Therapist telephone-delivered CBT and web-based CBT compared with treatment as usual in refractory irritable bowel syndrome: the ACTIB three-arm RCT

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London NHS Foundation Trust and the University of East Anglia outside the submitted work. The patient manual is background IP developed by Rona Moss-Morris and Trudie Chalder in previous work. The therapist manual was developed for the Assessing Cognitive–behavioural Therapy in Irritable Bowel (ACTIB) trial. These manuals were made available only once the 12-month ACTIB follow-up was complete. Sabine Landau reports support via the Biomedical Research Centre for Mental Health at South London and Maudsley NHS Foundation Trust and King's College London.

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Scientific summary

The ACTIB three-arm RCT

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Scientific summary

Background

Irritable bowel syndrome (IBS) is a common chronic gastrointestinal (GI) disorder affecting 10–22% of the UK population, with NHS costs of > £200M per year. Abdominal pain, bloating and altered bowel habits affect quality of life (QoL) and social functioning and can lead to time off work. Treatment relies on a positive diagnosis, reassurance, lifestyle advice and drug therapies. However, many patients suffer ongoing symptoms.

Face-to-face cognitive–behavioural therapy (CBT) has been shown to help IBS, reducing IBS symptoms and improving QoL measures, but NHS availability is poor and cost-effectiveness is uncertain. However, National Institute for Health and Care Excellence (NICE) guidance recommends CBT for patients with refractory IBS symptoms (i.e. ongoing symptoms after 12 months despite being offered appropriate medications and lifestyle advice) (NICE. *Irritable Bowel Syndrome in Adults: Diagnosis and Management of Irritable Bowel Syndrome in Primary Care*. Manchester: NICE; 2015).

Web-based CBT (WCBT) has been shown to be helpful for other long-term conditions (e.g. depression) and has advantages; for example, it can be completed at a time, place and rate convenient to the participant, without extra travel time and costs. Small pilot trials showed that WCBT had promise for helping IBS but indicated that some therapist input is needed. We previously developed a CBT self-management website to support patients with IBS (Regul8) and trialled it among 135 patients in the National Institute for Health Research (NIHR) Research for Patient Benefit-funded Management of Irritable Bowel Syndrome (MIBS) feasibility study (Everitt H, Moss-Morris R, Sibelli A, Tapp L, Coleman N, Yardley L, *et al.* Management of irritable bowel syndrome in primary care: the results of an exploratory randomised controlled trial of mebeverine, methylcellulose, placebo and a self-management website. *BMC Gastroenterol* 2013;**13**:68).

This NIHR Health Technology Assessment (HTA) Assessing Cognitive–behavioural Therapy in Irritable Bowel (ACTIB) trial was in response to a commissioned call (HTA number 11/69/02) to assess the clinical effectiveness and cost-effectiveness of psychological interventions for patients with refractory IBS.

Objectives

To estimate the clinical effectiveness and cost-effectiveness of therapist telephone-delivered CBT (TCBT) and a web-based CBT (WCBT) compared with treatment as usual (TAU) in lessening IBS symptom severity and improving functioning at 3, 6 and 12 months after randomisation in adults with refractory IBS.

Methods

The trial protocol is published as Everitt H, Landau S, Little P, Bishop F, McCrone P, O'Reilly G, *et al.* Assessing Cognitive behavioural Therapy in Irritable Bowel (ACTIB): protocol for a randomised controlled trial of clinical-effectiveness and cost-effectiveness of therapist delivered cognitive behavioural therapy and web-based self-management in irritable bowel syndrome in adults. *BMJ Open* 2015;**5**:e008622.

Design: three-arm multicentre randomised controlled trial

Adult patients with refractory IBS were individually randomised to TCBT, WCBT [a previously developed CBT website (Regul8) with low-level therapist support] or TAU with 12-month follow-up.

Setting: participants' homes via telephone and internet

Therapists were based in the South London and Maudsley NHS Foundation Trust (SLAM). Participants were recruited from London and the south of England from primary and secondary care.

