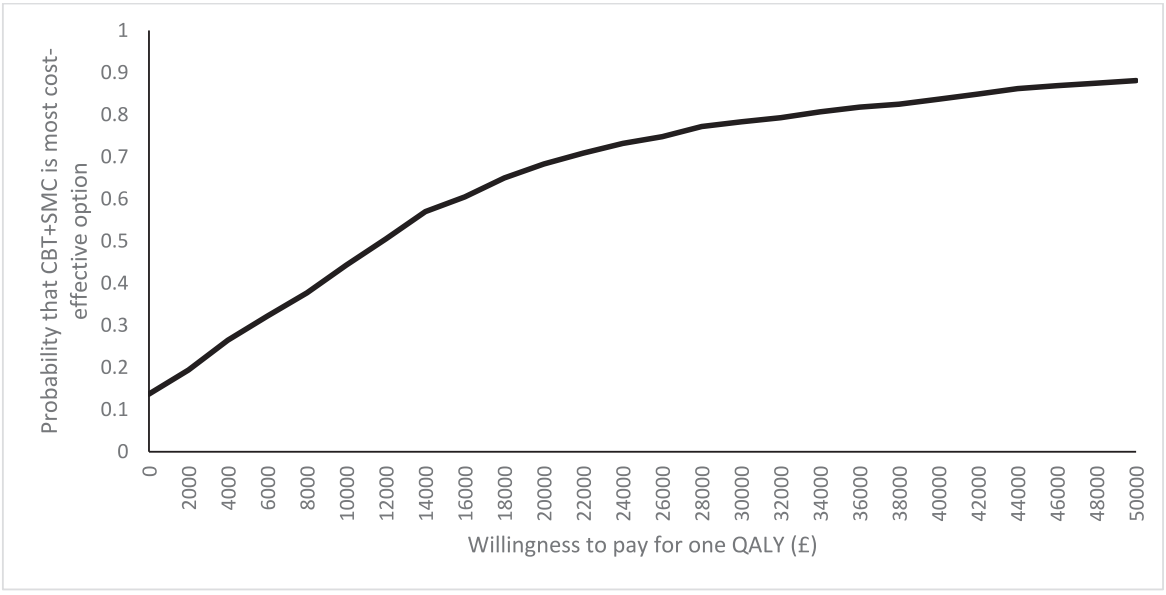

Fig. 2. Cost-effectiveness acceptability curve.
Note: The curve shows the probability that TDT-CBT + SMC is the most cost-effective option for different values placed on a QALY.

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CRediT authorship contribution statement

Paul McCrone: Writing – review & editing, Writing – original draft, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Meenal Patel:** Writing – review & editing, Project administration. **Matthew Hotopf:** Writing – review & editing, Methodology, Funding acquisition. **Rona Moss-Morris:** Writing – review & editing, Methodology, Funding acquisition, Conceptualization. **Mark Ashworth:** Writing – review & editing, Methodology, Funding acquisition, Conceptualization. **Anthony S. David:** Writing – review & editing, Methodology, Funding acquisition, Conceptualization. **Mujtaba Husain:** Writing – review & editing, Project administration, Methodology. **Kirsty James:** Writing – review & editing, Methodology, Investigation. **Sabine Landau:** Writing – review & editing, Methodology, Funding acquisition, Conceptualization. **Trudie Chalder:** Writing – review & editing, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization.

Declaration of competing interest

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Appendix A. Appendix

Unit costs used in cost calculations.

Service	Cost
General practitioner contact	£45
Psychiatrist contact	£217
Other doctor contact	£217
Practice nurse contact	£18
Pharmacist contact	£25
Psychologist contact	£222
Physiotherapist contact	£78
Social worker contact	£73
Mental health worker contact	£80
Complementary healthcare contact	£50 (assumed)
Occupational therapist contact	£105
Inpatient day	£666
Accident and emergency visit	£257
MRI scan	£171
CT scan	£116
Ultrasound scan	£64
X-Ray	£28
EEG	£335
Blood test	£5
Cognitive behavioural therapy session	£115

Costs obtained or derived from Unit Costs of Health and Social Care and 2021/22 National Cost Collection Data Publication (inflated to 2022/23 prices). [17,18]

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