Inclusion criteria

Those meeting the inclusion criteria were adults (aged ≥ 18 years) with refractory IBS {defined as fulfilling the Rome III criteria for IBS: reporting ongoing clinically significant symptoms [i.e. an IBS Symptom Severity Score (IBS SSS) of ≥ 75], had been offered first-line therapies [e.g. antispasmodics, antidepressants or fibre-based medications] and had experienced continuing IBS symptoms for ≥ 12 months}. Participants aged > 60 years were included only if they had received a consultant review in the previous 2 years to confirm that their symptoms were IBS related and to exclude other serious bowel conditions (there is an increased risk of bowel cancer in those aged > 60 years and clinical guidance suggests that further investigations are needed in this group).

Exclusion criteria

The exclusion criteria were having unexplained rectal bleeding or weight loss or a diagnosis of inflammatory bowel disease (IBD), coeliac disease, peptic ulcer disease or colorectal carcinoma. People were excluded if they were unable to participate in CBT because they had speech or language difficulties or had no access to an internet-enabled computer to be able to undertake the WCBT, or had received CBT for IBS in the past 2 years; also excluded were those who had previously had access to the Regul8 website or who were currently participating in an IBS/intervention trial.

Interventions

Two methods of delivering CBT were assessed: TCBT (total of 8 hours of telephone therapy contact time) and a lower-intensity WCBT (the Regul8 website) with 2.5 hours of therapist support.

The CBT content of the two treatments was the same, based on an empirical cognitive–behavioural model of IBS. It consisted of education, behavioural and cognitive techniques aimed at improving bowel habits, developing stable and healthy eating patterns, addressing unhelpful thoughts, managing stress, reducing symptom focusing and preventing relapse.

Participants randomised to the TCBT arm received a detailed CBT manual including homework. They received six 1-hour telephone sessions with a CBT therapist over 9 weeks and two 1-hour booster sessions at 4 and 8 months. Participants randomised to the WCBT arm received access to the Regul8 website and were advised to undertake the eight online weekly sessions and homework tasks. They received weekly automated e-mail reminders, three 30-minute telephone therapy support calls over 9 weeks and two 30-minute booster sessions at 4 and 8 months.

Trained CBT therapists provided the TCBT sessions for both therapy arms. Each therapist received 2 days' training and a therapy manual. Post training, therapists received monthly supervision with an experienced therapist. Treatment fidelity was assessed using audio-recordings of therapy sessions.

Treatment as usual

Patients in all three arms received TAU, with the control arm being TAU alone. TAU was defined as continuation of current medications and usual general practitioner (GP) or consultant follow-up with no psychological therapy for IBS. All GPs or consultants received a copy of the NICE guidance for IBS to ensure that all clinicians had the standard best practice information on IBS management. All participants received a standard information sheet on lifestyle and diet related to IBS, which was based on the NICE guidance. TAU-only participants had access to the WCBT website at the end of the trial follow-up period, but without therapist support.

Recruitment

Participants were recruited from general practice surgeries and gastroenterology clinics in two regions [Southampton and London (Guy's and St Thomas' NHS Foundation Trust, and King's College Hospital)]. Primary care patients were identified by searching GPs' lists for those with a diagnosis of IBS and by opportunistically recruiting patients presenting with IBS. An invitation letter was sent, including a patient information sheet and a reply slip to be returned to the research team. In secondary care, when available, clinic lists were also searched for patients with a diagnosis of IBS and potential participants were invited by letter. However, most recruitment was opportunistic during gastroenterology clinics. Advertisements were placed in relevant general practice and GI clinics and on NHS websites.

Study procedures

The study team undertook initial telephone screening for eligibility. Any patient indicating that they might have a 'red flag' symptom (i.e. unexplained weight loss or rectal bleeding) was referred back to their GP for further assessment.

Those eligible after telephone screening completed online consent and were invited for screening blood tests at their general practice surgery or hospital clinic for full blood count, C-reactive protein and tissue transglutaminase (as recommended in NICE guidelines). If the blood test results were within normal limits, the participant was invited to complete baseline questionnaires and be randomised.

Randomisation

Randomisation was carried out by an independent randomisation service at King's College London Clinical Trials Unit (CTU), which was accessed by study sites via a web-based system. Randomisation was at the level of the individual, using block randomisation with randomly varying block sizes, stratified by recruitment centre (Southampton general practices, Southampton secondary care, London general practices, London secondary care).

Blinding participants to therapy was not possible and the research assistants responsible for allocating patients to therapists could not be blinded. However, the principal investigators and statisticians remained blinded.

The baseline measures included outcome measures, sociodemographic details, current medication, medical history and medications, duration of IBS symptoms and previous or current psychiatric diagnoses.

The outcome measures were completed by participants at baseline and at 3, 6 and 12 months after randomisation.

Primary outcomes

The IBS SSS measures the severity and duration of abdominal pain, abdominal distension/tightness, bowel habit and QoL (score of 0–500).

The Work and Social Adjustment Scale (WSAS) measures the effect of IBS on people's ability to work and manage at home, participate in social and private leisure activities and maintain relationships.

Secondary outcome measures

The Subject's Global Assessment (SGA) of relief measures responses to treatment and the Patient Enablement Questionnaire (PEQ) assesses any change in participants' ability to cope with their illness and life after treatment. Mood was measured by the Hospital Anxiety and Depression Scale (HADS). The Client Service Receipt Inventory (CSRI) and EuroQol-5 Dimensions (EQ-5D) were used to gather information on use of health services and health-related QoL, respectively.

Adherence to therapy was measured by the number of telephone sessions and/or web sessions. Compliance was defined as patients randomised to WCBT completing at least four web sessions and one or more of the

telephone support calls. For patients randomised to TCBT, compliance was defined as completing at least four of the initial telephone CBT sessions.

Patients' GP notes were reviewed at 12 months to assess GP and other consultations in the year prior to entering the study and in the 12 months since study entry.

Sample size

A 35-point difference between therapy groups and TAU on the IBS SSS at 12 months was regarded as clinically significant (assuming a 15-point placebo response in the TAU arm in the trial). Assuming a within-group IBS SSS standard deviation (SD) of 76 (MIBS pilot study), this equates to an effect size of 0.46. To achieve 90% power at a 2.5% significance level (adjusting for two primary outcomes) required 119 subjects per group. This sample size was increased by an inflation factor of 1.32 to take account of therapist effects, decreased by a deflation factor of 0.84 assuming that baseline values are predictive of post-treatment values (correlation 0.4) and further inflated (factor 1.25) for attrition of < 20%. The final sample size was 165 patients per group, or 495 patients in total. For WSAS, this would be sufficient to detect a clinically important difference between WCBT (or TCBT) and TAU.

Statistical analysis

The Trial Steering Committee (TSC) approved the statistical analysis plan. All analyses followed the intention-to-treat principle. Group differences for IBS SSS and WSAS were assessed using a mixed linear regression model for repeated measurements. The mixed models accounted for missing outcome data under the missing-at-random assumption. Secondary outcomes were analysed similarly (as appropriate for continuous or dichotomous outcomes).

Economic evaluation

A health service and societal perspective was used. Service use was measured with a service receipt schedule at baseline and at each follow-up. Societal costs were calculated by including family care costs and lost work costs. Cost-effectiveness was assessed by combining the cost data with the IBS SSS and WSAS score at 12-month follow-up and quality-adjusted life-years (QALYs) (generated from the EuroQol-5 dimensions, five-level version). Sensitivity analyses were conducted by varying the therapy costs and imputing missing cost and QALY data.

Results

In total, 558 (38.4%) out of the 1452 patients screened for eligibility were recruited between May 2014 and March 2016: 186 were randomised to TCBT, 185 to WCBT and 186 to TAU. The most common reasons for exclusion at screening were not having refractory IBS (defined as an IBS SSS of ≥ 75), being > 60 years of age and not having had recent consultant review and not having been offered first-line therapies. Over-recruitment from the original sample size was undertaken (within the original recruitment time frame) to compensate for a lower follow-up rate than had been allowed for in the original sample size calculation.

Follow-up rates of 76.5% at 3 months (427/558), 72.9% at 6 months (407/558) and 70.3% at 12 months (392/558) were achieved. The 1-year follow-up was completed in April 2017.

The proportion of female participants was 75.8% (423/558). The mean age of participants was 43.1 years (SD 13.2 years) and the median time since diagnosis was 7.4 years (range 0.3–64.6 years); 10.2% of participants had seen a GI consultant. Their mean IBS SSS was 265 (SD 95.5), indicating moderately severe IBS, and the baseline mean WSAS score was 12.5, suggesting significant, but not severe, functional impairment. The median time from the start of symptoms to diagnosis was 3.0 years (range 0.0–47.0 years); 30.3% of participants (169/558) reported having received treatment for anxiety and 39.4% (220/558) reported having received treatment for depression. The mean baseline HADS anxiety score was 10.7 (SD 4.2) and the mean baseline HADS depression score was 5.7 (SD 3.7). This suggests that participants were more

anxious than depressed at baseline but that, overall, there was no significant mental health comorbidity. Baseline characteristics were well balanced between the groups, indicating that randomisation had been successful.

Mean IBS SSS were 61.6 (95% CI 89.5 to 33.8) lower ($p < 0.001$) in the TCBT arm and 35.2 (95% CI –12.6 to 57.9) lower ($p = 0.002$) in the WCBT arm than in the TAU arm (mean IBS SSS of 205.6 at 12 months) at 12 months. The mean WSAS score in TAU arm was 10.8 at 12 months and was 3.5 (95% CI 5.1 to 1.9) lower ($p < 0.001$) in the TCBT arm and 3.0 (95% CI 4.6 to 1.3) lower ($p = 0.001$) in the WCBT arm.

Secondary outcomes also showed significant improvement in the therapy arms. For SGA of relief, 84.8% of participants were responders in the TCBT arm at 12 months, compared with 41.7% in the TAU arm [odds ratio (OR) 6.1, 95% CI 2.5 to 15.0; $p < 0.001$] and 75.0% in the WCBT arm (OR 3.6, 95% CI 2.0 to 6.3; $p < 0.001$). For the PEQ, 78.3% of participants were responders in the TCBT arm, compared with 23.5% in the TAU arm (OR 9.3, 95% CI 4.5 to 19.3; $p < 0.001$) and 54.8% in the WCBT arm (OR 3.5, 95% CI 2.0 to 5.9; $p < 0.001$). For HADS, compared with the TAU arm [mean HADS score 16.4 (SD 6.9) at 12 months], scores were 2.8 (95% CI 4.1 to 1.5) lower ($p < 0.001$) in the TCBT arm and 2.3 (95% CI 3.7 to 1.0) lower ($p < 0.001$) in the WCBT arm at 12 months.

There was no evidence that the interventions had an impact on the use or cost of other health-care services. Health service costs during the follow-up period were £956 higher for TCBT than for TAU (bootstrapped 95% CI £601 to £1435) and £224 higher for WCBT than for TAU (bootstrapped 95% CI –£11 to £448). TCBT produced 0.0429 more QALYs and WCBT produced 0.0290 more QALYs than TAU. The incremental cost-effectiveness ratio for TCBT compared with TAU was £22,284 and for WCBT compared with TAU was £7724; the ratios after imputation were £29,000 and £19,593, respectively.

In a nested qualitative study, 52 participants (17 or 18 from each trial arm) were interviewed at 3 months and 42 participants were interviewed again at 12 months. This highlighted an increased capacity to cope with symptoms, negative emotions and other challenges of daily life in the CBT arms. It also suggested that therapists are important in supporting patients to engage with CBT and to make sense of the therapy and their IBS. Patients valued having therapist support available alongside the Regul8 website and this may have helped enhance their engagement and outcomes.

Conclusions

This is believed to be the largest trial of CBT for IBS worldwide. It recruited from primary and secondary care sites in the UK. Both CBT arms showed significant improvements in IBS outcome measures compared with TAU at 12 months. WCBT had a lower cost per QALY than TCBT. Therapist input was found to be important in supporting web-based CBT. This large, rigorously conducted randomised controlled trial indicates that these CBT interventions can provide sustained improvements in IBS symptoms at an acceptable cost.

Trial registration

This trial is registered as ISRCTN44427879.

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